



**ESHRE, ASRM, CRE WHIRL and  
IMS Guideline Group on POI**

## **Evidence-based Guideline: Premature ovarian insufficiency**

### **LITERATURE REPORT**

**2024**





## ANNEX: Literature report

This document complements the ESHRE Guideline on Premature Ovarian Insufficiency.

For each key question, details are provided on the literature searches (PICO terms and search strings, databases searched, flowchart), the evidence (evidence tables) and the factors taken into considerations when formulating recommendations.

Evidence processing: Studies were selected and appraised by one reviewer using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. No studies met inclusion criteria for this review.

According to the GRADE Evidence to decisions framework<sup>1</sup>, these factors are tabulated as:

- Desirable effects: What are the desirable anticipated effects and how substantial are they? (Large, moderate, small, trivial, varies, unclear)
- Undesirable effects: What are the undesirable anticipated effects and how substantial are they? (Large, moderate, small, trivial, varies, unclear)
- Certainty of evidence: What is the overall certainty of the evidence of effects? (very low, low, moderate, high)
- Values: Is there important uncertainty about or variability in how much people value the main outcomes?
- Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?
- Resource use, equity, acceptability and feasibility: Is there any impact on resource use, or health equity, and is the intervention acceptable and feasible?

Where relevant, subgroup considerations are added as a factor to be considered.

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<sup>1</sup> <https://guidelines.grade.pro.org/profile/3879A46D-7E19-FEBA-9B96-BC2B3F996EB1>



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## I. Risk factors for POI

Due to significant overlap in terminology and studies between risk factors and causes of POI, a broad literature search including both risk factors and causes was performed. Data pertaining to risk factors, were separately summarized.

Family history and demographic factors							
	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
Family history of POI (menopause <40)		OR 8.4; 95% CI 2.5 to 31.2		(Cramer <i>et al.</i> , 1995)	Study	344 early menopause + 344 controls	US
Family history of early menopause (menopause <45)		OR 6.1 (95% CI 4.0 to 9.3) **					
Multiple family members affected with early menopause		OR 12.4 (95% CI 4.4 to 34.2)					
Sister with early menopause		OR 9.1 (95% CI 3.1 to 26.5)					
Mother with early menopause		OR 6.20 (95% CI 2.31 to 16.65)		(Morris <i>et al.</i> , 2011)	Study	2 060 individuals	UK
Sister with early menopause		OR 5.46 (95% CI 3.32 to 8.96)					
Monozygotic twin sister with early menopause		OR 18.00 (95% CI 1.08 to 298.99) <sup>c</sup>					
Relative with POI	RR 4.6 (95% CI 3.3 to 6.5)			(Silvén <i>et al.</i> , 2022)	Study	5011 women with POI + population based controls	Finland
First degree relatives of POI case (vs controls)	RR 18.52 (95% CI 10.12 to 31.07)			(Verrilli <i>et al.</i> , 2023)	Study	396 POI + relatives (2,132 first-degree, 5,245 second-degree, 10,853 third-degree)	US
Second degree relatives of POI case	RR 4.21 (95% CI 1.15 to 10.79)						
Third degree relatives of POI case	RR 2.65 (95% CI 1.14 to 5.21)						
Family history of a relative with menstrual abnormalities	OR 28.12 (95% CI 8.84 to 89.46)			(Wang <i>et al.</i> , 2015).	Study	553 POI + 400 controls	China
Early life factors							
	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
Being part of a multiple birth		OR 1.55** (95% CI 1.13 to 2.13)		(Ruth <i>et al.</i> , 2016)	Study	273 474 women	UK
Being part of a twin	3- to 5-fold increased prevalence			(Gosden <i>et al.</i> , 2007).	Study	832 female twin-pairs	Australia and UK
Pre-term birth (born before 37 weeks of gestation)	OR 4.66 (95% CI 1.3 to 16.7)			(Sadrzadeh <i>et al.</i> , 2017)	Study	59 women with POI and 92 controls	Netherlands
Post-term birth (born after 41 weeks of gestation)	OR 8.23 (95% CI 1.63 to 41.4)						
Birth weight	No association			(Sadrzadeh <i>et al.</i> , 2017)	Study	59 women with POI and 92 controls	Netherlands
Birth weight		OR 1.08** (95% CI 0.97 to 1.19)		(Ruth <i>et al.</i> , 2016)	Study	273 474 women	UK



Birth weight (standardized for gestation)		No association		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri-/premenopausal women	UK
Duration of exclusive breastfeeding (vs <1month breast feeding)				(Langton <i>et al.</i> , 2020).	Study	108887 premenopausal women	US
• 1 to 6 months		HR 0.95 (95%CI 0.85 to 1.07)					
• 7 to 12 months		HR 0.72 (95%CI 0.62 to 0.83)					
• 13 to 18 months		HR 0.80 (95%CI 0.66 to 0.97)					
• 19 or more months		HR 0.89 (95%CI 0.69 to 1.16)					
Not breastfed as a baby (vs yes)		OR 1.00** (95% CI 0.88 to 1.15)		(Ruth <i>et al.</i> , 2016)	Study	273 474 women	UK
Breastfed (< 1 month vs ≥ 1 month)		OR 1.30 (95% CI 1.05 to 1.60)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri-/premenopausal women	UK
Adverse parenting or childhood experiences	/		Associated	(Giri and Vincent, 2020)			
Father's social class - No father in household		OR 2.20 (95% CI 1.48 to 3.28)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri-/premenopausal women	UK
Maternal smoking around birth (vs no)		OR 1.08** (95% CI 0.95 to 1.24)		(Ruth <i>et al.</i> , 2016)	Study	273 474 women	UK
Mother smoked during pregnancy		OR 1.24 (95% CI 1.03 to 1.49)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri-/premenopausal women	UK

### Reproductive factors

	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
At least one live birth			Associated later age at menopause HR 0.79 (95% CI 0.74 to 0.85)	(Roman Lay <i>et al.</i> , 2020).	Review	19 studies	
Nulliparity	RR 2.26** (95% CI 1.84 to 2.77)	RR 1.32 (95% CI 1.09 to 1.59)		(Mishra <i>et al.</i> , 2017).	Review	9 studies - 51450 postmenopausal women	UK/ Scandinavia/ Australia/ Japan
Pregnancies vs nulliparous				(Langton <i>et al.</i> , 2020).	Study	108887 premenopausal women	US
• 1 pregnancy		HR 0.92 (95%CI 0.79 to 1.06)					
• 2 pregnancies		HR 0.84 (95%CI 0.73 to 0.96)					
• 3 pregnancies		HR 0.78 (95%CI 0.67 to 0.92)					
• 4 or more pregnancies		HR 0.81 (95%CI 0.66 to 1.01)					



Higher Parity (Higher number of childbirths)			Associated with higher age at natural menopause	(Gottschalk <i>et al.</i> , 2022).	Study	310147 women	Norway
Parity (1 vs 0)			OR 0.85 (95% CI 0.52 to 1.39)	(Pokoradi <i>et al.</i> , 2011).	Study	5113 postmenopausal women	UK
Number of live births (decreasing)		OR 1.09 (95% CI 1.05 to 1.13)		(Ruth <i>et al.</i> , 2016)	Study	273 474 women	UK
Later age at first birth			Associated later age at menopause B 0.21 SD (95% CI 0.13 to 0.29)	(Prince <i>et al.</i> , 2022).	Study	502,682 individuals (BIOBANK)	UK
Age at menarche			Not associated	(van Noord <i>et al.</i> , 1997)	Study	3756 women	Netherlands
Age at menarche			Not associated HR 1.01 (95% CI 0.93 to 1.11)	(Otero <i>et al.</i> , 2010)	Study	1462 women	Brazil
Age at menarche			Associated with ~8 weeks earlier ANM per-year earlier menarche.	(Ruth <i>et al.</i> , 2021)	study		
Age at menarche, mean (STD)	Not significant OR 0.95 (95% CI 0.87 to 1.03)			(Wang <i>et al.</i> , 2015).	Study	553 POI + 400 controls	China
Age at menarche (per year)		No association OR 0.98 (95% CI 0.90 to 1.07)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri-/premenopausal women	UK
Age at menarche ≤9 (vs. 12) years		HR 1.28 (95% CI 0.99 to 1.67)		(Whitcomb <i>et al.</i> , 2018a)	Study	108 811 premenopausal women	USA
Early menarche (≤11 years)	RRR 1.80 (95% CI 1.53 to 2.12)	RRR 1.31 (95% CI 1.19 to 1.44)		(Mishra <i>et al.</i> , 2017)	Study	9 studies 51450 postmenopausal women	UK/ Scandinavia via/ Australia/ Japan
Early age at menarche (decreasing)		OR 1.05** (95% CI 1.00 to 1.09)		(Ruth <i>et al.</i> , 2016)	Study	273 474 women	UK
Age at menarche ≥13 years			Associated with later age at menopause HR 0.90 (95% CI 0.84 to 0.96)	(Roman Lay <i>et al.</i> , 2020).	Review	9 studies; 232,010 women	
Shorter menstrual cycle length <25 days (at ages 18 - 22 yrs)		HR, 1.70 (95% CI 1.47 to 1.96)		(Whitcomb <i>et al.</i> , 2018a)	Study	108 811 premenopausal women	USA
Longer menstrual cycle length ≥40 day cycles		HR 0.44 (95% CI 0.34 to 0.58)		(Whitcomb <i>et al.</i> , 2018a)	Study	108 811 premenopausal women	USA
Irregular cycle length vs regular cycles		HR 0.51 (95% CI 0.43 to 0.60)		(Whitcomb <i>et al.</i> , 2018a)	Study	108 811 premenopausal women	USA
Ever use of oral contraceptives (OC)			Associated later age at menopause HR 0.87 (95% CI 0.82 to 0.93)	(Roman Lay <i>et al.</i> , 2020).	Review	17 studies; 337,833 women	
Ever-use of oral contraceptives			HR 0.85 (95% CI 0.75 to 0.97)	(Gold <i>et al.</i> , 2013).	Study	16,065 community-based women	US
Ever-use of oral contraception vs never use			OR 1.37 (95% CI 1.14 to 1.63)	(Pokoradi <i>et al.</i> , 2011).	Study	5113 postmenopausal women	UK



History of pelvic surgery, incl ovarian cystectomy, unilateral oophorectomy, tubal ectopic pregnancy surgery	OR 5.53 (95% CI 2.15 to 14.23)			(Wang <i>et al.</i> , 2015).	Study	553 POI + 400 controls	China
Tubal Sterilization			OR1.38 (95% CI 1.02 to 1.87)	(Pokoradi <i>et al.</i> , 2011).	Study	5113 postmenopausal women	UK
HRT up to age of menopause vs no HRT			OR 0.28 (95% CI 0.20 to 0.41)	(Pokoradi <i>et al.</i> , 2011).	Study	5113 postmenopausal women	UK
<b>Body Mass Index</b>							
	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
Underweight (BMI < 18.5 kg/m <sup>2</sup> ) vs normal BMI			Associated with early age at menopause HR 1.08 (95% CI 1.03 to 1.14)	(Tao <i>et al.</i> , 2015)	Review	9 studies 313 482 participants	
Low BMI (< 18.5 kg/m <sup>2</sup> )		OR 1.30 (95% CI 1.08 to 1.57)		(Szegda <i>et al.</i> , 2017)	Study	78 759 premenopausal women	UK
Underweight (BMI < 18.5 kg/m <sup>2</sup> ) vs normal BMI		RRR 2.15** (95% CI 1.50 to 3.06)		(Zhu <i>et al.</i> , 2018b)	Review	11 studies 24 196 postmenopausal women	
Underweight (BMI < 18.5 kg/m <sup>2</sup> ) vs normal BMI			OR 1.09 (95% CI 0.63 to 1.89)	(Pokoradi <i>et al.</i> , 2011).	Study	5113 postmenopausal women	UK
Low BMI (< 18.5 kg/m <sup>2</sup> )	HR 1.52 (95% CI 0.71 to 3.23)			(Chemaitilly <i>et al.</i> , 2017).	Study	921 cancer survivors	USA
Normal vs underweight			RR 0.91 (95% CI 0.80 to 1.03)	(Hardy <i>et al.</i> , 2000)	Study	1572	UK
Overweight (BMI 25-29.9 kg/m <sup>2</sup> ) vs normal BMI			Associated with late age at menopause. HR 0.93 (95% CI 0.91 to 0.96)	(Tao <i>et al.</i> , 2015)	Review	9 studies 313 482 participants	
High BMI (25.0–27.4 kg/m <sup>2</sup> )		OR 0.71 (95% CI 0.54 to 0.92)		(Szegda <i>et al.</i> , 2017)	Study	78 759 premenopausal women	UK
Overweight (BMI 25-29.9 kg/m <sup>2</sup> ) vs normal BMI			associated with late menopause (≥56) RRR 1.52 (95% CI 1.31 to 1.77)	(Zhu <i>et al.</i> , 2018b)	Review	11 studies 24 196 postmenopausal women	
Overweight (BMI 25-29.9 kg/m <sup>2</sup> ) vs normal BMI			OR 1.02 (95% CI 0.80 to 1.30)	(Pokoradi <i>et al.</i> , 2011).	Study	5113 postmenopausal women	UK
Overweight			WMD 0.05 (95% CI -0.25 to 0.35)	(Schoenaker <i>et al.</i> , 2014).	Meta-analysis	6/46 studies	
Obese (BMI >30 kg/m <sup>2</sup> ) vs normal BMI			Associated with late age at menopause HR 0.95 (95% CI 0.79 to 1.15)	(Tao <i>et al.</i> , 2015)	Review	9 studies 313 482 participants	
Obese (BMI ≥ 30 kg/m <sup>2</sup> ) vs normal BMI			associated with late menopause (≥56) RRR 1.54 (95% CI 1.18 to 2.01)	(Zhu <i>et al.</i> , 2018b)	Review	11 studies 24 196 postmenopausal women	
Obese (BMI ≥ 30 kg/m <sup>2</sup> ) vs normal BMI	HR 0.43 (95% CI 0.22 to 0.86)			(Chemaitilly <i>et al.</i> , 2017).	Study	921 cancer survivors	USA



Inactive vs moderate/high physical activity			WMD -0.34 (95% CI -0.62 to -0.07)	(Schoenaker <i>et al.</i> , 2014).	Meta-analysis	3/46 studies	
Thinner comparative body size at age 10 (vs average)		OR 1.10** (95% CI 0.96 to 1.27)		(Ruth <i>et al.</i> , 2016)	Study	273 474 women	UK
BMI at 16 (per kg/m <sup>2</sup> )		No association OR 1.03 (95% CI 0.99 tot 1.07)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri-/premenopausal women	UK
BMI at 30/33 (per kg/m <sup>2</sup> )		No association OR 0.99 (95% CI 0.96 tot 1.02)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri-/premenopausal women	UK

### Socio-economic status

	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
Middle vs low education			WMD 0.30 (95% CI 0.10 to 0.51)	(Schoenaker <i>et al.</i> , 2014).	Meta-analysis	11/46 studies	
High vs low education			WMD 0.64 (95% CI 0.26 to 1.02)	(Schoenaker <i>et al.</i> , 2014).	Meta-analysis	9/46 studies	
Education	no significant difference 0.81 (0.51 to 1.30) 1.22 (0.73 to 2.05)			(Wang <i>et al.</i> , 2015).	Study	553 POI + 400 controls	China
Educational level (decreasing)		OR 1.09 (95% CI 1.07 to 1.12)		(Ruth <i>et al.</i> , 2016)	Study	273 474 women	UK
Lower levels of education	More prevalent in POI vs controls			(Silvén <i>et al.</i> , 2022)	Study	5011 women with POI + population-based controls	Finland
No education versus secondary/higher education	Higher risk			(Jungari and Chauhan, 2017).		124 385 women	India
Cognitive ability at 10/11 (per SD)		OR 0.64 (95% CI 0.57 to 0.71)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri- and pre-menopausal women	UK
Middle vs low occupation level			WMD 0.25 (95% CI 0.02 to 0.49)	(Schoenaker <i>et al.</i> , 2014).	Meta-analysis	4/46 studies	
High vs low occupation level			WMD 0.76 (95% CI 0.44 to 1.09)	(Schoenaker <i>et al.</i> , 2014).	Meta-analysis	4/46 studies	
Lower socio-economic status	More prevalent in POI vs controls			(Silvén <i>et al.</i> , 2022)	Study	5011 women with POI + population based controls	Finland
Living in rural areas vs urban areas	Higher risk			(Jungari and Chauhan, 2017).		124 385 women	India
Poorest wealth group vs richer women	Higher risk			(Jungari and Chauhan, 2017).		124 385 women	India
Occupation	no significant difference 0.79 (0.57 to 1.12) 1.04 (0.68 to 1.60)			(Wang <i>et al.</i> , 2015).	Study	553 POI + 400 controls	China
Social class at age 38/42 (unemployed vs employed)		OR 1.43 (95% CI 1.13 to 1.81)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri-/premenopausal women	UK

### Smoking



	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
Smoking			earlier age of natural menopause WMD -0.91 (95% CI -1.34 to -0.48)	(Schoenaker <i>et al.</i> , 2014)		15/46 studies	
Former smoker vs never smoker	RRR 1.13 (95% CI 1.04 to 1.23)	RRR 1.15 (95% CI 1.05 to 1.27)		(Zhu <i>et al.</i> , 2018a)	review	17 studies 234 811 postmenopausal women	
Current smoker vs never smoker	RRR 2.05 (95% CI 1.73 to 2.44)	RRR 1.80 (95% CI 1.66 to 1.95)					
Current smoker vs never smoker			48.9±0.2 years vs 47.8±0.3 years	(Oboni <i>et al.</i> , 2016)	study	6711 participants	Switzerland
Tobacco smoking			earlier ANM**	(Ruth <i>et al.</i> , 2021)	study		
Smoking (>10 cigarettes per day)		40% increase in risk of earlier menopause		(Kato <i>et al.</i> , 1998)		4694 premenopausal women	USA
Smoking			No association	(van Noord <i>et al.</i> , 1997).		3756 women	netherlands
Smokers (>30 packs/year) vs non-smokers			OR 1.71 (95% CI 1.30 to 2.24)	(Pokoradi <i>et al.</i> , 2011).	Study	5113 postmenopausal women	UK
Current smokers vs nonsmokers			1.74 years earlier (t = 3.78)	(McKinlay <i>et al.</i> , 1985)	Study	7828 women	USA
Smokers vs non-smokers			RR 1.65 ** (95% CI 1.29 to 2.29)	(Hardy <i>et al.</i> , 2000)	Study	1572	UK
Smokers or been smokers vs non-smokers		OR 2.46 (95% CI 1.08 to 5.59)		(Bustami <i>et al.</i> , 2021).	Study	244 menopausal	Jordan
current smokers vs never-smokers		HR 1.90 (95% CI 1.71 to 2.11)	(Zhu <i>et al.</i> , 2018a)	(Whitcomb <i>et al.</i> , 2018b)	Study	116,429 female nurses	US
Former smokers vs never-smokers		HR 1.10 (95% CI 1.00 to 1.21)		(Whitcomb <i>et al.</i> , 2018b)			
Current smokers vs never-smokers			HR 1.26 (95% CI 0.97 to 1.65)	(Gold <i>et al.</i> , 2013).	Study	16,065 community-based women	US
Smoking status, previous smoker (vs never)		OR 1.13** (95% CI 0.93 to 1.36)		(Ruth <i>et al.</i> , 2016)	Study	273 474 women	UK
Smoking status, current smoker (vs never)		OR 1.37** (95% CI 1.04 to 1.79)		(Ruth <i>et al.</i> , 2016)	Study	273 474 women	UK
Passive smoking			HR 1.09 (95% CI 0.92 to 1.29)	(Gold <i>et al.</i> , 2013).	Study	16,065 community-based women	US
Smoking at 16		OR 1.51 (95% CI 1.19 to 1.92)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri- and pre-menopausal women	UK
<b>Alcohol</b>							
	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
Drinking alcohol versus not		RR 0.90 (95%CI 0.79 to 1.02)	RR 0.86 (95% CI 0.78 to 0.96)	(Taneri <i>et al.</i> , 2016)	Meta-analysis	20 studies	



Consuming more than one drink per week vs non-drinkers			RR 0.60 (95% CI 0.49 to 0.75) a			41 339 + 63 868 women	
Three or fewer drinks per week vs non-drinkers			RR 0.75 (95% CI 0.60 to 0.94)				
Moderate alcohol intake (10.0–14.9 g/day) vs non-drinkers			HR 0.81 (95% CI 0.68 to 0.97)	(Freeman <i>et al.</i> , 2021)	Study	116 429 female nurses	US
High alcohol intake (≥30.0 g/day) vs non-drinkers			HR 0.88 (95% CI 0.64 to 1.22)				
>4 Units of alcohol per week, vs 0 units			OR 0.82 (95% CI 0.64 to 1.06)	(Pokoradi <i>et al.</i> , 2011).	Study	5113 postmenopausal women	UK
Increased alcohol consumption			earlier ANM <sup>2</sup>	(Ruth <i>et al.</i> , 2021)	Study		
Alcohol consumption at 30/33 (monthly vs less often/never)		OR 0.76 (95% CI 0.57 to 1.00)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri-/pre menopausal women	UK

### Infectious causes

	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
various infections, including mumps, HIV, herpes zoster, cytomegalovirus, tuberculosis, malaria, varicella, and shigella	Inconclusive results			(Goswami and Conway, 2005, Kokcu, 2010).	Review		
mumps oophoritis	Mumps oophoritis may cause POI Explaining 3 to 7% of POI cases			(Kokcu, 2010)(Morrison <i>et al.</i> , 1975).			
History of Mumps	OR 3.26 (95% CI 2.38 to 4.47)			(Wang <i>et al.</i> , 2015).	Study	553 POI + 400 controls	China
HIV vs non-HIV	POI prevalence 26% vs 10%	27.9% vs 2.7%		(Van Ommen <i>et al.</i> , 2021).	Review	9 studies	
Women with HIV	Same as general pop	Same as general pop		(Bullington <i>et al.</i> , 2022)	Study	3059	US

### Coexisting medical conditions

	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
PCOS vs controls		adjusted HR 8.31 (95% CI 7.05 to 9.81)					
PCOS who did not receive metformin treatment		adjusted HR 9.93 (95% CI 8.28 to 11.90)		(Pan <i>et al.</i> , 2017)	Study	7049 PCOS - 70490 without PCOS	Taiwan
PCOS who received metformin treatment		adjusted HR 5.66 (95% CI 4.36 to 7.35)					
Galactosemia			only 68% achieved spontaneous menarche; fewer than 50% of these women were still cycling regularly after 3 years, and fewer than 15% were cycling regularly after 10 years	(Frederick <i>et al.</i> , 2018)	Study	102 post-pubertal girls and women with galactosemia	US
History of endometriosis			OR 2.49 (95% CI 1.42 to 4.37)	(Pokoradi <i>et al.</i> , 2011).	Study	5113 postmenopausal women	UK

<sup>2</sup> women who drank alcohol at the maximum recommended limit experienced ~1 year earlier menopause compared to those who drank little



Periods or other gynaecological problems by 30/33		OR 1.68 (95% CI 1.36 to 2.06)		(Peycheva <i>et al.</i> , 2022)	Study	6805 (natural) menopausal, peri- and pre-menopausal women	UK
<b>Chemical exposures</b>							
	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
Highest EDC levels (15 EDCs with long half-lives and phthalates) vs without			mean ages of menopause 1.9 to 3.8 years earlier	(Grindler <i>et al.</i> , 2015)	Study	31 575 females	US
Urinary levels of Monoisobutyl phthalate (MiBP) (phthalate metabolites)	OR 1.38 (95% CI 0.73 to 2.61)			(Cao <i>et al.</i> , 2020)	Study	173 POI- 246 control	China
Urinary levels of 3-PBA (Pyrethroid Pesticide)	OR 2.344 (95% CI 1.193 to 4.607)			(Li <i>et al.</i> , 2018)	Study	172 POI – 247 control	China
High vs low levels of dioxin-like PCBs (DL-PCBs)	OR 1.31 (95% CI 0.67 to 2.57)			(Pan <i>et al.</i> , 2019)	Study	157 POI - 217 control	China
High vs low levels of p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT)	OR 3.15 (95% CI 1.63 to 6.10)						
Benzo(a)pyrene (BaP) (polycyclic aromatic hydrocarbons)	OR 2.191 (95%CI 1.634 to 2.938)			{Ye, 2020 #2438}	Study	157 POI – 217 healthy	China
Levels of perfluorooctanate (PFOA) (High vs low levels)	OR 3.80 (95%CI 1.92 to 7.49)			(Zhang <i>et al.</i> , 2018)	Study	120 POI - 120 healthy control	China
perfluorooctane sulfonate (PFOS) (High vs low levels)	OR 2.81 (95%CI 1.46 to 5.41)						
perfluorohexanesulfonate (PFHxS) (High vs low levels)	OR, 6.63 (95%CI 3.22 to 13.65)						
Exposure to chemical agents	OR 4.47 (95% CI 2.09 to 9.58)			(Wang <i>et al.</i> , 2015).	Study	553 POI + 400 controls	China
Exposure to agricultural chemicals	OR 11.56 (95% CI 5.51 to 24.25)			(Wang <i>et al.</i> , 2015).	Study	553 POI + 400 controls	China
Urinary thallium concentrations	OR1.63 (95% CI 1.25 to 2.13)			(Ma <i>et al.</i> , 2022)	Study	169 POI - 209 healthy women	China
Urinary arsenic concentrations (High vs low levels)	OR 2.66 (95% CI 1.43 to 4.95)			(Pan <i>et al.</i> , 2020)	Study	169 POI - 209 healthy women	China
Urinary concentrations of cadmium	OR 2.50 (95% CI 1.34 to 4.65)			(Pan <i>et al.</i> , 2021)	Study	169 POI - 209 healthy women	China
high concentrations of perfluoro compounds			earlier menopause HR 1.63 (95% CI 1.08 to 2.45)	(Ding <i>et al.</i> , 2020).	Study	1120 premenopausal women	USA
<b>Vaccines</b>							
	Risk of POI	Risk of Early menopause	Association with age at menopause	REFERENCE	Type	Sample size	Country
Quadrivalent human papillomavirus (HPV) vaccination vs controls	RR 0.47 (95% CI 0.14 to 1.5)			(Torella <i>et al.</i> , 2023).	Review	4 studies 1 253 758 females	
bivalent HPV vaccination vs 9-valent vaccine	RR 0.93 (95% CI 0.33 to 2.64)						



tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed vaccination	Adjusted HR 0.88 (95% CI 0.37 to 2.10)			(Naleway <i>et al.</i> , 2018).	study	199 078 females of which 120 with diagnoses suggestive of POI.	
meningococcal conjugate (MenACWY) vaccination	Adjusted HR 0.94 (95% CI 0.27 to 3.23)						

\*\*adjusted for confounders



## II. Symptoms, diagnosis and initial assessment

### II.1. Symptoms

#### KEY QUESTION: WHAT ARE THE SYMPTOMS OF PREMATURE OVARIAN INSUFFICIENCY?

<b>Population</b>	POI / Women suspected of POI
<b>Interventions</b>	
<b>Control</b>	
<b>Outcomes</b>	signs OR symptoms OR symptom OR "clinical manifestation"

#### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (signs OR symptoms OR symptom OR "clinical manifestation" OR "clinical presentation") AND (symptoms[MeSH Major Topic])

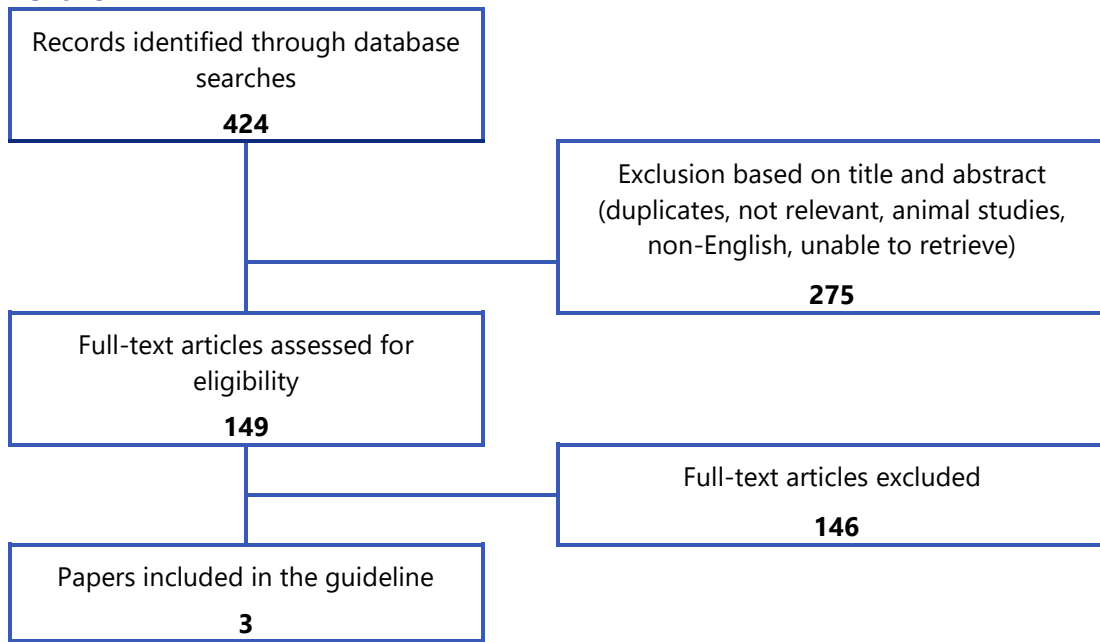
Literature search was limited to the period between 01/01/2014 and 17/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.

#### List of papers included in the guideline – narrative approach (11)

(Rebar and Connolly, 1990, Conway, 2000, Smith *et al.*, 2004, Welt, 2008, Knauff *et al.*, 2009, Davis and Jane, 2011, Deeks *et al.*, 2011, Gibson-Helm *et al.*, 2014, Allshouse *et al.*, 2015, Jiao *et al.*, 2017, Huang *et al.*, 2021)



## Flowchart





## II.2. Diagnosis

### PICO QUESTION: WHAT INVESTIGATIONS SHOULD BE PERFORMED FOR DIAGNOSIS OF POI?

<b>Population</b>	Women suspected of POI
<b>Interventions</b>	Laboratory tests: FSH levels - Serum prolactin - TSH / T4 – Estradiol - LH levels – AMH - Progestin withdrawal test - Ovarian biopsy / laparoscopy - Pelvic ultrasound - clinical examination
<b>Control</b>	(Elevated FSH levels)
<b>Outcomes</b>	Diagnosis of POI

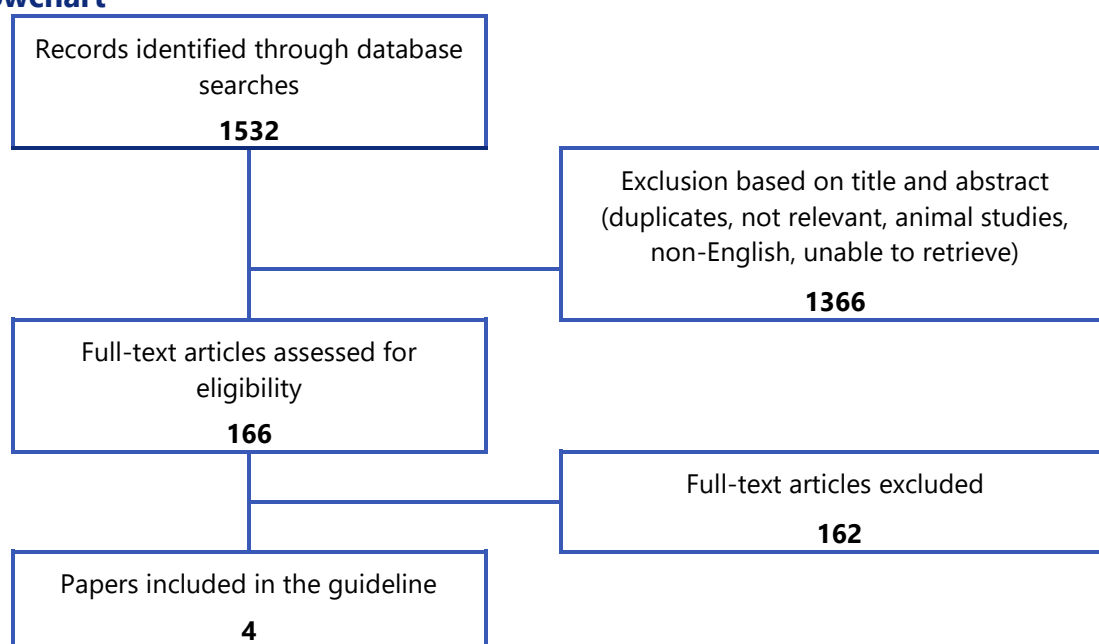
### Search strings

Database	Search String
<b>PUBMED</b>	((("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (FSH OR "Follicle-stimulating hormone" OR "Follicle Stimulating Hormone" OR "Serum prolactin" OR TSH/T4 OR "thyroid-stimulating hormone" OR "thyroid stimulating hormone" OR TSH OR T4 OR thyroxin OR estradiol OR LH OR "Luteinizing hormone" OR AMH OR "antimüllerian hormone" OR "anti-mullerian hormone" OR "anti-müllerian hormone" OR "Antimullerian Hormone" OR "Ovarian biopsy" OR "laparoscopy" OR "Ovarian histology" OR Pelvic ultrasound OR clinical examination OR "Inhibin") AND (diagnosis OR diagnose OR diagnostic OR sensitivity OR specificity) )OR ("Progestin withdrawal test" OR "progesterone withdrawal")OR ((("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (Diagnosis/Narrow[filter]))

Literature search was limited to the period between 01/01/2014 and 17/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## INCLUDED AS BACKGROUND INFORMATION:

(Nelson, 2009, NICE, 2015, Gordon *et al.*, 2017, NICE, 2019, Ishizuka, 2021) (De Vos *et al.*, 2010, ACOG, 2014, Webber *et al.*, 2016)

## Evidence

### Evidence table – FSH

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Gordon <i>et al.</i>, 2017)</b>	Cohort study	58 women with primary  176 with secondary amenorrhea	FSH (radioimmunoassay)	Histological evaluation of ovarian biopsies		No follicles in:  Primary amenorrhea + FHS>33 mIU/ml  secondary amenorrhea am + FHS>40 mIU/ml	Plasma FSH levels reliably predict presence or absence of ovarian follicles in women with amenorrhea	
<b>{, 2014 #2477 }</b>			FSH >40 or				Initial laboratory evaluation for suspected primary ovarian insufficiency includes measurements of basal FSH and basal estradiol levels and tests to rule out causes such as pregnancy, thyroid disease, and hyperprolactinemia. Gonadotropin and estradiol values may be altered by concomitant use of hormonal preparations and thus should only be obtained in patients who are not taking hormonal medications, including OCs. If gonadotropins are elevated into the menopausal range (typically, basal FSH levels will be greater than 30–40 mIU/mL, depending on the laboratory used), a repeat FSH measurement is indicated in 1 month. If the result indicates that FSH is elevated, a diagnosis of primary ovarian insufficiency can be established. Estradiol	



						levels of less than 50 pg/mL indicate hypoestrogenism.		
<b>(Ishizuka, 2021).</b>	review					FSH levels have been used in making the diagnosis of POI, but precise cut-off levels have not been determined. Initially, a number of papers used FSH levels >40, 50, or 20 mIU/ml as the criteria based on older reports, but some patients with POI sometimes show FSH levels lower than these cut-off levels.		
<b>(Nelso n, 2009).</b>	Review						criteria as defined by the reporting laboratory (FSH level in the menopausal range)	
<b>(La Marca et al., 2009).</b>	Cohort study	92 POI: 66 =idiopathic 26 = SCA+	Idiopathic POI : FSH > 40 SCA-POI: FSH > 25	FSH (idiopathic vs SCA+)		SCA+: lower FSH levels (median 37 mIU/ml; range 26-64 mIU/ml) vs idiopathic POI (median 99 mIU/ml; range 61-166 mIU/ml; p=0.001)		AMH was undetectable in all idiopathic POI women, but normal in most SCA-POI women who had been diagnosed < 5 years as SCA-POI.  Limitation is no ultrasound have been performed.

### Evidence table – Estradiol

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(ACOG, 2014)</b>	Guideline						estradiol levels of less than 50 pg/mL (183.6 pmol/L) indicate hypoestrogenism	Guideline

### Evidence to recommendations

QUESTION	What investigations should be performed for diagnosis of POI?
RECOMMENDATION	<b>HCPs should diagnose POI based on the presence of spontaneous amenorrhea or irregular menstrual cycles and biochemical confirmation.</b>



Desirable effects	There is agreement that POI is characterised by oligo/amenorrhoea, and that a diagnosis can be established through biochemical confirmation of raised gonadotropins, and low estradiol.
Undesirable effects	It has been shown that FSH levels can fluctuate (De Vos <i>et al.</i> , 2010) Underdiagnosis and diagnostic delays have been reported in POI
Certainty of evidence	Low
Values	
Balance of effects	A clear statement on diagnosis was set to prevent underdiagnosis or diagnostic delays
Resource use, equity, acceptability and feasibility	There is no indication that an FSH test would not be available in certain contexts

QUESTION	What investigations should be performed for diagnosis of POI?
GOOD PRACTICE POINT	<p><b>The guideline group recommends the following diagnostic criteria: disordered menstrual cycles (spontaneous amenorrhea or irregular menstrual cycles) for at least 4 months and an elevated FSH concentration &gt; 25 IU/l.</b></p> <p><b>FSH assessment should be repeated after 4–6 weeks if there is diagnostic uncertainty. FSH testing for the diagnosis of POI does not have to be timed to a specific day of the menstrual cycle.</b></p>
	<p>The guideline group recommends that HCPs consider these points when diagnosing POI:</p> <ul style="list-style-type: none"> <li>• Pregnancy should be excluded in women presenting with amenorrhea.</li> <li>• Use of hormonal therapy (including oral, injectable, or long-acting contraceptives) may conceal or cause amenorrhea or irregular menstrual cycles, and potentially lower FSH concentrations. Some hormonal therapy (e.g. combined oral contraceptive) may need to be ceased before a diagnosis of POI can be confirmed.</li> <li>• Women who had bilateral salpingo-oophorectomy (BSO) before age 40 have a diagnosis of POI, and additional diagnostic testing is unnecessary.</li> </ul>
	<p>The guideline group does not recommend diagnosing POI based on serum estradiol concentrations. However, a low estradiol concentration indicates hypoestrogenism, and in combination with an elevated FSH concentration, provides additional confirmation of the POI diagnosis.</p>
Justification for the GPP	<p>In the absence of new data, the previous diagnostic criteria were accepted by the Guideline development group. An elevated FSH &gt; 25 IU represents a value greater than the physiological peak observed in premenopausal women and will encompass women with POI due to autoimmune causes. Often, the diagnosis is clear after a single biochemical test. Repeat FSH</p>



and estradiol testing is indicated where there is uncertainty: as discussed below, AMH may sometimes be of value. As fluctuating ovarian function may occur with POI, FSH concentrations may also vary considerably, including into the normal range.



## II.2.a. Measurement of AMH in women with POI

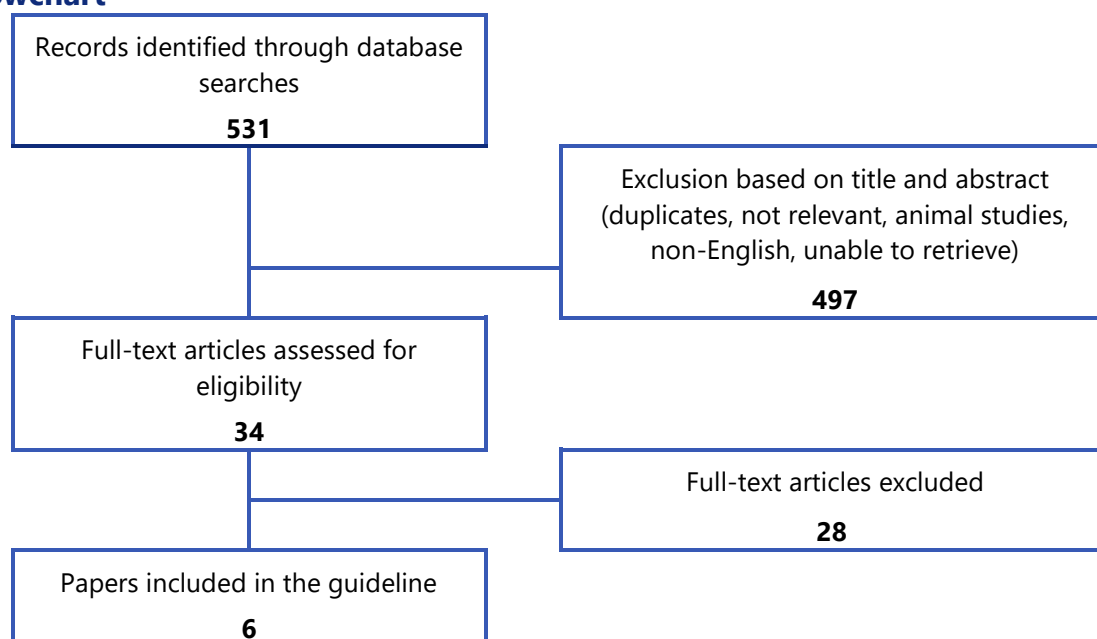
### PICO QUESTION: WHAT IS THE ROLE OF AMH TO PREDICT/ DIAGNOSE POI?

<b>Population</b>	Women suspected of POI
<b>Interventions</b>	AMH
<b>Control</b>	
<b>Outcomes</b>	Diagnosis of POI

### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (AMH OR "Anti-Mullerian Hormone" OR "Anti-Mullerian Hormone"[Mesh] OR "Anti-Muellerian Hormone" OR "Antimullerian Hormone")

### Flowchart





## Evidence

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Nelso n et al., 2023)</b>	system atic review	41 publication incl 11 studies examining the role of AMH in the diagnosis and prediction of POI [n=4537]	AMH (different assays)		Values in women with POI + diagnostic value	There was evidence that undetectable, or extremely low AMH, may aid early diagnosis of POI in young women with a family history of POI, and women presenting with primary or secondary amenorrhoea (11 studies).	We identified a small number of studies that have investigated the value of AMH in the diagnosis of POI, demonstrating a progressive decline in women across the stages of declining ovarian function to POI, although it remained normal in many women until POI was established (Knauff et al., 2009; Li et al.,2011; Desongnis et al.,2021; Jiao et al., 2021). Testing of diagnostic accuracy showed very good discrimination from other causes of oligo/amenorrhoea, notably PCOS, hypogonadotropic hypogonadism and hyperprolactinaemia, where AMH levels are characteristically normal or high (Li et al.,2011; Barbakadze and Kristasashvili, 2014; Bradbury et al.,2017; Bell et al., 2021a). Thus, serum AMH may be useful in young women where there is diagnostic uncertainty of the cause of amenorrhoea,  with the caveat that AMH can be normal in some women with incipient POI (Guzel et al., 2017). While indirect evidence indicates AMH may be of value in assessing family members of a proband with POI (Guzel et al.,2017), the Doetinchem Cohort Study (de Kat et al.,2019) showed low discriminatory performance of AMH in menopause prediction in young women. Thus, the general utility of AMH in young women remains to be confirmed.	
<b>(Ande rson et al., 2022)</b>	System atic review	women treated for cancer	AMH (different assays)		diagnostic value for ovarian reserve and POI	AMH levels were strongly impacted by anticancer treatment, with recovery and its degree determined by treatment regimen, age and pre-treatment AMH level.  In 16/31 (52%) publications, oligo/amenorrhoea was associated with	AMH can be used to identify the damaging effect of cancer treatments on ovarian function.  While there was evidence for its value in the diagnosis of POI after cancer treatment, further studies across a range of diagnoses/treatment regimens and patient ages are required to clarify this, and to quantify its predictive value. A major limitation for	



						<p>lower post-treatment AMH consistent with impending POI, although menstruation and/or pregnancy were reported in patients with low or undetectable AMH. Long-term (&gt;5 years) follow-up of paediatric patients following cancer treatment also found significantly lower AMH compared with control groups in 14/20 (70%) of studies, with very variable effect sizes from complete loss of AMH to full recovery depending on treatment exposure, as in adult patients.</p>	<p>the use of AMH clinically is the very limited data relating post-treatment AMH levels to fertility, duration of reproductive lifespan or time to POI; analysis of these clinically relevant outcomes will be important in further research.,</p>
<b>(Iwase et al., 2024)</b>	Systematic review	95 articles	AMH	clinical utility		Recommendations for practice	
<b>(Harlow et al., 2012).</b>	Consensus					<p>Update of the Stages of Reproductive Aging Workshop (STRAW) criteria.</p> <p>STRAW + 10 provides a more comprehensive basis for assessing reproductive aging in research and clinical contexts.</p>	Consensus
<b>(Anderson et al., 2017)</b>	Cohort study	Cohort of premenopausal women with breast cancer (n = 73)	AMH - 24 months after diagnosis	FSH	Value to detect POI	<p>AMH below the level of detection showed good diagnostic accuracy for POI (n = 73) with ROC area under the curve of 0.86, sensitivity 1.0 and specificity 0.73 at the assay limit of detection.</p> <p>In women aged &gt;40 at diagnosis who did not receive goserelin, AMH measured at end of chemotherapy also gave good prediction of POI at 24 months (AUC 0.89 95% CI 0.75–1.0, n = 32), with sensitivity 0.91, specificity 0.82,</p>	<p>Using this sensitive AMH assay, the finding of an undetectable AMH level in women aged &gt;40 at the end of chemotherapy for eBC gave a good prediction that ovarian function would not return. This may allow alterations in post-chemotherapy endocrine</p>



						diagnostic odds ratio (DOR) 42.8. FSH gave slightly lower AUC, and specificity was low at 0.55. Age but not tamoxifen impacted on AMH levels.	management.	
<b>(Anderson et al., 2022)</b>	PRELIMINARY STUDY	206 premenopausal women aged 40–45 years with eBC, before and at intervals after chemotherapy.	AMH		diagnostic accuracy of AMH for loss of ovarian function at 30 months after chemotherapy and the predictive value for that of AMH measurement at 6 months	Undetectable AMH showed a high diagnostic accuracy for absent ovarian function at 30 months with AUROC 0.89 (95% CI 0.84–0.94, P < 0.0001). PPV of undetectable AMH at 6 months for a menopausal estradiol level at 30 months was 0.77. In multivariate analysis age, pre-treatment AMH and FSH, and taxane treatment were significant predictors, and combined with AMH at 6 months, gave AUROC of 0.90 (95% CI 0.86–0.94), with PPV 0.79 for loss of ovarian function at 30 months.	AMH is a reliable diagnostic test for lack of ovarian function after chemotherapy in women aged 40–45 with eBC. Early analysis of AMH after chemotherapy allows identification of women who will not recover ovarian function with good accuracy.	

QUESTION	WHAT IS THE ROLE OF AMH TO PREDICT/ DIAGNOSE POI?
RECOMMENDATION	<b>Anti-Müllerian hormone (AMH) should not be used as the primary diagnostic test for POI.</b>
GOOD PRACTICE POINT	
Desirable effects	The evidence at present does not support its value over the existing, FSH-based, approach. (summarized in (Nelson <i>et al.</i> , 2023))
Undesirable effects	In some contexts, there may be reasons not to perform an AMH test, for example when a low result risks limiting access to fertility treatment.
Certainty of evidence	As AMH is a direct product of the small growing follicles of the ovary, it has theoretical value as a diagnostic test in POI, but more evidence is needed to further clarify the clinical value of AMH.
Values	It may become of value in identifying women at risk of POI, where a risk factor is identified, but this is not clearly supported by current evidence.
Balance of effects	Based on the available data, it was decided to only recommend AMH in cases of diagnostic uncertainty.
Resource use, equity, acceptability and feasibility	Availability of the test, particularly in primary care, remains limited.



Subgroup considerations (if applicable)	Not applicable
-----------------------------------------	----------------

QUESTION	WHAT IS THE ROLE OF AMH TO PREDICT/ DIAGNOSE POI?
GOOD PRACTICE POINT	<b>The guideline group recommends that AMH testing may be useful to confirm POI diagnosis where FSH results are inconclusive, but AMH results need to be interpreted within the clinical context.</b>
	<b>The guideline group recommends that HCPs do not routinely perform AMH testing to predict POI due to insufficient evidence of accuracy.</b>
justification	Due to the absence of clear evidence on the clinical relevance, this GPP was added to recommend clinicians to look at the entire clinical picture rather than AMH as a stand-alone test.



## II.3.a Iatrogenic POI

GOOD PRACTICE POINT	<b>The guideline group recommends that HCPs inform women with POI of the different causes of POI, the limitations of current knowledge and testing for causes of POI, and that an exact cause may not be identified.</b>
	<b>The guideline group recommends that HCPs discuss the risk of POI as part of the consent process before a medical or surgical intervention that may cause POI.</b>

## II.3.b POI and genetic causes

### PICO QUESTION: WHAT ARE THE KNOWN CAUSES OF POI AND HOW SHOULD THEY BE INVESTIGATED?

P	I	C	O
Patients diagnosed with POI (X-chromosome abnormalities)	Physical examination Karyotype testing Family history		Gonadal dysgenesis Turner's syndrome Perrault's syndrome 46XX gonadal dysgenesis 46XY gonadal dysgenesis as cause of POI
Patients diagnosed with POI  (Genetic cause)	FRAXA premutations Family history Genetic testing Karyotype testing		Fragile X syndrome (FMR1 mutation) as cause of POI
	newborn screening galactose-1-phosphate uridyl transferase galactokinase UDP galactose epimerase Genetic testing		Galactosaemia as cause of POI
	Genetic testing drooping, tethered eyelids		BPES (Blepharophimosis, ptosis and epicanthus inversus Syndrome)
	Genetic testing		Enzyme defects – P450c17 Small X chromosome defects FSH receptor mutations LH receptor mutations
Patients diagnosed with POI  (Autoimmun cause)	Ovarian antibodies		Autoimmune oophoritis as cause of POI or as a marker of risk of other endocrinopathies
	Adrenal antibodies steroidogenic antibodies		Risk of Addison's disease adrenal insufficiency, an association of POI
	Thyroid function tests Thyroperoxidase Thyroglobulin Thyroid antibodies		Thyroid involvement (hypothyroidism, hypoparathyroidism) as an association of POI and a marker of risk of other endocrinopathies
	Anti-transglutaminase antibodies Anti-tTG antibodies anti-gliadin (AGA)		Celiac disease - an association of POI



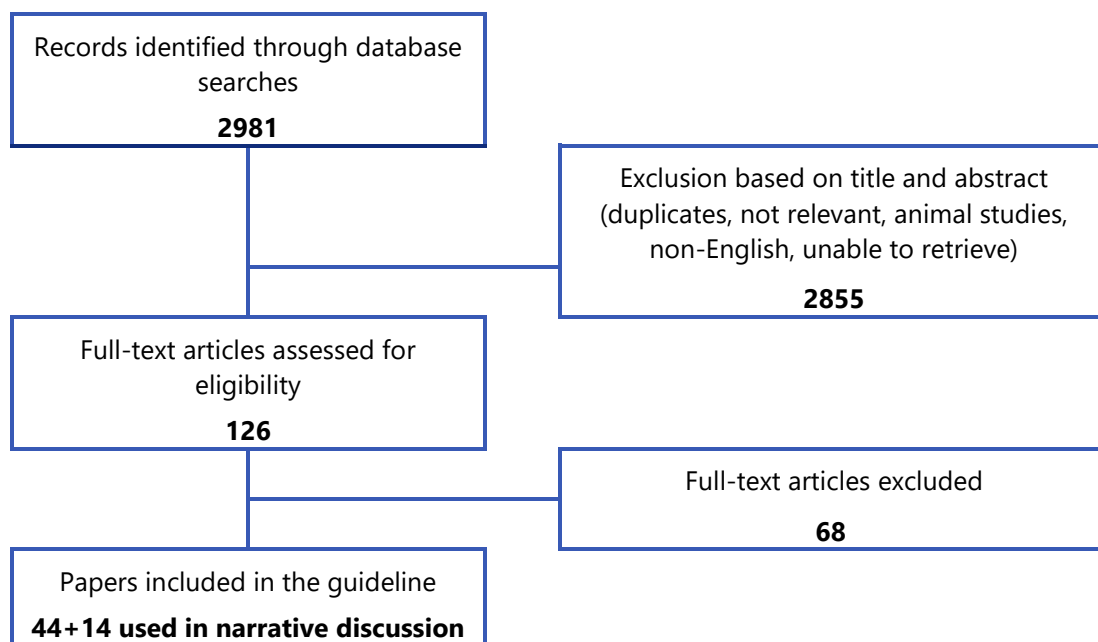
	anti-endomysium (EMA) antibodies		
	Markers for autoimmune disorders associated with POI		Autoimmune Polyendocrinopathy Syndrome 1 - APECED Autoimmune Polyendocrinopathy Syndrome 2 Polyglandular syndrome Dry-eye syndrome Myasthenia gravis Rheumatoid arthritis Diabetes mellitus Systemic lupus erythematosus
Patients diagnosed with POI (infectious cause)			Viral oophritis viruses Mumps oophoritis,
Patients diagnosed with POI after cancer treatment / pelvic surgery	History		Iatrogenic cause of POI (chemotherapy, radiotherapy, pelvic surgery)
Patients diagnosed with POI (cause unknown)			Environmental toxins smoking, epilepsy,

## Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (("karyotype analysis" OR "karyotype testing" OR "genetic analysis" OR "genetic testing" OR "examination" OR "family history") AND ("Turner's syndrome" OR "Turners syndrome" OR (45,X) OR "45,X/46,XX" OR "Turner Syndrome"[Mesh] OR "Gonadal Dysgenesis, 46,XX"[Mesh] OR "Gonadal Dysgenesis, 46,XY"[Mesh] OR "Gonadal Dysgenesis, Mixed"[Mesh] OR "Perrault syndrome" OR "Perrault's syndrome" OR "Fragile X syndrome" OR "Fragile X Syndrome"[Mesh] OR "Marker X Syndrome" OR "Fra(X) Syndrome" OR "Martin Bell Syndrome" OR "FRAXE Syndrome" OR "Mar (X) Syndrome" OR "FRAXA Syndrome" OR Abnormalities of the X chromosome OR "Sex Chromosome Disorders of Sex Development"[Mesh] OR "Genetic Diseases, X-Linked"[Mesh] OR "Sex Chromosome Disorders"[Mesh]) OR ("genetic analysis" OR "genetic testing" OR "examination" OR "family history") AND (ATM OR "Ataxia-telangiectasia gene" OR FOXL2 OR "blepharophimosis-ptosis-epicanthus inversus syndrome" OR BPES OR Galactose-1-phosphate OR galactosaemia)) OR ("Ovarian antibody" OR "anti-ovarian antibody" OR "Autoimmune oophoritis") OR ("Adrenal antibodies" OR "Adrenal antibody" OR "steroidogenic antibodies" OR "steroidogenic antibody" OR "Addison's disease" OR "Addison Disease"[Mesh] OR "adrenal insufficiency" OR "Adrenal Insufficiency"[Mesh]) OR ("Thyroid function" OR "Thyroperoxidase" OR "Thyroglobulin" OR "Thyroid antibodies" OR "Thyroid antibody" OR "Thyroid involvement" OR hypothyroidism OR "Hypothyroidism"[Mesh] OR hypoparathyroidism OR "Hypoparathyroidism"[Mesh]) OR ("Anti-transglutaminase antibodies" OR "Anti-tTG antibodies" OR "anti-gliadin" OR "anti-endomysium antibodies" OR EMA OR Celiac disease) OR ("Polyglandular syndrome" OR "Polyendocrinopathies, Autoimmune"[Mesh] OR "Dry-eye syndrome" OR "Dry Eye Syndromes"[Mesh] OR "Myasthenia gravis" OR "Myasthenia Gravis"[Mesh] OR "Rheumatoid arthritis" OR "Arthritis, Rheumatoid"[Mesh] OR "diabetes mellitus" OR "Diabetes Mellitus"[Mesh] OR "Systemic lupus erythematosus" OR "Lupus Erythematosus, Systemic"[Mesh]) OR (iatrogenic OR chemotherapy OR radiotherapy OR "pelvic surgery") OR ("Environmental factors" OR toxins OR toxics OR chemicals OR smoking OR cigarette OR epilepsy) OR ("Viral oophoritis" OR virus OR viral OR Mumps OR cytomegalovirus OR HIV OR infection OR infectious OR papillomavirus)

Literature search was limited to the period between 01/01/2014 and 17/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.

## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table - Chromosomal anomalies

Ref.	Study Type	Patients	Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Frequency of chromosomal anomalies</b>								
(Chen <i>et al.</i> , 2023).								NARRATIVE REVIEW
(Jiao <i>et al.</i> , 2012)	COHORT STUDY	531 Chinese patients with proven POF (FSH > 40 mIU/ml)	Karyotype analysis and correlation to phenotypes		Prevalence Chromosomal abnormalities		Chromosomal abnormalities were present in 64 of 531 (12.1%) POF cases, of which 32 were X-structural aberrations (7 mosaic): 15 del(Xq), 2 del(Xp), 11 isochromosomes [6 i(Xp); 5 i(Xq)], 1 ring chromosome (mosaic), 1 inversion (mosaic), 1 isodicentric chromosome and 1 complex arrangement. Nine non-mosaic X-autosome translocations were detected, all but 1 involving Xq. Aneuploidy without a structurally abnormal X was found in 19 cases: 7 non-mosaic 45,X, 9 45,X mosaicism and 3 47,XXX (1 mosaic with 46,XX line). Karyotypic abnormalities were more frequent in patients with primary amenorrhea (15/70, 21.4%) than those with secondary amenorrhea (49/461, 10.6%; P = 0.01). 45,X and 45,X/46,XX mosaicism were the complements most frequently associated with primary	



						amenorrhea (46.7%). Two of the three cases with 46,XY or 45,X/46,XY karyotype presented with 'secondary amenorrhea'. One balanced autosomal Robertsonian translocation was also detected.	
<b>(Lakhal et al., 2010)</b>	Cohort study	1000 POI patients	Frequency of chromosomal anomalies (karyotyping + FISH)			chromosomal abnormalities: 108 (10.8%)  Anomalies in 61 / 432 primary amenorrhea patients (14.12%) and 47 / 568 secondary amenorrhea patients (8.27%).  In 23 POF patients among 200 (11.5%) with 46,XX normal karyotype and explored using interphase FISH analysis, the percentage of cells with X-chromosome monosomy was significantly higher as compared with controls in the same age.	
<b>(Silven et al., 2023).</b>	population-based study	5011 women with POI	Frequency of chromosomal anomalies		OR	OR TS: 275 (95% CI 68.1 to 1110)  OR other sex chromosome abnormalities: 12.7 (95% CI 4.1 to 39.1)	
<b>(Kalantari et al., 2013).</b>		primary amenorrhea vs secondary amenorrhea	Abnormal karyotypes			primary amenorrhea (21%) vs secondary amenorrhea (11%)	
<b>Gruber, 2020 #161}</b>		POI	chromosomal anomalies		Incidence, age	the incidence is higher at younger age of POI diagnosis	

## Chromosomal Aneuploidy

Narrative discussion on chromosomal aneuploidy expressed as Turner syndrome (TS), based on the following studies/reports;

(Taylor et al., 1996, Sybert and McCauley, 2004, Hadnott et al., 2011, Castronovo et al., 2014, Bernard et al., 2016, Gravholt et al., 2017, Rossetti et al., 2017, Tuke et al., 2019, Ibarra-Ramírez et al., 2023, Gravholt et al., 2024)

Narrative discussion on chromosomal aneuploidy expressed as Triple X syndrome, based on the following studies/reports;

(Sybert, 2002, Tartaglia et al., 2010, Franić-Ivanišević et al., 2016, Berglund et al., 2019, Rafique et al., 2019, Davis et al., 2020, Rogol, 2023).

<b>(Baroncelli et al., 2011).</b>	case-control study	269 women with POI			TXS frequency	Frequency TXS: 0.7%  5-fold higher prevalence in POI compared to 46,XX women	
<b>(Jiao et al., 2012)</b>	cohort study	531 women with POI			TXS frequency	Frequency TXS: ~0.6%	

## Gonadoblastoma and dysgerminoma



<b>(Liu et al., 2014)</b>	cohort study	102 women with differences of sex development (DSD) and karyotypic Y chromosome or Y-derived sequences 16-34 years			incidence of gonadoblastomas  optimal protocol of management	17.6% malignancy: =>17 gonadoblastoma + 1 dysgerminoma  Gonadoblastoma were observed in 2/21 patients with sex chromosome structural abnormalities (9.5%), 3/33 patients with gonadal dysgenesis (9.1%), 9/30 patients with CAIS (30.0%) and 3/18 patients with PAIS (16.7%).		Cohort: 47.1% complete/partial androgen insensitivity syndrome (CAIS/PAIS) (46XY), 32.4% gonadal dysgenesis (46XY) 20.1% mixed gonadal dysgenesis (with sex chromosome structural abnormalities).
<b>(Dendri nos et al., 2015)</b>	Retrospective cohort study	16 patients with karyotype of 45,X/46,XY or variant who underwent gonadectomy			incidence of gonadoblastomas	In patients who underwent bilateral gonadectomy, gonadoblastomas were detected in 36.4% (4 of 11), and all were identified in patients with normal female external genitalia (4 of 8 [50.0%]).		
<b>(Matsmoto et al., 2020)</b>	cohort study	34 TS patients with Y chromosome material present			incidence of gonadoblastomas	18% (6 of 34)  unilateral dysgenetic testis and a contralateral streak gonad detected in 20 (59%), bilateral streak gonads in 9 (26%), and bilateral dysgenetic testes in 5 (15%).		

### Evidence table - FMR1 premutation

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Murray et al., 2014)</b>	cohort population study	254 women with POI and 1881 with early menopause  Breakthrough Generations Study, UK	FMR1 CGG repeat number		prevalence of FMR1 premutation	2.0% in women with POI, 0.7% in early menopause, and 0.4% in controls, corresponding to OR of 5.4 (95% CI 1.7 to 17.4; p=0.004) for POI and 2.0 (95% CI 0.8 to 5.1; p=0.12) for early menopause		



<b>(Tosh et al., 2014).</b>	Cohort Study	289 POI samples and 360 control	FMR1 premutation testing		FMR1 premutation frequency	29 different CGG repeat sizes (alleles), ranging from 7 to 40. Within this population, we found that the CGG repeat length polymorphisms were within the normal range of 6-55 in both patients as well as control samples.	no association between FMR1 premutation and POI in the study
	meta-analysis	11 case-control studies: 1,313 POI and 3,132 control				significant difference in the incidence of FMR1 premutation between POI cases and control subjects with p value <0.001 (OR 5.41; 95 % CI 2.53, 11.61).	Asian population
<b>(Guo et al., 2014).</b>	case-control study	379 Chinese women with well-defined 46, XX non-syndromic sporadic POI and 402 controls.	FMR1 premutation testing		FMR1 premutation frequency	0.5% (2/379) in POI, 0% in controls The prevalence of intermediate FMR1 (41-54) was not increased significantly in sporadic POI vs controls (2.9% vs. 1.7%, P = 0.343). POI more often carried a single additional CGG repeat in a single allele vs fertile women (allele-1: 29.7 vs. 28.8, P<0.001; allele-2: 32.6 vs. 31.5, P < 0.001). POI patients with both alleles of CGG repeats outside (below or above) the normal range (26-34) showed an earlier age of cessation of menses than those with two alleles within normal range (hom-high/high vs. norm: 20.4 ± 4.8 vs. 24.7 ± 6.4, p < 0.01; hom-low/high vs. norm: 18.7 ± 1.7 vs. 24.7 ± 6.4, p < 0.01).	Asian population
<b>(Tang and Yu, 2020).</b>	cross-sectional, case-control study	124 POI 57 DOR 111 normal menopausal controls.	FMR1 premutation testing		FMR1 premutation frequency	two premutation carriers in the POI group (1.6%) and one in the control group (0.9%). frequency of FMR1 premutations was not different between POI or DOR and controls. The most common CGG repeat was 29 and 30, and the repeat length for allele 2 had a secondary peak around 36-39 repeats.	Asian population
<b>(Huang et al., 2019).</b>	meta-analysis	18 case-control or cohort studies involving 3394 idiopathic POI patients and 8461 controls	FMR1 premutation testing		FMR1 premutation frequency and association	FMR1 gene premutation is significantly associated with overt POI (OR = 8.13; 95% CI: 4.35-15.19; p < .00001), whereas there was no significant correlation between intermediate repeat length and overt POI (OR = 0.86; 95% CI: 0.62-1.18; p = .34). (based on 13 studies, n=2047 POI + 6912 Controls)  Association between premutation and occult POI was significant (p < .00001), with a pooled fixed effects OR of 11.32 (4.45-28.80), and no significant correlation of intermediate size to occult POI was found in the case-control comparison (OR = 1.00; 95% CI: 0.68-1.47; p = .98). (based on 7 studies, n=1347 POI + 1948 Controls)	



(Movaghar et al., 2019)	population-based cohort	20 000 patients, FMR1 genotyping.	FMR1 premutation testing		anxiety	increased rates of anxiety conditions in both female and male premutation carriers compared to non-carriers	
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### Other genetic causes of POI

POI -type	Country	Prevalence of gene positivity	Comments	Reference
Familial or consanguineous POI	Turkey	30.5%		(Jolly et al., 2019)
Familial or consanguineous POI	North Africa + Turkey	36.7 %	Panel with 88 and 95 validated genes	(Heddar et al., 2022).
sporadic + familial POI	International (n=375)	29.3%	Panel with 88 and 95 validated genes	(Heddar et al., 2022)
Sporadic POI	Europe	26%	Panel with 88 and 95 validated genes	(Heddar et al., 2022)
Sporadic POI	China (n=1030)	23.5%	whole-exome sequencing	(Ke et al., 2023)
Syndromic POI		58.3%	Panel with 88 and 95 validated genes	(Heddar et al., 2022)
POI - Primary amenorrhea	China (n=1030)	28.5%	whole-exome sequencing	(Ke et al., 2023).
POI - Secondary amenorrhea	China (n=1030)	17.8%	whole-exome sequencing	(Ke et al., 2023).
POI	Brazil	12-20%		(Yang et al., 2019)
POI (idiopathic)	China (n=74)	15.07%	Targeted NGS	(Shen et al., 2021)
POI	China (n=500)	14.4%	NGS	(Luo et al., 2023)
POI	Norway (n=100)	16%		(Vogt et al., 2024)

QUESTION	What are the known causes of non-iatrogenic POI and how should they be investigated?
GOOD PRACTICE POINT	<b>The guideline group recommends that HCPs discuss the implications of genetic testing before the test is performed. Referral for comprehensive genetic counselling should be considered.</b>
Justification	<p>Any genetic test should only be performed after informing the patient of the nature of the tests, the implications, and possible associated comorbidities. Genetic counselling should include education on the usefulness and impact of the tests on the patient, but also the possibility and implications for their families. Specific guidance on genetic counseling is outside the scope of the current guideline, but it should adhere to the relevant national guidelines.</p> <p>Information and written consent should be obtained from the patient and all family members tested before genetic testing.</p>

QUESTION	What are the known causes of non-iatrogenic POI and how should they be investigated?
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RECOMMENDATION	<p>Chromosomal analysis testing is recommended for all women with non-iatrogenic POI.</p> <p><i>FMR1 premutation (Fragile X syndrome gene) testing is recommended for all women with non-iatrogenic POI</i></p>
Desirable effects	Chromosomal anomalies are common among women with POI, affecting 10-13% of patients. FMR1 premutations are found to in 1 to 5% of women with sporadic POI and up to 13% in women with a positive family history of POI
Undesirable effects	
Certainty of evidence	NA
Values	Identifying the genetic cause of POI can be helpful for patients and families.
Balance of effects	<p>Based on the significant prevalence of chromosomal anomalies in women with POI and the implications thereof, chromosomal analysis is recommended.</p> <p>Based on its prevalence and potentially severe implications, Fragile X premutation testing is indicated in all women diagnosed with POI. This needs to be performed as a specific test as multigene panels and NGS are not useful in detecting FMR1 premutation. Genetic counselling for FMR1 should include education about FMR1-related disorders and the possibility and implications for the patients and their families (Poteet <i>et al.</i>, 2023).</p>
Resource use, equity, acceptability and feasibility	There were no concerns on the availability and acceptability of testing for Chromosomal anomalies or FMR1 premutation.
Subgroup considerations (if applicable)	NA

QUESTION	What are the known causes of non-iatrogenic POI and how should they be investigated?
RECOMMENDATION	Where available and after comprehensive genetic counselling, additional genetic testing (e.g. next-generation sequencing) can be offered to all women with non-iatrogenic POI to identify other potential genes that may cause POI
Desirable effects	<p>potential of the tests to uncover a genetic cause for POI which has psychological benefits for the patients and their family and allows genetic counselling and personalised patient care.</p> <p>Large cohorts of women with POI shown diagnostic positivity in up to 30% using NGS</p>
Undesirable effects	NA
Certainty of evidence	NA
Values	Identifying the genetic cause of POI can be helpful for patients and families.
Balance of effects	Testing can be considered where available
Resource use, equity, acceptability and feasibility	NGS is not universally available to women with POI. - The availability of NGS tests in specialised laboratories and the associated costs are currently barriers to widespread use.
Subgroup considerations (if applicable)	



QUESTION	What are the known causes of non-iatrogenic POI and how should they be investigated?
GOOD PRACTICE POINT	The guideline group recommends that the age of a woman with POI should not be used to restrict access to genetic testing.
Justification	For equity reasons, and based on the observation that genetic causes can be identified also if women are older at the time of testing

## II.3.c POI and autoimmune causes

### PICO QUESTION: WHAT ARE THE KNOWN CAUSES OF POI AND HOW SHOULD THEY BE INVESTIGATED?

PICO terms and search string are included above.

#### Evidence

##### Summary of Findings Table

Not applicable

##### Evidence table - Markers of autoimmune oophoritis

(references from studies prior to 1990 were included in the text for completeness, but not detailed in the evidence table (Vallotton and Forbes, 1966, Blizzard *et al.*, 1967, Tang and Faiman, 1983, Coulam and Ryan, 1985, Moncayo *et al.*, 1989)).

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Bakalov <i>et al.</i>, 2005)</b>	Cohort study	123 consecutive POI patients all received ACTH test and adrenal antibody testing	Adrenal Ab screen followed by ATCH stim test and Aldo/Renin ratio		association with autoimmunity	4/123 previously unsuspected had adrenal insufficiency. They all had pos adrenal abs and 21 OH abs. 2 other women had false pos ACTH test. Overall 6/123 had pos AB test. A morning cortisol was misleadingly normal in 3/4 women with adrenal insufficiency.  Sp POI adrenal auto abs are highly associated with prim adrenal insuff. (p< 0.001) sens 1.0; spec 0.98; PPV=0.67; NPV=1.0	3.2% prevalence among 123 POI women (95% CI 0.2-6%)  All POI women should be screened for adrenal antibodies.  ACTH should not be used as a routine screening tool, as 2/123 were false pos. Morning cortisol should not be used as screening tool as 3/4 of the women with adrenal insufficiency were normal.	
<b>(Hoek <i>et al.</i>, 1997)</b>	Review				association with autoimmunity		POI in association with adrenal autoimmunity and/or Addison's	Narrative review, used as background information



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
							disease (2-10% of the idiopathic POI patients) is indeed an autoimmune disease.	
<b>(Khastgir et al., 1994)</b>	Opinion							used as background information
<b>Antibody tests and prevalence</b>								
<b>(Chen et al., 1996)</b>	Cohort study	Auto antibodies in women with: 1. APS ; 2., APS 2; 3. pos ACA without Addison's disease; 4. Addison's disease; 5. Patients with isolated POF (without ACA) (n=17)	Abs: ACA, SCA, 17OH, p450SCC, 21OH		Ab positivity	Effectively all negative for POI only – 1 result for 17OHP equivocal	No isolated POF patients were pos for P450scc, 21 OH antibodies and only one (in the low range) was pos for 17 OH antibodies.	
<b>(Falorni et al., 2002)</b>	Cohort study	135 POI	Abs 21OH, 17OH, P450SCC Follow up with AMH data not useful as no controls		Ab positivity	35/135 positive for one of the 3		
<b>(Dal Pra et al., 2003)</b>	Cohort study	62 total. 15 with POI and Add; 26 with other AI and 31 isolated	Abs: ACA, SCA, 17OH, p450SCC, 21OH		Ab positivity	Useful outcome for 31 Isolated POI: 10% positive for both SCA, 13% for ACA and 21OHP	SCA and ACA, 21OHP - Ab testing may be useful	Not clear if the subjects overlap with earlier 1997 paper from same group
<b>(La Marca et al., 2010)</b>	Cohort study	auto immune POI.	21-OH antibody test		Ab positivity	21-OH antibody test is the marker with the highest diagnostic sensitivity for auto immune POI. In the absence of 21OHAB, < 0.5% of POI can be found pos for ovarian/17OH, P450AB in. In SCAPOI selective destruction of theca cells takes place, resulting in low E2 (no substrate), high FSH, high Inhibin B and normal AMH (for several years, but not always, after 5 years AMH is no longer detectable in 93% of women)	By measuring steroidogenic antibodies 4-5% of SCA POI can be detected. This is important when in vitro folliculogenesis of ivm is will be possible. And also research regarding autoimmune treatment	Measuring 21 OH AB and possibly Inhibin B and AMH
<b>(Gao et al., 2017)</b>	Study	250 patients with POI and 256 age-matched healthy women Incl: secondary amenorrhea for at least 4 months before the age of 40 years, and two	Detection of AAA was by indirect immunofluorescence assay on monkey adrenal gland sections + Non-organ-specific antibodies (ANA, ACA, and anti-dsDNA) were determined by		Ab positivity	In 48 out of 250 women with POI (19.2%) AAA was found positive, which is significantly higher than controls (15/256, 5.9%) (P<0.01). For non-specific antibodies-ACA, ANA and anti-dsDNA, no differences were found between the POI and control groups.	Significantly higher positive frequency of AAA in patients with POI confirmed the role of autoimmune disturbance in POI pathogenesis	Ref High prev AAAs in POI but AAAs are unspecific markers of ovarian autoimmunity so



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
		serum FSH > 40 IU/l (drawn more than 1 month apart)	commercially available enzyme-linked immunosorbent assays + Ovarian biopsy was conducted to confirm the presence of histologically autoimmune oophoritis.			No significant clinical or biochemical differences between patients with positive and negative AAA (including ovarian histology of 6 AAA+ and 7 AAA-women).  15 AAA pos women followed-up for 3 years, only one showed symptoms of Addison's	This suggests that AAA may serve as a marker for ovarian autoimmunity.	
<b>(Forges et al., 2004)</b>	Review							Used as background information
<b>{Ryan, 2004 #342}</b>	Case report	patient with myasthenia gravis and POI						Used as background information
<b>(Kelkar et al., 2005)</b>	Cohort study	15 POI, 7 normally cycling and 8 menopausal women	antiovarian antibodies (AOA) by immunohistochemistry		Ab positivity	10 /15 POI (66.6%) Of these, two demonstrated antibodies to the zona pellucida (ZP) as well as strong immunoreactivity to granulosa cells (Azg)  1/15 controls	ZP is an important ovarian antigen in autoimmune POI	
<b>(Sundblad et al., 2006)</b>	Cohort study	110 POI + 60 normally menstruating women with no record of autoimmune diseases (controls).	antiovarian antibodies (AOA)		Ab positivity	21/110 POI 0/60 controls  After purification and analysis by mass spectrometry, the antigen was identified as alpha-enolase.	Determination of the presence of circulating anti alpha-enolase antibodies might be instrumental in identifying a possible autoimmune aetiology for POI.	
<b>(Takamizawa et al., 2007)</b>	Cohort study	27 idiopathic POI, 30 control women, and 30 healthy males	antizona pellucida (ZP) antibodies		Ab positivity	7/27 POI 0/60 controls  sera from POI patients reacted significantly stronger than those of control women and healthy males. However, no obvious difference could be found by the same assay using porcine ZP among these three groups.	Some idiopathic POF patients have anti-ZP antibodies in their sera, which were detected with high specificity by a newly developed microdot assay using a very small amount of human ZP.	
<b>(Pires and Khole, 2009)</b>	Cohort study	50 POI, 65 infertile women, and 60 normally menstruating fertile women	autoantibodies to human heat-shock protein 90-beta - HSP90		Ab positivity	presence of ovarian autoantibodies to human HSP90 in sera of women with infertility.	HSP90 could be involved in human ovarian autoimmunity and thereby be a causative factor in early ovarian failure.	
<b>(Luborsky et al., 1999)</b>	Cohort study	30 POI	Antibodies to ovary (OVAB), thyroid (THYAB; thyroid		prevalence	Organ-specific antibodies (ovary and thyroid) were present significantly greater	only ovarian antibodies were	



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
		38 + 15 unexplained infertility (UI) 12 normal cycling 53 blood bank controls	peroxidase and thyroglobulin), cardiolipin, and 8 nuclear antigens were assessed by enzyme immunoassay			frequency than non-organ-specific antibodies (nuclear and cardiolipin) in POI and UI (60% (50/83) vs 16% (13/83) resp; P<0.0001).  OVAB (53%, 44/83) were significantly more frequent than THYAB (30%, 25/83) in POI and UI (P = 0.0030). THYAB did not differ among all groups (P = 0.78). In POI and treated or untreated UI OVAB frequencies were 53, 61, and 33%, respectively, and were significantly more frequent than in the population (17%) (P = 0.0001).	significantly more frequent than other antibody markers of autoimmunity in POI and UI.	
<b>(Wheatcroft et al., 1994)</b>	Study	45 POI (5 iatrogenic ovarian failure, 9 associated autoimmune disease, and 27 idiopathic)  4 women with infertility due to Turner's syndrome  41 pre- and post-menopausal controls.	ovarian antibodies		frequency	24% and 60% of the ovarian failure patients reacted in an ELISA (P < 0.05 and P < 0.001 compared with controls)  The apparent aetiology of ovarian failure did not correlate with the presence of ovarian antibodies.	ovarian antibodies are common in POI, but their specificity and pathogenic role are questionable	
<b>(Novosad et al., 2003)</b>	Cohort study	26 young women with 46,XX spontaneous POI  26 control women with regular menstrual cycles (matched for age, race, and parity)  26 control men	ovarian antibody test + other autoantibodies associated with ovarian autoimmunity.		Ab positivity	POI: increased incidence of thyroid and gastric parietal cell autoimmunity (p < 0.05).  ovarian antibodies 50% in POI 31% in control women	ovarian antibodies as detected by this indirect immunofluorescence method have poor specificity. The specificity of any ovarian antibody test should be established before it is used clinically.	
<b>(Winqvist et al., 1995)</b>	Study	patients with Addison's disease (n = 13) and APS-I (n = 7)	Ab to cytochrome P450 enzyme 21-hydroxylase and the side-chain cleavage enzyme (SCC)					Background info as no POI patients
<b>(Arif et al., 1999)</b>	Cohort study	48 POI	Ab to 3BHSD		Ab positivity	10/48 positive	Ab 3BHSD could be a marker for POI	
<b>(Reato et al., 2011)</b>	Cohort study	258 but only 52 with POI	StCA, 17OHP and P450SCC Abs				StCA ab is a marker for POI in pts with established Addison's	This only addresses women with established Addison's then screening for POI. Not really informative.



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Brozzetti et al., 2015)</b>	Case control study	1) 172 Addison's disease, 2) 41 Addison and POI, 3) 119 idiopathic POI, 4) 19 APS1 5) 211 healthy controls P OI (all with 46,XX karyotype and negative for FRAX) With onset of clinical and biochemical signs of hypergonadotrophic hypogonadism before the age of 40 year	radioimmuno assay for NALP5/MATER		When 20 000 cpm of 35S-NALP5/MATER was used, 33.4% ± 7.3% of thetracer was immunoprecipitated by the positive control serum as compared with 1.0% ± 0.2% immunoprecipitation obtained with the two negative control sera.  NALP5/MATER index 0.008 ± 0.009, and the upper level of normal was set at 0.035.	0 of 119 idiopathic POI 0 of 109 healthy controll  This study demonstrates that three groups of patients with different autoreactivity to NALP5-MATER exist: patients with APS1 who show the strongest reactivity, patients with AAD and POI who show a less frequent but still statistically significant reactivity, and patients with idiopathic POI and healthy control subjects who do not exhibit any (or almost any) autoreactivity at all.		Ref NALP5 autoantibody tests do not give additional information regarding ovarian autoimmunity
<b>(Betterle et al., 2005)</b>	Cohort study	100 patients with ACA/21 OH pos				Risk of Addison's disease in patients with ACA/21 OH pos:  31/100 patients developed clinical AD after 3-121 months	It is important to perform ACTH test s in patient s with pos ACA/21 OH antibodies.	
<b>(Del Pilar Larosa et al., 2018)</b>	Cohort study	100 autoimmune Addison's disease	steroid 21-hydroxylase (21-OH Ab) ELISA	steroid 21-hydroxylase (21-OH Ab) immunoprecipitation assay based on 125I-labeled 21-OH.		86 (86%) were positive for 21-OH Ab whereas 84 (84%) were positive in immunoprecipitation assay.  Controls positive by ELISA: 6/928 (0.6%) healthy adult blood donors, 1/49 (2.0%) adults with type 1 diabetes mellitus (T1DM)  0/50 Graves' disease 0/29 celiac disease 0/9 SLE 0/20 rheumatoid arthritis  2/51 (3.9%) children with GD, 3/69 (4.3%) children with Hashimoto's thyroiditis (HT) and 3/119 (2.5%) children with T1DM alone or associated with autoimmune thyroid disorders were ELISA positive.	The new assay should be useful for screening patients known to be at increased risk of developing clinical autoimmune Addison's disease	



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Vogt et al., 2022)</b>	Cross sectional study	6870 women from 15 study centers in 8 European countries –  Post-menopausal 1448  Menopause < 40 years 195	autoantibodies against 21 OH and SCC			POI identified in 2.8% iatrogenic causes found in 91 (47%) and non-ovarian causes in 27 (14%) women, while 77 (39%) women were classified as POI of unknown cause, resulting in a 1.1% prevalence of idiopathic POI. After adjustments nulliparity was the only variable significantly associated with POI (OR 2.46; 95% CI 1.63–3.42). Based on the presence of autoantibodies against 21 OH and SCC, 4.5% of POI cases were of likely autoimmune origin.	POI affects 1.1% of all women and almost half of the women with premature menopause. Autoimmunity explains 4.5% of these cases judged by positive steroidogenic autoantibodies	
<b>(Vogt et al., 2024)</b>	cross-sectional study	100 women with newly diagnosed POI of unknown cause	standard recommended diagnostic investigations including screening for chromosomal anomalies and premutations in the fragile X mental retardation 1 gene (FMR1) we used whole exome sequencing, including targeted analysis of 103 ovarian-related genes, and assays of autoantibodies against steroid cell antigens.		Diagnosis/prevalence	autoimmune POI in 3%		

### Evidence table Associated autoimmune disease.

(references from studies prior to 1990 were included in the text for completeness, but not detailed in the evidence table (Coulam, 1983))

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Kirshenbaum and Orvieto, 2019)</b>	Review	POI and autoimmunity.  PubMed/MEDLINE and the Cochrane library were searched for the best available evidence on this topic				Patients with POI and coexisting autoimmunity are indistinguishable from those with negative autoimmune screen with regard to age of onset, prevalence of primary amenorrhea, or their endocrine profiles. A specific noninvasive reliable diagnostic test for the diagnosis of an autoimmune etiology is lacking; therefore, patients should be screened	Nowadays, guidelines for the treatment of autoimmune POI are not available. Large clinical studies are needed to investigate the true impact of autoimmunity on POI and to identify the selected groups of patients who	Good overview of: The immune system and ovarian physiology Autoimmune Oophoritis POI and autoimmune disorders Treatment of autoimmune POI



						for the most common autoantibodies, i.e., steroid cell antibodies, anti-ovarian antibodies, and anti-thyroid antibodies. Moreover, treatment strategies to POI infertility are lacking and controversial.	are most likely to benefit from immunosuppressive treatment	
<b>(La Marca et al., 2010)</b>								See above
<b>(Panay et al., 2020).</b>	Guideline							Used as background information
<b>(Bakalov et al., 2005)</b>								See above
<b>(Reato et al., 2011)</b>								See above
<b>(Vogt et al., 2021)</b>								See above
<b>(Webber et al., 2016)</b>	Guideline							Used as background information
<b>(Husebye et al., 2018)</b>	Review	Autoimmune Polyendocrine Syndromes						Used as background information
<b>(Saari et al., 2020)</b>	Longitudinal follow-up study	40 females with APECED aged $\geq 12$ years  APECED = autoimmune polyendocrineopathy-candidiasis-ectodermal dystrophy, also called autoimmune polyendocrine syndrome type I.  Follow up to the average age of 37.3 (range: 14.6-61.9) years; 16 females (40%) were $\geq 40$ years.	Diagnosis of POI was based on delayed puberty or POI symptoms with amenorrhea, and/or FSH $\geq 40$ IU/L R		Prevalence of POI	Pubertal development started spontaneously in 34 patients and 29 had spontaneous menarche. POI developed in 28 patients (70%) at the median age of 16.0 years (range: 11.3-36.5), and in 20 of them (71%) before attaining adult height. In 11 cases puberty was induced or completed by hormonal therapy. Patients with POI were significantly shorter at menarche, but adult heights did not differ from non-POI females. Patients with POI had more often primary adrenocortical insufficiency (93% vs 58%, $P = 0.017$ ) and ovarian antibodies (81% vs 30%, $P=0.003$ ) compared to those with normal ovarian function ( $n = 12$ ).	POI developed in the majority of patients with APECED, often before or shortly after menarche.	



<b>(Garelli et al, 2021)</b>	Cohort study	158 Italian APS-1 patients (103 females and 55 males; F/M 1.9/1) at the onset and during a follow-up of 23.7 ± 15.1 years.	Autoimmune conditions and associated autoantibodies (Abs) were analyzed in AIRE mutations were determined.		POI prevalence	The prevalence of APS-1 was 2.6 cases/million (range 0.5-17 in different regions). At the onset 93% of patients presented with one or more components of the classical triad and 7% with other components. At the end of follow-up, 86.1% had CH, 77.2% AD, 74.7% CMC, 49.5% POI, 29.7% autoimmune intestinal dysfunction, 27.8% autoimmune thyroid diseases, 25.9% autoimmune gastritis/pernicious anemia, 25.3% ectodermal dystrophy, 24% alopecia, 21.5% autoimmune hepatitis, 17% vitiligo, 13.3% cholelithiasis, 5.7% connective diseases, 4.4% asplenia, 2.5% celiac disease and 13.9% cancer.	APS-1 is a rare disorder presenting with the three major manifestations and associated with different AIRE gene mutations. IFN $\omega$ Abs are markers of APS-1 and other organ-specific autoantibodies are markers of clinical, subclinical or potential autoimmune conditions.		
<b>Autoimmune thyroid hormone disorders</b>									
<b>(Silva et al, 2014)</b>	opinion								Propose diagnostic criteria for evaluating autoimmune cause of POI
<b>(Kirshenbaum and Orvieto, 2019)</b>									See above
<b>(Chaker et al, 2022)</b>	Review								Background on Hypothyroidism
<b>(Grossmann et al, 2020)</b>	Cohort study	52 POI, aged 18-40 years	screened by a rheumatologist for the presence of underlying autoimmune disease		Prevalence	Of 52 participants, 40.4% (n = 21) had at least one confirmed autoimmune disease, including Hashimoto's disease, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, Crohn's disease, polyglandular autoimmune syndrome and coeliac disease. Response rates for hormonal stimulation therapy were low and the presence of autoimmune disease was associated with	We found a high prevalence of autoimmune disease in women with POI. Screening for autoimmune diseases should be offered to all women with POI.		



						poor infertility treatment outcome.		
<b>(Hsieh and Ho, 2021)</b>	Cohort study	Patients with autoimmune thyroid disease between 20 and 40 years of age: Hashimoto's and Grave's. The comparison cohorts consisted of patients in without autoimmune thyroid disease matched by age at a ratio of 1:4			incidence POI	Hashimoto patients exhibited an 89% higher risk of amenorrhoea (95% CI 1.36–2.61) and a 2.40-fold higher risk of infertility due to ovarian failure than the non-HDsubjects (HR 2.40, 95% CI 1.02–5.68). Graves patients exhibited a 68% higher risk of amenorrhoea (95% CI 1.43–1.98) after adjustment. According to the Kaplan–Meier analysis, the cumulative incidence of amenorrhoea and menopausal syndrome was significantly higher in women with thyroid autoimmunity than in the control groups.	Autoimmune thyroid disease is highly associated with POI, the options for infertility treatment may be re-directed to more efficient methods in infertile patients diagnosed with the disease. If the ovarian reserve is normal at the time of diagnosis of thyroid autoimmune disease, close follow-up of ovarian reserve may be highly recommended.	Ref higher incidence POI in autoimmune thyroid disease. Incidence of amenorrhoea of the Hashimoto and control cohorts were 12.6 and 9.03 per 1000 person-years. Incidence rates of amenorrhoea of the Graves and non-Graves cohorts were 13.5 and 10.5 per 1000 person-years,
<b>(Poppe et al., 2008)</b>	Review	The role of thyroid autoimmunity in fertility and pregnancy						Used as background information
<b>(Khizroeva et al., 2019)</b>	Review	Infertility in women with systemic autoimmune diseases						Used as background information
<b>(Persani et al., 2009)</b>	Review	POI X chromosome defects and autoimmunity						Used as background information
<b>(Monteleone et al., 2011)</b>	Study	euthyroid infertile women with thyroid autoimmunity undergoing in vitro fertilization (IVF)	Anti-thyroglobulin and anti-thyropoxidase levels were measured in both follicular fluid and serum (day of OPU)  Serum TSH, FT3, and FT4 levels measured before treatment initiation, on the day of OPU and of pregnancy test.		Presence of AB + impact on IVF outcome	Oocyte fertilization, grade A embryos, and pregnancy rates were lower in women with thyroid autoimmunity than in negative controls, while early miscarriage rate was higher. Anti-thyroid antibodies were measurable in follicular fluid in all affected women and were strongly correlated with serum levels. No significant changes in thyroid hormone	The presence of anti-thyroid antibodies in ovarian follicles, as demonstrated for the first time in this study, may play a critical role in female infertility related to thyroid autoimmunity.	



						levels were recorded in any women.		
<b>(Osuka et al., 2018)</b>	Cohort study	153 euthyroid infertile women POI	Serum AMH levels thyroid autoantibodies (TPOAb and TgAb)		AMH compared between patients with positive and negative thyroid autoantibodies.  Correlation between AMH and each thyroid autoantibody	No significant differences were found in serum AMH levels between the TPOAb- or TgAb-positive women and the antibody-double negative women. Serum AMH levels did not show a significant correlation with the concentration of TgAb or TPOAb. On the other hand, serum AMH levels negatively correlated with TSH levels in patients who were either positive for TPOAb or TgAb.	Thyroid autoantibodies are not likely to influence ovarian reserve in euthyroid women whose TSH levels fall within the normal range although elevated TSH levels may be involved in the decline of serum AMH levels.	contribution of thyroid autoantibodies or elevated thyroid-stimulating hormone (TSH) levels to decreased ovarian reserve
<b>(Li et al., 2022)</b>	Review	30 studies included and 5 were selected for detailed review.			association of Hashimoto's thyroiditis (HT) with ovarian reserve.	no statistically significant difference in ovarian reserve parameters (AMH, AFC, FSH, E2) between females with HT and the controls. In subgroup meta-analyses, reproductive aged women with HT had a statistically significant reduction in AMH (SMD -0.35; 95% CI: -0.51, -0.19; P < 0.0001; I(2) = 52%), AFC (MD -0.43; 95% CI: -0.56, -0.30; P < 0.00001; I(2) = 62%), and increase in basal FSH (SMD 0.1; 95% CI: 0.01, 0.19; I(2) = 19%; P = 0.04) compared with age matched controls. Furthermore, POA in reproductive aged women was associated with higher frequency of positive TPOAb (OR 2.26, 95% CI: 1.31-3.92, p = 0.004) but not positive TgAb (OR 3.17, 95% CI: 0.89-11.38, p = 0.08).	These bidirectional associations suggested that reproductive aged women with HT have a significantly higher risk of diminished ovarian reserve.	
<b>(Tanska et al., 2022)</b>	review				influence of TPOAb or TPOAb/TgAb positivity without thyroid dysfunction on reproduction.	TAI may negatively affect female fertility; several studies have found an increased prevalence of TAI in infertile women, especially in those with unexplained infertility and polycystic ovary syndrome. According to some observations, TAI might also be connected with premature ovarian insufficiency and endometriosis. The relationship between TAI and an increased risk of pregnancy loss is well documented. The pathophysiological background of these observations remains unclear, and researchers hypothesize on the direct infiltration of reproductive organs by thyroid antibodies, co-existence of TAI with other autoimmune		



						diseases (either organ specific or systemic), immunological dysfunction leading to inhibition of immune tolerance, and relative thyroid hormone deficiency. Interestingly, in the current literature, better outcomes of assisted reproductive technology in women with TAI have been reported compared with those reported in earlier publications. One plausible explanation is the more widespread use of ICSI. The results of RCTs have shown that levothyroxine supplementation is ineffective in preventing adverse pregnancy outcomes in women with TAI, and future research should probably be directed toward immunotherapy.			
<b>(Hollowell et al, 2002)</b>	Cohort study	13,344 without thyroid disease, goiter, or taking thyroid medications (disease-free population)  Excluding those pregnant, taking androgens or estrogens, who had thyroid antibodies, or biochemical hypothyroidism or hyperthyroidism.	mean concentrations of TSH, T(4), TgAb, and TPOAb.  + The influence of demographics on TSH, T(4), and antibodies was examined. (not reported here)			Hypothyroidism was found in 4.6% of the U.S. population (0.3% clinical and 4.3% subclinical) and hyperthyroidism in 1.3% (0.5% clinical and 0.7% subclinical). (Subclinical hypothyroidism / mild hypothyroidism)  Using the reference population, geometric mean TSH was 1.40 +/- 0.02 mIU/liter and increased with age  Arithmetic mean total T(4) was 112.3 +/- 0.7 nmol/liter	TSH and the prevalence of antithyroid antibodies are greater in females, increase with age,  TgAb alone in the absence of TPOAb is not significantly associated with thyroid disease.	NHANES III	
<b>Type 1 diabetes mellitus</b>									
<b>(Dorman et al, 2001)</b>	Study	adult individuals who were identified from the Children's Hospital of Pittsburgh Type 1 Diabetes Registry for the years 1950-1964 and their family members. Unrelated nondiabetic control probands and their relatives were also evaluated.			Age at menarche  menstrual irregularities  Age at menopause	Women with type 1 diabetes (n = 143) compared with nondiabetic sisters (n = 186) or unrelated control subjects (n = 160) were more likely to have an older age at menarche (13.5, 12.5, and 12.6 years, respectively, P < 0.001), more menstrual irregularities before 30 years of age (45.7, 33.3, and 33.1%, respectively, P = 0.04), and a younger ANM (41.6, 49.9, and 48.0 years, resp, P = 0.05). This resulted in a 6-year reduction in the number of reproductive years (30.0, 37.0, and 35.2 years, resp, P = 0.05) for women with diabetes.  Multivariate analysis: type 1 diabetes (HR 1.98, P = 0.056), menstrual	We hypothesize that an earlier menopause, which resulted in a 17% decrease in reproductive years, is a major unstudied complication of type 1 diabetes.		



						irregularities by 30 years of age (HR 2.36, P = 0.01), and unilateral oophorectomy (HR 9.76, P < 0.0001) were independent determinants of earlier menopause	
<b>(Brand et al, 2015)</b>	study	258 898 women from the European Prospective Investigation into Cancer and Nutrition (EPIC), enrolled between 1992 and 2000.	Questionnaires  Diabetes  age at diabetes diagnosis  Age at menopause		Age at menopause (ANM)	no association between diabetes and ANM was found (HR 0.94; 95% CI 0.89-1.01). However, women with diabetes before the age of 20 years had an earlier menopause (10-20 years: HR 1.43; 95% CI 1.02-2.01, <10 years: HR 1.59; 95% CI 1.03-2.43) compared with non-diabetic women, whereas women with diabetes at age 50 years and older had a later menopause (HR = 0.81; 95% CI 0.70-0.95).	Although there was no overall association between diabetes and age at menopause, our study suggests that early-onset diabetes may accelerate menopause.
<b>(Sjöberg et al, 2011)</b>	population-based study	978 women with childhood-onset type 1 diabetes.	Questionnaire  gynecological and reproductive histories, diabetes and its management, other diseases, and lifestyle factors  (repeated after 3 years)		age at menopause	median age at cessation of menstruation observed in women with type 1 diabetes was 52.5 years, not lower than that of the general Finnish population (median, 51 y). Women with end-stage renal disease (prevalence ratio, 2.22; 95% CI, 1.22-4.02; P = 0.009) or proliferative retinopathy (prevalence ratio, 1.89; 95% CI, 1.11-3.21; P = 0.02) were more likely than others to have entered menopause by the time of the study. Both associations remained statistically significant after age adjustment.	Age at menopause in women with type 1 diabetes is not lower than that in the general population in Finland. The only statistically significant factors independently associated with earlier menopause in our study were microvascular complications, that is, end-stage renal disease and proliferative retinopathy.
<b>(Kim et al, 2014)</b>	secondary analysis of RCT cohort	657 women with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT),	intensive versus conventional diabetes treatment  Cox regression analyses were used to examine associations with treatment group, time-varying estimates of hemoglobin A1c (HbA1c), insulin		cumulative incidences of natural menopause and surgical menopause.	after an average of 28 years of follow-up, 240 (38%) women had experienced natural menopause and 115 (18%) women had experienced surgical menopause. Age at natural menopause was similar in the intensive versus conventional groups (49.9 vs. 49.0 years; P	In the DCCT/EDIC, intensive versus conventional treatment group and HbA1c level were not associated with menopause risk. Greater insulin dose



			dosage, BMI, and microvascular complications (retinopathy, nephropathy, and neuropathy).			= 0.28), and age at surgical menopause was similar in the intensive versus conventional groups (40.8 vs. 42.0 years; P = 0.31).  In multivariable models, treatment group, HbA1c, and microvascular complications were not associated with risk of natural or surgical menopause. Each 10 unit/day increase in insulin dosage decreased risk of natural menopause (HR 0.91, 95% CI 0.75-0.98) and each kg/m(2) increase in BMI increased risk of surgical menopause (HR 1.08, 95% CI 1.00-1.16).	was associated with lower menopause risk.	
<b>(Yarde et al, 2015)</b>	cross-sectional study	140 post-menopausal women with diabetes, and 5426 post-menopausal women without diabetes	standardized questionnaire including report of their age at last menstrual period.		Age at menopause	Mean age at natural menopause was 49.8 ± 4.7 years in women with type 1 diabetes and 49.8 ± 4.1 in women without diabetes. Linear regression analyses showed that type 1 diabetes was not associated with an earlier menopause compared with the reference group without diabetes, after adjustment for age, smoking history and parity (difference in age at menopause between women with type 1 diabetes and reference group 0.34 years, 95% CI -0.34, 1.01).	No clear evidence was provided that type 1 diabetes is a determinant of accelerated ovarian ageing resulting in an early menopause.	
<b>(Stuenkel, 2017)</b>	Narrative review							Used as background information
<b>(Thong et al, 2020)</b>	Narrative review							Used as background information
<b>Coeliac disease</b>								
<b>(Kotze, 2004)</b>	Cohort study	76 adult celiac patients + 18 children/adolescents  Controls: 84 adults and 22			gynaecological and obstetrical disturbances	Adult celiac patients, irrespective of the nutritional status, were younger than controls, presented delayed menarche, secondary amenorrhea, a higher percentage of spontaneous abortions, anemia	gluten per se could explain the disturbances and malnutrition would worsen the disease in a consequent vicious cycle.	



		adolescents with irritable bowel syndrome				and hypoalbuminemia. No differences were observed regarding the number of pregnancies, age at menopause and duration of the reproductive period. After treatment, patients presented with normal pregnancies and one patient presented spontaneous abortion. The adolescents who were not adherent to gluten-free diet presented delayed menarche and secondary amenorrhea.	Therefore, celiac disease should be included in the screening of reproductive disorders.	
<b>(Cakmak et al., 2018)</b>	Cohort	46 CD female patients and 40 healthy female subjects of reproductive age, ages 18-45 years.  no statistically significant differences between CD and control groups in terms of mean age, BMI, or median gravidity/parity/abortions/alive counts (p>0.05).	AMH AFCs  ovarian volume		ovarian reserve	no statistically significant differences between the 2 groups in terms of mean FSH, LH, E2, PRL levels, right and left ovarian volumes, and median right and left ovarian AFCs (p>0.05).  AMH level was significantly lower in the CD group (p=0.032).	AMH level and ovarian reserve was decreased in CD patients	
<b>(Comba et al., 2020)</b>	case-control multicenter trial	21 (47.7%) celiac patients with a mean age of 15.8 ± 1.3 years,  24 (52.3%) healthy control subjects with a mean age of 16.2 ± 1.2.	On days 2-5 of the menstrual cycle, measurements of serum FSH, LH, estradiol, prolactin, and AMH w  Antral follicle counts and ovarian volumes were determined on the same day. RESULTS:		whether celiac disease affects ovarian reserve assessed by AFC, ovarian volume, and AMH	No difference between the groups in respect of right and left ovarian volumes (p = 0.790 and p = 0.670, respectively). Serum AMH of the celiac patients and controls were found comparable [(3.7 ± 2.9 (0.5-12) and 3.6 ± 1.8 (1.2-8.1)] ng/mL, respectively, p = 0.915).	Celiac disease may not affect the ovarian reserve determined with established ovarian reserve markers including AFC; ovarian volume, and AMH in adolescent patients.	
<b>(Tata et al., 2005)</b>	Cohort study	1521 women with celiac disease with data for 7732 age- and practice-matched	computerized primary care data on fertility and adverse pregnancy outcomes		Prevalence of reduced fertility and increased adverse pregnancy-related events	Crude fertility rates were 48.2 and 47.7 live births per 1000 person-years for women with and without celiac disease, resp (rate	Overall, women with celiac disease have fertility similar to that of the general female	



		women without celiac disease.				ratio, 1.01; 95% CI 0.90-1.14). Age-specific fertility rates showed that women with celiac disease had lower fertility when younger but higher fertility when older compared with women without celiac disease. This increase in relative fertility with increasing age held whether women had treated or untreated celiac disease. Risks of cesarean section (odds ratio, 1.33; 95% CI 1.03-1.70) and miscarriage (rate ratio, 1.31; 95% CI 1.06-1.61) were moderately higher in women with celiac disease, but risks of assisted birth, breech birth, preeclampsia, postpartum hemorrhage, ectopic pregnancy, stillbirth, and termination were similar	population, but they have their babies at an older age. Although our findings may reflect a disease effect, the age shift in fertility rates and the increase in cesarean section risk is consistent with socioeconomic or educational advantages of women with celiac disease.
<b>(Zugna et al, 2010)</b>	Swedish population-based cohort study.	11,495 women with CD, aged 18-45 years,  51,109 age-matched reference women.	Registry based analysis		Fertility defined as the number of children	During follow-up, 16,309 births occurred in women with CD and 69,245 in the reference women. The cumulative number of children slightly increased in women with CD compared with the reference group. Adjusting for age, calendar period and parity and stratifying by education, the overall fertility hazard ratio (HR) in CD was 1.03 (95% CI 1.01 to 1.05). Specifically, the fertility HR was 1.05 (95% CI 0.96 to 1.14) for CD diagnosed in women before 18 years, 1.04 (95% CI 1.01 to 1.07) for CD diagnosed in women between 18 and 45 years and 1.02 (95% CI 0.99 to 1.04) for CD diagnosed in women > 45 years of age. Taking date of CD diagnosis into account, fertility was decreased 0-2 years before time of diagnosis (HR=0.63; 95% CI 0.57 to 0.70), was identical to that	Overall, women with CD had a normal fertility, but their fertility was decreased in the last 2 years preceding CD diagnosis.



						of controls 0-5 years subsequent to diagnosis and increased to 1.12 (95% CI 1.03 to 1.21) thereafter.		
<b>(Lasa et al., 2014)</b>	meta-analysis	12 studies included in the analysis			association between celiac disease and infertility	A significant association was found between women with a diagnosis of infertility and undiagnosed celiac disease [OR 3.09 (95% CI 1.74-5.49)]. When considering those studies assessing the occurrence of infertility in subjects with already-diagnosed celiac disease, no difference was found between celiac disease patients and control subjects [OR 0.99 (0.86-1.13)].	Undiagnosed celiac disease is a risk factor for infertility. Women seeking medical advice for this particular condition should be screened for celiac disease. Adoption of a gluten-free diet could have a positive impact on fertility in this group of patients.	
<b>(Singh et al., 2016)</b>	meta-analysis	105 relevant studies, 5 studies included for calculation of pooled OR. Four additional studies, where data on controls were not available, were also considered for calculation of pooled prevalence of CeD.			association between celiac disease and infertility	Women with infertility had 3.5 times higher odds of having CeD in comparison with control population (OR=3.5; 95% CI, 1.3-9; P<0.01). Similarly, women with "unexplained infertility" had 6 times higher odds of having CeD than controls (OR=6; 95% CI, 2.4-14.6). Of 884 women with infertility, 20 had CeD indicating a pooled prevalence of 2.3% (95% CI, 1.4-3.5). Of 623 women with "unexplained infertility," 20 had CeD. The pooled prevalence of CeD in women with unexplained infertility was 3.2 (95% CI, 2-4.9).	CeD is more prevalent in women with "all-cause" infertility and "unexplained" infertility than that in general population.	
<b>(Walker et al., 2019)</b>	Case report and review	CD			endocrine disorders related to celiac disease	fracture risk is increased by 30-40%, while risk for hip fracture is approximately doubled.  Fertility is reduced in women with CD before diagnosis by 37% while male fertility in the absence of hypogonadism	CD is associated with a wide range of endocrine manifestations.	The risk for other endocrine disorders, particularly autoimmune endocrinopathies, is also increased in those with CD compared to



						does not appear to be affected.		the general population.
<b>Other autoimmune diseases</b>								
<b>Studies all included above</b>								

## EVIDENCE TO RECOMMENDATIONS

QUESTION	WHAT ARE THE KNOWN AUTOIMMUNE CAUSES OF NON-IATROGENIC POI AND HOW SHOULD THEY BE INVESTIGATED?
RECOMMENDATION	<b>Screening for 21-hydroxylase autoantibodies (21OH-Abs) should be performed in women with POI of unknown cause.</b>
Desirable effects	Antibodies against 21OH-Ab are currently the marker with the highest diagnostic accuracy for autoimmune POI.
Undesirable effects	There is no specific treatment option for autoimmune POI
Certainty of evidence	Data mainly from cohort studies showing associations (••••)
Balance of effects	Identification of women with autoimmune POI is clinically relevant for diagnosing subclinical or latent autoimmune adrenal insufficiency.
Resource use, equity, acceptability and feasibility	21OH-Ab is considered available, even if no data were available on this.
Subgroup considerations (if applicable)	Not applicable

QUESTION	WHAT ARE THE KNOWN AUTOIMMUNE CAUSES OF NON-IATROGENIC POI AND HOW SHOULD THEY BE INVESTIGATED?
RECOMMENDATION	<b>Screening for anti-ovarian autoantibodies should not be used to diagnose autoimmune POI.</b>
Desirable effects	Anti-ovarian autoantibodies are not specific in POI, with a high presence of these antibodies also in healthy women
Undesirable effects	There is no specific treatment option for autoimmune POI
Certainty of evidence	Cohort studies only
Values	Not applicable
Balance of effects	As there is no relevance/benefit of the test for clinical management, a recommendation was formulated against measurement of anti-ovarian autoantibodies
Resource use, equity, acceptability and feasibility	Not applicable
Subgroup considerations	Not applicable



QUESTION	WHAT ARE THE KNOWN AUTOIMMUNE CAUSES OF NON-IATROGENIC POI AND HOW SHOULD THEY BE INVESTIGATED?
RECOMMENDATION	<b>Thyroid function should be assessed by measuring thyroid-stimulating hormone (TSH) at POI diagnosis. TSH measurement should be repeated every 5 years or when symptoms arise.</b>
Desirable effects	Significant prevalence of thyroid dysfunction in POI Standardised tests, with impact on clinical management. Untreated hypothyroidism can impact general health and quality of life. Furthermore, because of the detrimental effects on foetal neurocognitive development, it is important to treat hypothyroidism in women where pregnancy is desired (spontaneous or after oocyte donation).
Undesirable effects	No clear undesirable effects linked to thyroid function assessment
Certainty of evidence	Cohort studies, significant data on impact of thyroid dysfunction on general health
Values	Measuring thyroid function and treatment of dysfunction is of benefit to patients with POI
Balance of effects	Screening for TSH should be performed in women with POI.
Resource use, equity, acceptability and feasibility	thyroid function assessment is considered widely available.
Subgroup considerations (if applicable)	Not applicable

QUESTION	WHAT ARE THE KNOWN AUTOIMMUNE CAUSES OF NON-IATROGENIC POI AND HOW SHOULD THEY BE INVESTIGATED?
GOOD PRACTICE POINT	<b>The guideline group recommends that HCPs do not routinely perform thyroid peroxidase (TPO) antibody screening as part of testing for autoimmune causes of POI due to the high prevalence of positive TPO antibodies in the general community.</b>
Justification	Included in the recommendation



## PICO QUESTION: HOW OFTEN SHOULD TESTS FOR AUTOANTIBODIES BE REPEATED?

<b>Population</b>	<p>Innate and Acquired POI</p> <p>Patients diagnosed with POI</p> <p>Negative test result for autoantibodies:</p> <ul style="list-style-type: none"> <li>• Ovarian antibodies</li> <li>• Adrenal antibodies</li> <li>• steroidogenic antibodies</li> <li>• Thyroid function tests</li> <li>• Thyroperoxidase</li> <li>• Thyroglobulin</li> <li>• Thyroid antibodies</li> </ul> <p>Markers for autoimmune disorders associated with POI</p>
<b>Interventions</b>	<p>Repeat test, redo test, second test, relevance of negative test result, interval between tests</p> <p>Referral to endocrinologist (indications, when,..)</p> <p>Follow-up / Monitoring</p>
<b>Control</b>	
<b>Outcomes</b>	<p>Risk of developing (or having) an autoimmune endocrinopathy</p> <p>Management of associated autoimmune diseases, or the risk thereof</p>

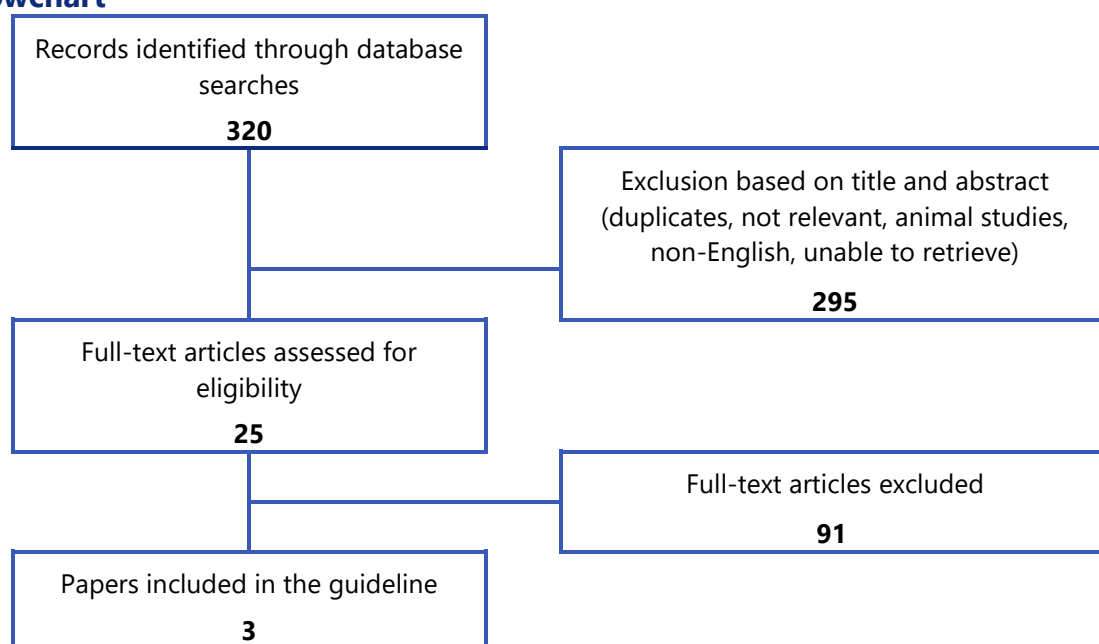
### Search string

Database	Search String
<b>PUBMED</b>	<p>("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (((Ovarian OR antiovarian OR anti-ovarian) AND (antibody OR antibodies OR autoimmunity)) OR ("Adrenal antibodies" OR "Adrenal antibody" OR "steroidogenic antibodies" OR "steroidogenic antibody" OR "Thyroid function" OR "Thyroid peroxidase" OR "Thyroglobulin" OR "Thyroid antibodies" OR "Thyroid antibody" OR "Anti-transglutaminase antibodies" OR "Anti-tTG antibodies" OR "anti-gliadin" OR "anti-endomysium antibodies" OR EMA))</p>

Literature search was limited to the period between 01/01/2014 and 17/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence table – repeating autoantibody tests

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
(Vogt <i>et al.</i> , 2021)								Included above
(Naletto <i>et al.</i> , 2019)	Study	29 patients with APS-1 and 114 patients with APS-2 or APS-4 were followed up for a median of 10 years (range 6 months to 33 years)	ACTH test.  Univariate and multivariate Cox proportional hazard models were used for statistical analysis.		The risk of AAD was estimated according to age, gender, stage of adrenal dysfunction, associated diseases and antibody titer.	The cumulative risk (CR) of developing AAD was higher in APS-1 patients (94.2%) than in patients with APS-2/APS-4 (38.7%). The CR was high in both male and female APS-1 patients, while in patients with APS-2/APS-4 it was high only in males. Stage 1 (increased plasma renin) for patients with APS-1 and Stage 2 (no response of cortisol to ACTH test) for patients with APS-2/APS-4 were established as the points of no return in the progression to AAD. Adjusted hazard ratio analyses by multivariate Cox model for AAD showed that gender, diseases and adrenal function were independent risk factors for developing clinical AAD. The risk of	A model for estimating the probability to survive free of AAD has been developed and should be a useful tool in designing appropriate follow-up intervals and future therapeutic strategies.	Adrenal cortex autoantibodies (ACAs) and/or 21-hydroxylase (21OHA) are markers of autoimmune Addison's disease (AAD) and progression to overt AAD.



						developing clinical AAD appears to subside after 19 years of follow-up	
(Husebye et al., 2021)	REVIEW	Adrenal insufficiency				clinical features are unintentional weight loss, anorexia, postural hypotension, profound fatigue, muscle and abdominal pain, and hyponatraemia  Despite state-of-the-art steroid replacement therapy, reduced quality of life and work capacity, and increased mortality is reported in patients with primary or secondary adrenal insufficiency.	Review on significant impact of adrenal insufficiency

## EVIDENCE TO RECOMMENDATIONS

QUESTION	HOW OFTEN SHOULD TESTS FOR AUTOANTIBODIES BE REPEATED?
RECOMMENDATION	<b>Women with POI and positive 21OH-Abs should be referred to an endocrinologist for testing of adrenal function.</b>
Desirable effects	The evidence of association between positive 21 OH autoantibodies and autoimmune adrenal disease is substantial. As the consequence of adrenal insufficiency is potentially detrimental, endocrinological evaluation and follow-up of women with POI with increased risk is crucial.
Undesirable effects	Not applicable for referral for further testing
Certainty of evidence	Cohort studies linking 21OH-Ab with adrenal dysfunction
Values	Prevention of possible significant negative impact of adrenal insufficiency
Balance of effects	With no or limited undesirable effects, referral is recommended
Resource use, equity, acceptability and feasibility	There could be issues with implementation
Subgroup considerations (if applicable)	Not applicable

QUESTION	HOW OFTEN SHOULD TESTS FOR AUTOANTIBODIES BE REPEATED?
RECOMMENDATION	<b>If 21OH-Abs are negative in women with POI, there is no indication for re-testing later in life, unless signs or symptoms of adrenal insufficiency develop.</b>
Desirable effects	There is no evidence regarding the natural history of autoimmunity in women with POI who have negative autoantibodies at initial screening, and as such no evidence of benefit of repeated testing.
Undesirable effects	Resource use
Certainty of evidence	Cohort studies
Values	Not applicable
Balance of effects	Without evidence for benefit of testing, testing should not be performed.



Resource use, equity, acceptability and feasibility	Not applicable
Subgroup considerations (if applicable)	If symptoms of disease are present, further autoantibody testing is indicated. This is specified in the recommendation.

QUESTION	HOW OFTEN SHOULD TESTS FOR AUTOANTIBODIES BE REPEATED?
RECOMMENDATION	<b>Women with POI with abnormal TSH levels should be evaluated and treated for thyroid hormone disorders.</b>
Desirable effects	Untreated thyroid dysfunction can impact general health and quality of life, and pregnancy/neonatal outcomes.
Undesirable effects	No undesirable effects anticipated for further evaluation of thyroid function, and possible linked treatment
Certainty of evidence	Cohort studies
Values	Prevention of possible significant negative impact of thyroid dysfunction
Balance of effects	With no or limited undesirable effects, referral is recommended
Resource use, equity, acceptability and feasibility	There could be issues with implementation. The recommendation first suggesting referral to a specialist was amended after stakeholder review based on comments stating that follow-up of thyroid disorders can be performed in primary care
Subgroup considerations (if applicable)	Not applicable



### 1 III. Implications for relatives of women with POI

#### 2 KEY QUESTION: WHAT ARE THE IMPLICATIONS FOR RELATIVES OF WOMEN WITH 3 POI?

QUESTION	WHAT ARE THE IMPLICATIONS FOR RELATIVES OF WOMEN WITH POI?
GOOD PRACTICE POINT	<b>The guideline group recommends that relatives of women with the FMR1 premutation or other identified genetic causes of POI should be offered genetic counselling and testing.</b>
Justification	The implications for relatives of women with POI with an underlying genetic cause, particularly a Fragile X premutation, are more extensive than reproductive issues. For these relatives, genetic counselling should be offered (see also II.3.b. Genetic background of POI).

QUESTION	WHAT ARE THE IMPLICATIONS FOR RELATIVES OF WOMEN WITH POI?
RECOMMENDATION	<b>Female relatives (such as sisters or daughters) of women with non-iatrogenic POI should be counselled that they are at increased risk of developing POI themselves.</b>
Desirable effects	Although there seems to be a familial factor in POI and there is evidence of heritability of age at menopause, the specific genetic associations in POI have not been completely elucidated and more research is needed. Women with at least one affected family member may be at increased risk of POI and should speak to their HCP about their options.
Undesirable effects	Not applicable for counselling on increased risk of developing POI
Certainty of evidence	Observational data only (••••)
Values	Support for family members is important to patients
Balance of effects	Benefit of counseling
Resource use, equity, acceptability and feasibility	We consider counselling on increased risk of developing POI should be feasible
Subgroup considerations (if applicable)	Not applicable

QUESTION	WHAT ARE THE IMPLICATIONS FOR RELATIVES OF WOMEN WITH POI?
GOOD PRACTICE POINT	<b>The guideline group recommends that female relatives (such as sisters or daughters) of women with non-iatrogenic POI are offered support regarding their increased risk of POI, and ovarian reserve testing may be helpful.</b>
Justification	Family members of women with POI may require support to cope with their newfound risk of POI.

QUESTION	WHAT ARE THE IMPLICATIONS FOR RELATIVES OF WOMEN WITH POI?
GOOD PRACTICE POINT	<b>The guideline group recommends that female relatives (such as sisters or daughters) of women with non-iatrogenic POI should be informed of the</b>



	<b>signs and symptoms of POI and should promptly seek medical advice if this occurs.</b>
Justification	It is not currently possible to predict or prevent POI. Awareness of the increased risk of POI among relatives of women with POI would improve the likelihood of diagnosing POI earlier, thereby preventing unfavourable health outcomes (Silvén <i>et al.</i> , 2022), such as bone loss or other sequelae of POI that could have been prevented by prompt institution of HT.

7

QUESTION	WHAT ARE THE IMPLICATIONS FOR RELATIVES OF WOMEN WITH POI?
GOOD PRACTICE POINT	<b>The guideline group recommends that female relatives (such as sisters or daughters) of women with non-iatrogenic POI should be informed that there are no established methods for predicting or preventing POI. Some relatives may wish to consider family planning and fertility preservation options.</b>
Justification	While it is not currently possible to predict or prevent POI, ovarian assessment may be appropriate in some women. It may be appropriate for these women not to postpone pregnancy, although the decision to start a family is multifactorial. Oocyte freezing may be an option for fertility preservation but there are legal restrictions in some countries. Egg and embryo freezing are well established methods of fertility preservation, however there are no studies on the effectiveness of oocyte freezing specifically in women with a familial link to POI.

8



## 9 IV. POI and life expectancy

### 10 KEY QUESTION: WHAT ARE THE CONSEQUENCES OF POI FOR LIFE 11 EXPECTANCY?

<b>Population</b>	People with POI of any cause including iatrogenic.
<b>Interventions</b>	/
<b>Control</b>	/
<b>Outcomes</b>	Life expectancy OR mortality

12

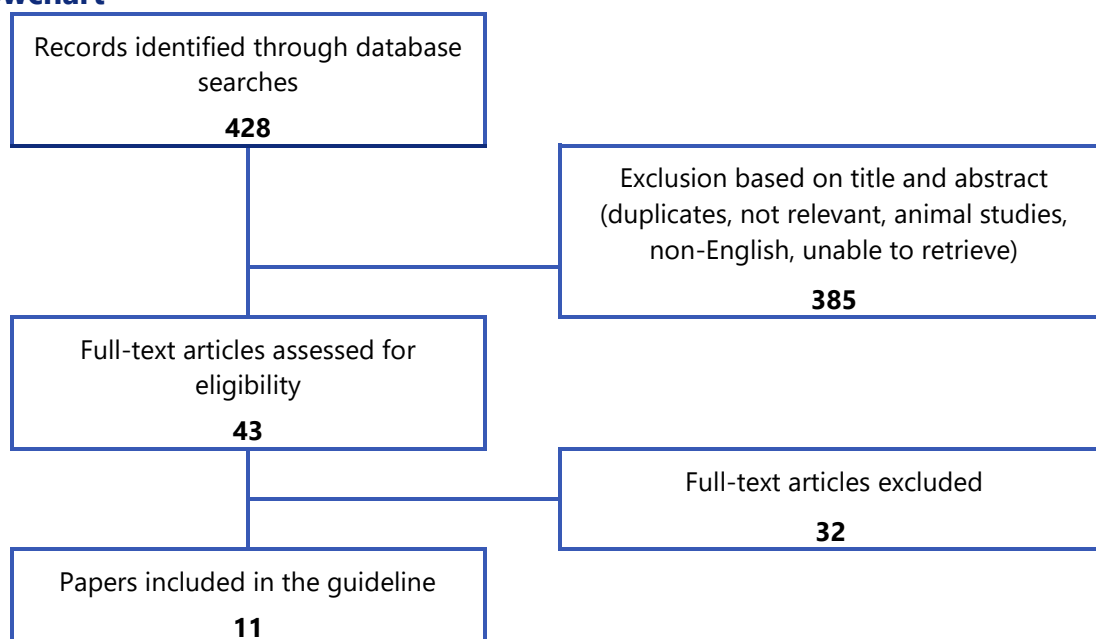
### 13 Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("Life expectancy" OR "mortality" OR "Life Expectancy"[Mesh] OR "Mortality"[Mesh])

14

15 Literature search was limited to the period between 01/04/2014 and 15/09/2022 and updated and  
16 26/01/2024. Studies and data published prior to 01/04/2014 were assessed in the development of the  
17 POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published  
18 prior to 01/04/2014 were retained.

### 19 Flowchart



20



21 Evidence

22 Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Bilateral oophorectomy and mortality</b>								
<b>(Cusimano et al., 2021)</b>	Population based cohort study.	200549 women (aged 30-70 years) undergoing hysterectomy for non-malignant disease stratified into premenopausal (<45 years), menopausal transition (45-49 years), early menopausal (50-54 years), and late menopausal (≥55 years) groups according to age at surgery"	Bilateral salpingo-oophorectomy at time of Hx.	Hx with ovarian conservation	all-cause death cause-specific death (cancer / non-cancer) median follow-up: 12 years (interquartile range 7-17)	<p>Bilateral salpingo-oophorectomy was performed in 19%, 41%, 69%, and 81% of women aged &lt;45, 45-49, 50-54, and ≥55 years, respectively.</p> <p>All-cause death Age &lt;45: increased in BSO vs ovarian conservation (HR 1.31; 95% CI 1.18-1.45; p&lt;0.0001) - driven by non-cancer death =&gt; absolute risk increase of 1.4% (0.8% to 2.1%; number needed to harm 71) at 20 years.</p> <p>Age 45-49: increased in BSO vs ovarian conservation (HR 1.16, 95% CI 1.04 to 1.30, P=0.007) - driven by non-cancer death =&gt; absolute risk increase of 0.7% (-0.12% to 1.45%; number needed to harm 152) at 20 years</p> <p>Age 50-54: not increased in BSO (HR 0.83, 95% CI 0.72 to 0.97, P=0.018)</p> <p>Age ≥55 years: not increased in BSO (HR 0.92, 95% CI 0.82 to 1.03, P=0.16)</p>	Bilateral salpingo-oophorectomy at non-malignant hysterectomy appeared to be associated with increased all-cause mortality in women aged <50 years, but not in those aged ≥50 years. While caution is warranted when considering bilateral salpingo-oophorectomy in premenopausal women without indication, this strategy for ovarian cancer risk reduction does not appear to be detrimental to survival in postmenopausal women.	
<b>(Jacoby et al., 2011).</b>	Observational study	25 448 Women's Health Initiative Observational Study  Follow up : 8 years	Hysterectomy with BSO	no oophorectomy	Mortality	<p>No increased mortality HR 0.98 [0.87-1.10]</p> <p>No increase in hip fracture HR 0.83 [0.63-1.10]</p>	No significant association between bilateral oophorectomy before age 40 years and mortality	Confounded by use of HRT in about 80% of participants
<b>(Rivera et al., 2009b).</b>	cohort study	Minnesota cohort  Oophorectomy, BSO or unilateral, before age 45 (n=2365)  Each subject with matched by age to a referent woman from the same	BSO	no BSO	Mortality for neurological or mental diseases	<p>HR 5.24; 95% CI 2.02-13.6; p &lt; 0.001</p> <p>"mortality was similar in women who were or were not treated with estrogen from the time of oophorectomy through age 45 years"</p>	oophorectomy before age 45 years was also associated with increased mortality for neurological and mental diseases	



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
		population (n=2383)						
<b>(Rivera et al, 2009a).</b>	cohort study	Same as (Rivera et al, 2009b).	BSO	no BSO	Mortality from CVD  Sub-group analysis of HRT users vs no HRT	HR, 1.44; 95% CI, 1.01-2.05; P = 0.04  No HRT: HR, 1.84; 95% CI, 1.27-2.68; P = 0.001  Oestrogen-users: HR, 0.65; 95% CI, 0.30-1.41		
<b>(Parker et al, 2013)</b>	prospective cohort study	30,117 Nurses' Health Study participants undergoing hysterectomy for benign disease.  bilateral oophorectomy (n=16,914)  ovarian conservation (n=13,203).	BSO (hysterectomy and bilateral oophorectomy)	no BSO (ovarian conservation)	long-term mortality  28 years of follow-up	16.8% of BSO died from all causes compared with 13.3% no BSO (HR 1.13, 95% CI 1.06-1.21). Oophorectomy was associated with a lower risk of death from ovarian cancer (4 BSO vs 44 no BSO) and before age 47.5 years, a lower risk of death from breast cancer.  At no age was oophorectomy associated with a lower risk of other cause-specific or all-cause mortality. For women <50 years at the time of hysterectomy, BSO was associated with significantly increased mortality in women who had never used estrogen therapy but not in past and current users: assuming a 35-year lifespan after oophorectomy: number needed to harm for all-cause death=8, coronary heart disease death=33, and lung cancer death=50	Bilateral oophorectomy is associated with increased mortality in women aged younger than 50 years who never used estrogen therapy and at no age is oophorectomy associated with increased survival.	In the Nurse's Health Study, (Parker et al, 2013).
<b>(Gottschall et al, 2023)</b>	Cohort study	142 985 women with hysterectomy for a benign condition, 22 974 with BSO and 120 011 without	BSO	no BSO	long-term outcomes:  - overall hospitalization for CVD - overall cancer incidence - all-cause mortality	women with BSO < 45 years at surgery  - a higher 10-year cumulative risk for hospitalization for CVD (risk difference [RD], 1.19 percentage points [95% CI, 0.09 to 2.43 percentage points]).  - a higher 10-year cumulative risk for cancer for ages 45 to 54 years (RD, 0.73 percentage point [CI, 0.05 to 1.38 percentage points]), 55 to 64 years (RD, 1.92 percentage points [CI, 0.69 to 3.25 percentage points]), and 65 years or older (RD, 2.54 percentage points [CI, 0.91 to 4.25 percentage points]).  - higher 10-year mortality in all age groups, although the differences were statistically significant only for ages 45 to 54 years (RD, 0.79 percentage point [CI, 0.27 to 1.30 percentage points]). The mortality at 20 years was inconsistent with that at 10	these results support current recommendations for conserving ovaries in premenopausal women without a high risk for ovarian cancer and suggest a cautious approach in postmenopausal women.	



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
						years in women aged 65 years or older.		
<b>(Michelsen et al., 2023)</b>	Cohort study	18 673 women with both their ovaries and uterus intact.  1199 women with hysterectomy alone  907 with bilateral oophorectomy with or without hysterectomy	information regarding gynecological surgery and previous health.		mortality	The hysterectomy group had increased all-cause mortality (hazard ratio [HR] 1.30, 95% confidence interval [CI] 1.06-1.58) and cardiovascular mortality (HR 1.47, 95% CI 1.09-1.97). We found no significant association between bilateral oophorectomy and all-cause or cardiovascular mortality in the total population. However, among women ≤52 years at inclusion, cardiovascular mortality was increased in the hysterectomy group (HR 2.71, 95% CI 1.19-6.17) with a similar, but less precise estimate in the bilateral oophorectomy group (HR 2.42, 95% CI 0.84-6.93).	Hysterectomy was associated with increased all-cause and cardiovascular mortality, whereas bilateral salpingo-oophorectomy was not.	The Trøndelag Health Study (HUNT2) (1995-1997), linked to the Norwegian Cause of Death Registry,
<b>(Hassan et al., 2024).</b>	systematic review	38 studies included	BSO	no BSO	long-term outcomes	BSO : decreased risk of breast cancer (HR 0.78; 95% CI 0.73-0.84) increased risk of colorectal cancer (HR, 1.27; 95% CI 1.10-1.47). increased risk of total CVD, coronary heart disease, and stroke with HRs of 1.18 (95% CI, 1.11-1.25), 1.17 (95% CI, 1.10-1.25), and 1.20 (95% CI, 1.10-1.31), resp	Hysterectomy with bilateral salpingo-oophorectomy was associated with multiple long-term outcomes. The benefits of the addition of bilateral salpingo-oophorectomy to hysterectomy should be balanced against the risks.	
<b>Non-iatrogenic POI and mortality</b>								
<b>(Huan et al., 2021)</b>	Review	16 studies and 321,233 women  Early age at natural menopause was grouped into premature menopause (<40 years), early menopause (40-44 years), and relatively early menopause (45-49 years).			Risk for All-Cause and Cardiovascular Mortality linked to age at natural menopause	statistically significant association of early age at natural menopause with all-cause mortality risk (HR 1:08, 95% CI: 1.03 to 1.14, P =0:002; RR 1:05, 95% CI 1.01 to 1.08,P =0:005), but not with cardiovascular mortality risk.  In dose-response analyses, the association with all-cause mortality was significant for POI with (HR 1:10; 95% CI: 1.01 to 1.21; P =0:034) and without (RR =1:34; 95% CI: 1.08 to 1.66; P 0:007) considering follow-up intervals. As for cardiovascular mortality, marginal significance was noted for POI after considering follow-up intervals (HR 1:09; 95% CI: 1.00-1.19; P =0:045).	POI is a promising independent risk factor for both all-cause and cardiovascular mortality.	
<b>(Xu et al., 2022).</b>	Cohort study	UK Biobank, 178 379 women,	menopausal hormone therapy (MHT)		cause-specific mortality	(Compared with natural menopause at age 50–52 years) cardiovascular mortality natural menopause before the	Self-reported MHT use following early natural	



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
		recruited in 2006–2010.  36 790 had natural menopause, 17 569 had surgical menopause and 24 020 had hysterectomy alone				<p>age of 40 years : HR 2.38, 95%CI: 1.64, 3.45</p> <p>hysterectomy before the age of 40 years : HR: 1.60, 95% CI: 1.23, 2.07</p> <p>cancer mortality natural menopause before the age of 40 years : HR: 1.21, 95% CI: 0.90, 1.63</p> <p>hysterectomy before the age of 40 years: HR:1.11, 95% CI: 0.93, 1.32</p> <p>mortality from all other causes natural menopause before the age of 40 years : HR: 1.49, 95% CI: 1.20, 1.86</p> <p>MHT use MHT users had a lower risk of breast cancer mortality following natural menopause at &lt;45years (HR: 0.59, 95% CI: 0.36, 0.95) and a lower risk of colorectal cancer mortality following natural menopause at 45–49 years (HR: 0.47, 95%CI: 0.29, 0.76)</p> <p>MHT users had a lower risk of breast cancer mortality following surgical menopause at &lt;45 years(HR: 0.17, 95% CI: 0.08, 0.36), 45–49years (HR: 0.15, 95% CI: 0.07,0.35) or &gt;=50 years (HR: 0.28, 95% CI: 0.13, 0.63)</p> <p>Compared with MHT non-users, MHT users had a lower risk o breast cancer mortality following hysterectomy at&lt;45years (HR:0.49, 95% CI: 0.32, 0.74) and MHT users had a lower risk of cardio-vascular mortality following hysterectomy at &gt;=50 years (HR: 0.09, 95%CI: 0.02, 0.51)</p>	menopause, surgical menopause or premenopausal hysterectomy is associated with a lower risk of breast cancer mortality and is not consistently associated with the risk of mortality from cardiovascular disease or other causes	
<b>(Lee et al., 2023).</b>	Cohort study	1 159 405 postmenopausal women, (Korean National Health Insurance Service in 2009)			HRs of myocardial infarction (MI), ischemic stroke, and all-cause mortality, according to the history of premature menopause and age at menopause.	The women with premature menopause exhibited increased risks of MI (HR, 1.40 [95% CI, 1.31-1.50]), ischemic stroke (HR, 1.24 [95% CI, 1.17-1.31]), and all-cause mortality (HR, 1.19 [95% CI, 1.14-1.24]) when compared with women with menopause aged ≥50 years. The highest risk was evident with menopause between the ages of 30 and 34 years (HR for MI, 1.52 [95% CI, 1.30-1.78]; HR for ischemic stroke, 1.29 [95% CI, 1.12-1.48]; HR for all-cause mortality, 1.33 [95% CI, 1.20-1.47])	Earlier age at menopause was associated with increased risks for MI, ischemic stroke, and all-cause mortality.	
<b>(Xing et al., 2023)</b>	Follow-Up Study	National Health and Nutrition Examination Survey I Epidemiologi			all-cause mortality and life span	The unadjusted and adjusted HRs of all-cause mortality for women with premature menopause were 1.46 (95% CI: 1.08-1.96) and 1.53 (95% CI: 1.13-2.08), respectively,	POI significantly increased all-cause mortality risk and	



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
		<p>c Follow-up Study</p> <p>Mean age of 1,210 women was 55.4 ± 10.8 years at baseline.</p>				<p>compared to nonpremature menopause. Nonlinear associations were found between age at menopause, reproductive life span, all-cause mortality, and life span. Menopausal age &lt;37.5 years of age or reproductive life span &lt;24 years increased the risk of all-cause mortality. Women with menopausal age &lt;39 years of age or reproductive life span &lt;24 years had a lower mean life span than the overall average of 76 years.</p>	shortened life span in women.	
<b>Interaction of POI with other risk factors</b>								
<b>(Li et al., 2021b).</b>	Cohort study	<p>women age 35–64 years living in two communities of Beijing who were enrolled in the Chinese Multi-provincial Cohort Study in 1992.</p> <p>2104 eligible women</p>			<p>Risk of death of Fatal cardiovascular disease (other outcomes not relevant for life expectancy )</p> <p>Participants were followed until first cardiovascular event, death, or the end of follow-up (2018).</p>	<p>Age at menopause &lt;45 years Death: 10/160 women; HR: 1.32; 0.63-2.76</p> <p>Fatal cardiovascular disease : 3/160 women; HR0.86; 0.24-3.09</p> <p>Compared with women who experienced menopause at age 50–51years, the risk of death was higher in women with menopause at age 45–49years (HR 1.99, 95% CI 1.24–3.21; P=0.005), and the risk of ischemic stroke was higher in women with menopause at age&lt;45years (HR 2.16, 95% CI 1.04–4.51; P=0.04) and at age 45–49years (HR 2.05, 95% CI 1.15–3.63; P=0.01). Women who had menopause before age 50 years and at least one elevated risk factor at baseline had a higher risk of death (HR 11.10, 95% CI 1.51–81.41; P=0.02), CVD (HR 3.98, 95% CI 1.58–10.01; P=0.003), ischemic CVD (HR 4.53, 95% CI 1.63–12.62; P=0.004), coronary heart disease (HR 8.63, 95% CI 1.15–64.50; P=0.04), and stroke (HR 2.92, 95% CI 1.03–8.29; P=0.04) than those with menopause at age 50–51years and optimal levels of all risk factors.</p>	Earlier menopause may predict death and ischemic stroke. Furthermore, there is a combined effect of earlier menopause and elevated risk factors on death and CVD.	
<b>(Zhai et al., 2022).</b>	Cohort study	<p>post menopausal women with natural (n=1038) or surgical (n=628) menopause from the Pittsburgh Lung Screening Study.</p>			all-cause mortality	<p>women early natural menopause had a 40% increased risk of death (P=0.023), which was mainly driven by respiratory diseases (HR 2.32; P&lt;.001).</p>	Early natural menopause was found to be a risk factor for malignant and nonmalignant lung diseases and mortality in middle-aged and older female smokers.	646 (39%) women reported early menopause, including 198 (19.1%) women with natural menopause and 448



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
								(71.3%) women with surgical menopause (P<.001).
<b>Estrogen replacement therapy in POI</b>								
<b>(Rivera et al, 2009a)</b>								See above
<b>(Rocca et al, 2006).</b>	Cohort study	Minnesota cohort  Oophorectomy, BSO 1097, or unilateral 1293. Each subject matched by age to a referent woman from the same population (n=2390)	BSO	no BSO	Mortality all-cause in women after BSO aged <45	Hazard ratio 1.67 [95% CI 1.16-2.40], p=0.006  "This increased mortality was seen mainly in women who had not received oestrogen up to the age of 45 years" (HR 1.93; 95% CI 1.25 to 2.96) compared to women who had received therapy up to age 45 years or longer (HR 1.27; 95% CI 0.67 to 2.39)  No increase after unilateral SO	increased overall mortality was observed mainly in women who had undergone bilateral oophorectomy before age 45 years and had not received estrogen replacement therapy	direct or proxy interviews, medical records in a records-linkage system, and death certificates  Original cohort 1950-1987  analysis 2001-06
<b>(Parker et al, 2013).</b>								See above
<b>(Manson et al, 2019).</b>	RCT	9,939 women aged 50–79 years with prior hysterectomy and known oophorectomy status	BSO + Conjugated equine estrogens (CEE, 0.625 mg/day)  for a median of 7.2 years	placebo	Incidence of coronary heart disease and invasive breast cancer (the trial's two primary endpoints), all-cause mortality, and a "global index" (these endpoints plus stroke, pulmonary embolism, colorectal cancer, and hip fracture) during the intervention phase and 18-year	In age-stratified analyses of women with BSO, younger women (aged 50–59) and those aged 60–69 had treatment effects that were in a non-adverse direction,	The effects of CEE were not significantly different by BSO status in the overall cohort, but some findings varied by age. Among women with prior BSO, CEE led to adverse effects during the treatment period in women aged ≥70, whereas women randomized before age 60 appeared to derive mortality benefit over the long term	



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
					cumulative follow-up			

23

24 *Evidence to recommendations*

QUESTION	WHAT ARE THE CONSEQUENCES OF POI FOR LIFE EXPECTANCY?
RECOMMENDATION	<b>Women with POI should be informed that POI without HT is associated with reduced life expectancy, largely due to cardiovascular disease.</b>
Desirable effects	Both spontaneous and iatrogenic POI are associated with increased risk of premature death. The risk may be worsened by contributory factors such as cardiovascular risk factors or smoking and may be ameliorated by hormone therapy, but the evidence is only observational.
Undesirable effects	Not applicable – information provision
Certainty of evidence	Cohort studies
Values	
Balance of effects	Information provision is recommended
Resource use, equity, acceptability and feasibility	Not applicable – information provision
Subgroup considerations (if applicable)	Not applicable

25

QUESTION	WHAT ARE THE CONSEQUENCES OF POI FOR LIFE EXPECTANCY?
RECOMMENDATION	<b>HT is recommended for women with POI until the usual age of menopause for primary prevention to reduce the risk of morbidity and mortality, whether there are estrogen deficiency symptoms or not.</b>
Desirable effects	Although the studies have important limitations, the evidence is adequate to support a recommendation for hormone therapy. Unfortunately, the duration of treatment is also not well studied. Some authors have suggested treating women up to the usual age of menopause. (Kaunitz <i>et al.</i> , 2021, Rocca and Faubion, 2022). However, some evidence suggests that the longer the replacement therapy is used, the better the outcomes. Therefore, women should be given the opportunity to take hormone therapy long-term, and not only for 10 years after the onset of POI.
Undesirable effects	The adverse effects/risks of HT are considered low
Certainty of evidence	Cohort studies
Values	
Balance of effects	Benefits for mortality vs low adverse effects
Resource use, equity, acceptability and feasibility	Not applicable as HT is also indicated for other sequelae
Subgroup considerations (if applicable)	Not applicable

26

QUESTION	WHAT ARE THE CONSEQUENCES OF POI FOR LIFE EXPECTANCY?
GOOD PRACTICE POINT	<b>The guideline group recommends that women with POI should be encouraged to adopt a healthy lifestyle (including avoiding smoking, having a healthy diet and regular physical activity, and maintaining a healthy weight range) to reduce cardiovascular risk.</b>
Justification	Patients asking whether POI has an impact on their life expectancy can be informed about interventions that help reduce mortality in the general population





28 **V. POI, fertility and pregnancy**

29 **V.1. Fertility and fertility treatments**

30 **KEY QUESTION - WHAT ARE THE CONSEQUENCES OF POI FOR**  
 31 **FERTILITY?**

<b>Population</b>	Patients diagnosed with premature ovarian insufficiency (different etiologies)
<b>Interventions</b>	/
<b>Control</b>	/
<b>Outcomes</b>	Fertility / infertility / subfertility / Conception rate Chance of spontaneous pregnancy Miscarriage Health of child / Birth defects, congenital abnormalities, gestational growth; complications

32

33 **Search strings**

<b>Database</b>	<b>Search String</b>
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (Fertil* OR Fertility OR infertil* OR infertility OR subfertil* OR subfertility OR "Conception rate" OR "spontaneous pregnancy" OR "Fertility"[Mesh] OR "Infertility"[Mesh])
<b>COCHRANE</b>	

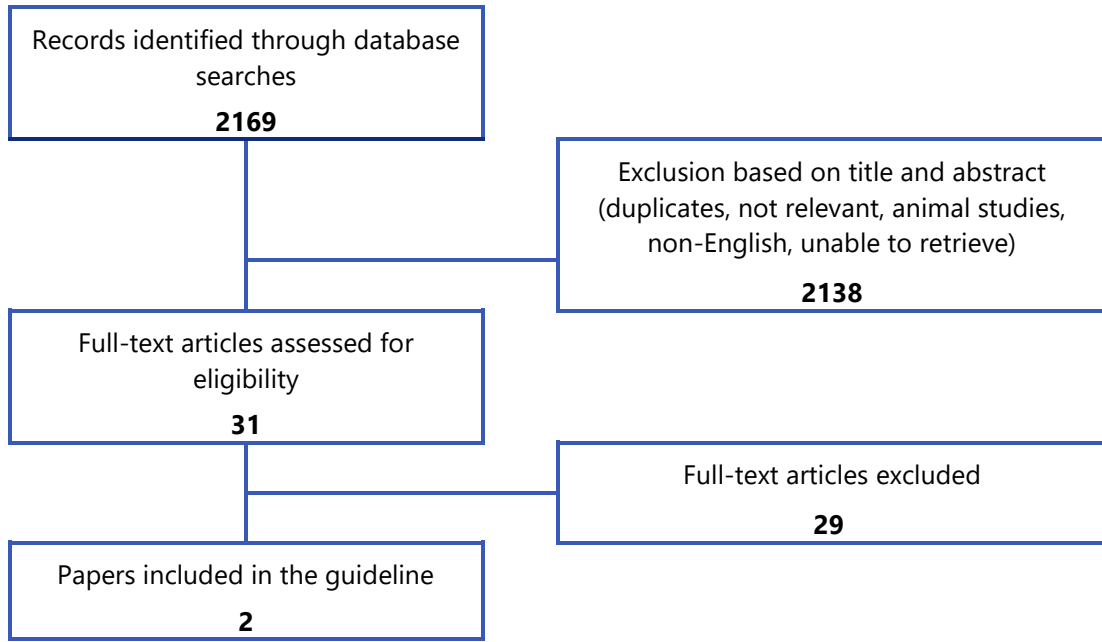
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35 Literature search was limited to the period between 01/01/2014 and 26/01/2024. Studies and data  
 36 published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still  
 37 relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were  
 38 retained.

39



40 **Flowchart**



41

42 **Evidence**

43 *Evidence table*

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Sauer, 1995)</b>	Retropective cohort study	300 consecutive patients undergoing oocyte donation  Grouped per age category: <30 years (n=8); 30-39 years (n=59); 40-49 years (n=107); 50-59 years (n=18).  Grouped per indication: POI (n=44), surgical castration (n=9), genetic disease carrier (n=12), transitional menopause (n=27), natural menopause (n=30), multiple IVF	oocyte donation treatments  oral micronized estradiol and intramuscular progesterone.  Oocytes were donated by fertile young women utilizing OS with menopausal gonadotropins.	NA	Pregnancy rate  Implantation rate  Effect of age  Effect of infertility diagnosis	Outcomes were not different among patients except for women who previously received chemotherapy, where a significantly elevated rate of spontaneous abortion was noted (P<0.05).		



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
		failures (n=62), and postchemotherapy (n=8)						
<b>(van Kastern et al., 1999)</b>	incidence study + pedigree study	63 idiopathic POI patients (secondary, oligo or amenorrhoea ≤ 40 years, with FSH >40U/l on at least 2 occasions, normal karyotyping and no history of radiation exposure or chemotherapy)  pedigree studies were performed on 6 families with at least 2 relatives with POI	Family study / pedigree study	NA	Incidence familial = at least one affected relative	8/63 familial cases (12.7%).	The familial form of idiopathic POI is not as common as has been suggested	
<b>(van Kastern and Schoemaker, 1999)</b>	REVIEW	52 case reports (pregnancy or return of ovulation in POI)  8 observational studies (number of POI patients that had become pregnant)  9 uncontrolled studies reported the number of patients that became pregnant in association with a specific intervention  7 controlled trials			Chance of pregnancy  Change of livebirth	In the observational studies, 4.8% of all women became pregnant, in the uncontrolled studies 18%, and in the controlled studies 1.5%. Overall, 6.3% of all women conceived after diagnosis.  Data on 112 pregnancies were available. 3 pregnancies were terminated on request, 19 miscarriages, 1 stillbirth at term, 1 tubal pregnancy, and 5 ongoing. Thus, 104 pregnancies resulted in the birth of 86 healthy children (three twin pregnancies). We did not find any reports on congenital malformations or chromosomal aberrations such as trisomy 21		



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Bidet et al., 2011).</b>	Cohort study	358 consecutive patients with POI			Resumption of Ovarian Function and Pregnancies Prevalence  Predictors	86 (24%) patients presented features indicating resumption of ovarian function, and in 77 cases (88%) within 1 yr of diagnosis.  21 spontaneous pregnancies in 15 (4.4%) patients (16 births, 5 miscarriages)  familial history, secondary amenorrhea, presence of follicles at US, and inhibin B and estradiol levels  (not predictors; autoimmune disease, AMH level, the presence of follicles on biopsy, and/or genetic abnormalities)	Intermittent ovarian activity in POI patients is not a rare phenomenon. A predictive score may help us to identify POF patients most likely to recover intermittent ovarian function.	
<b>(Bachelot et al., 2017)</b>	Cross-sectional study	507 POI patients were included in the study, with a follow-up of 3,44 ± 4,05 years (0–29). Of these, 117 (23%) had features of ovarian function resumption.			cumulative incidence of pregnancy	3.5% (entire cohort) 15.3% in patients with ovarian function resumption  55 patients (47%) experienced an arrest of their resumption during the follow-up period (risk factors for arrest: high FSH and DHEA, older age at diagnosis)	Resumption of ovarian function is not a rare or brief phenomenon in POI women.	
<b>(Fraisson et al., 2019)</b>	review	pregnancy in patients diagnosed with POI  15 studies included in the review : - 2 RCT - 2 observational studies - 11 interventional studies					Pregnancies and live births are uncommon in patients diagnosed with POI-but are not impossible.	Qualitative analysis



45 *Evidence to recommendations*

QUESTION RECOMMENDATION	What are the consequences of POI for fertility? <b>Women with POI should be informed that POI substantially reduces the chances of natural conception. Women with non-surgical POI should be informed that ovarian activity may occur. This is associated with a chance of natural conception.</b>
Desirable effects	Evidence suggests that women with POI (non-surgical) may experience resumption of ovarian activity (observational data only) and there is a larger chance of pregnancy when there is increased ovarian activity (observational data only)
Undesirable effects	No harms associated with providing information and advise in this context.
Certainty of evidence	Very low (observational data only)
Values	Unclear but, in general, women with POI have a preference for information and guidance
Balance of effects	Strong recommendation in favor of information provision
Resource use, equity, acceptability and feasibility	Not a significant factor to consider.
Subgroup considerations (if applicable)	This recommendation only applies to women with non-surgical POI, as women with surgical POI (after BSO) will have no ovarian activity and no chance of natural conception.

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QUESTION RECOMMENDATION GOOD PRACTICE POINT	What are the consequences of POI for fertility? <b>Women with non-surgical POI should be advised to use contraception if they wish to avoid pregnancy.</b>
Desirable effects	Evidence suggests that women with POI (non-surgical) may experience resumption of ovarian activity (observational data only) and there is a larger chance of pregnancy when there is increased ovarian activity (observational data only)
Undesirable effects	No harms associated with providing information and advise in this context.
Certainty of evidence	Very low (observational data only)
Values	Unclear but, in general, women with POI have a preference for information and guidance
Balance of effects	Strong recommendation in favor of information provision
Resource use, equity, acceptability and feasibility	Not a significant factor to consider.
Subgroup considerations (if applicable)	This recommendation only applies to women with non-surgical POI, as women with surgical POI (after BSO) will have no ovarian activity and no chance of natural conception.

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## PICO QUESTION: WHAT FERTILITY INTERVENTIONS ARE EFFECTIVE?

<b>Population</b>	Patients diagnosed with premature ovarian insufficiency / Patients at risk of POI
<b>Interventions</b>	<ul style="list-style-type: none"> <li>- Egg donation+ IVF</li> <li>- Embryo donation</li> <li>- Ovarian transplantation</li> <li>- Ovulation induction (clomiphene, gonadotrophins, stimulation with recombinant FSH, immunomodulating therapies)</li> <li>- Suppression of gonadotrophins (GnRHa / danazol)</li> <li>- Treatment of coexistent endocrine disease</li> <li>- HRT</li> <li>- Steroids</li> <li>- Glucocorticoids</li> </ul>
	<ul style="list-style-type: none"> <li>- stem cells and biomaterials</li> <li>- Platelet-Rich Plasma</li> <li>- in vitro activation</li> <li>- Ovarian tissue cryo</li> <li>- Ovarian suppression</li> <li>- Oocyte cryopreservation</li> <li>- Embryo cryopreservation</li> </ul>
<b>Control</b>	No intervention
<b>Outcomes</b>	Pregnancy Life birth miscarriage

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### Search strings

Database	Search String
<b>PUBMED 1</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("Oocyte Donation"[Mesh] OR "egg donation" OR "oocyte donation" OR "Ovum Donation" OR "embryo donation" OR "donor embryo" OR "ovarian tissue transplantation" OR "Ovarian transplantation" OR "Ovulation induction" OR "Ovulation Induction"[Mesh] OR clomiphene OR gonadotropins OR "Gonadotropins"[Mesh] OR "ovarian stimulation" OR "recombinant FSH" OR "Follicle Stimulating Hormone"[Mesh] OR "immunomodulating therapies" OR "GnRHa" OR danazol OR HRT OR "hormone therapy" OR "hormone replacement therapy" OR "Hormone Replacement Therapy"[Mesh] OR Steroids OR "Steroids"[Mesh] OR Glucocorticoids OR "Glucocorticoids"[Mesh]) AND ("Live Birth" OR Miscarriage OR pregnancy OR "Pregnancy"[Mesh] OR "Pregnancy Rate"[Mesh] OR "Abortion, Spontaneous"[Mesh])
<b>PUBMED 2</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("Oocyte cryopreservation" OR "Oocyte freezing" OR "Egg cryopreservation" OR "Egg freezing" OR "oocyte banking" OR "Oocyte vitrification" OR "egg vitrification" OR "Embryo cryopreservation" OR "embryo freezing" OR "Embryo slow freezing" OR "Embryo vitrification" OR "Cryopreservation"[Mesh] OR "Cryopreservation" OR "frozen embryo transfer" OR "ovarian tissue cryopreservation" OR ("ovarian tissue" AND "surgery") OR "ovarian tissue transplantation" OR "ovarian tissue freezing" OR "ovarian cortex cryopreservation" OR ("Gonadotropin-Releasing Hormone Agonist" OR "GnRH agonists" OR Triptorelin OR buserelin OR goserelin OR diphereline OR "leuprolide acetate" OR GnRHa) AND ("ovarian suppression" OR "ovarian protection" OR chemotherapy) OR "Platelet-Rich Plasma"[Mesh] OR "Platelet-Rich Plasma" OR "PRP" OR "Platelet Rich Plasma" OR "stem cell" OR "Stem Cell Transplantation"[Mesh] OR "in vitro activation")

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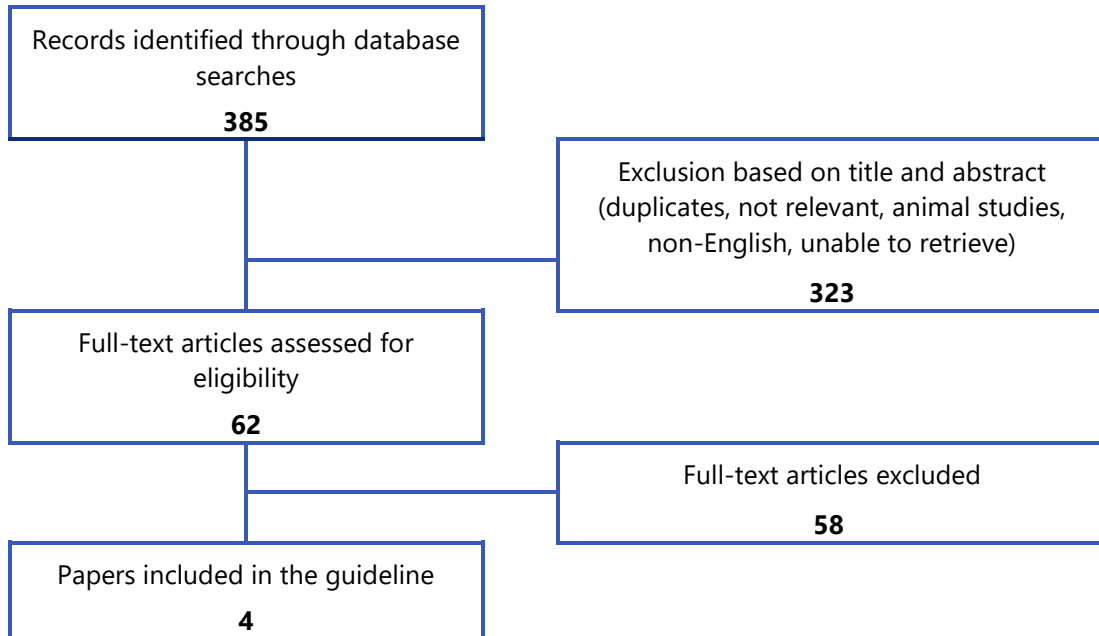
55

Literature search was limited to the period between 01/01/2014 and 26/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



56 For the literature search on the second group of interventions (PUBMED 2 - stem cells and biomaterials,  
 57 Platelet-Rich Plasma, in vitro activation, Ovarian tissue cryo, Ovarian suppression, Oocyte  
 58 cryopreservation, Embryo cryopreservation) no limits were set for the publication date.

59 **Flowchart**



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61 **References included as background information**

62 (Lutjen *et al.*, 1984, Sauer *et al.*, 1994, Templeton *et al.*, 1996, Zhang *et al.*, 2021)

63 **Evidence**

64 *Evidence table*

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
(van Kasteren <i>et al.</i> , 1999)	incidence study + pedigree study	63 idiopathic POI patients (secondary, oligo or amenorrhoea ≤ 40 years, with FSH > 40 U/l on at least 2 occasions, with normal karyotyping and no history of radiation exposure or chemotherapy.  pedigree studies on 6 families with at least 2 relatives with POI	Family study / pedigree study	NA	Incidence familial = at least one affected relative	8/63 familial cases (12.7%).	the familial form of idiopathic POI is not as common as has been suggested	
(Fraison <i>et al.</i> , 2019)	Review	pregnancy in patients diagnosed with POI					Pregnancies and live births are uncommon in patients diagnosed	Qualitative analysis



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
		15 studies included : - 2 RCT - 2 observational studies - 11 interventional studies					with POI-but are not impossible.	
<b>(Tartagni et al., 2007)</b>	RCT	50 POI mean age 32 amenorrhea for 16 months  20 patients also had autoimmune disorders (9 with anti-thyroglobulin antibody, 5 with anti-microsomal antibody, 5 with anti-adrenocortical antibody and 1 with anti-ovarian antibody). Nine patients had a family history of POI.	Oral ethinyl oestradiol for 2 weeks before Stimulation	Placebo	Ovulation  Concentrations of FSH  Pregnancy rate	32% vs 16%  in group one decreased from 68.3 +/- 20.0 IU/l (mean +/- SD) to 15.6 +/- 5.3 IU/l.  16% vs 0%	EE works but need FSH<15IU on EE	Included in review Fraison 2019
<b>(Pellicer et al., 2023)</b>	Review	established and experimental techniques to restore ovarian reproductive function.  Conditions of interest were POI, DOR, poor ovarian response and older age.			TECHNIQUES TO INDUCE OVARIAN RESCUE IN HUMANS:  IVA and ovarian fragmentation: varying degrees of success in women with DOR for POI (Kawamura et al., 2013; Suzuki et al., 2015; Zhai et al., 2016)  The use of stem cells:  umbilical cord-derived MSC (UCMSC) have been shown to increase the ovarian function in 61 young patients (mean age 31, range 39-34 yrs) with POI, after transvaginal intra-ovarian allogenic stem cell infusion of UCMS isolated from donor healthy full-term human placental samples (Yan et al., 2020) - overall PR 6.6% (4/61).  BM-MSC were employed in 30 women with POI who were aged 40 years or less, with one group receiving a direct laparoscopic infusion into the ovarian stroma, and the other group	CLINICAL DATA IN DOR, POI AND OLDER WOMEN  There is a clear demand to preserve fertility and/or to prevent injury in the ovaries. When the damage is irreversible in women with POI or DOR, follicle reactivation shows promising experimental outcomes, but clinical evidence is scarce although increasing.		



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
						<p>undergoing unilateral catheterization of the ovarian artery (Gabr et al., 2016). Overall, hormone improvement was observed in 86.7% of participants from both groups,</p> <p>while 60% showed ovulation at some point during follow-up. Only 10% of women underwent IVF cycles, and one natural conception was achieved. Comparable results were obtained in 10 women (26-33 years old) with POI after BM-MSC injection into both ovaries via laparoscopy (Edessy et al., 2016).</p> <p>Platelet-rich plasma</p> <p>A recent pilot study was performed in 311 women with POI who were less than 40 years age (Cakiroglu et al., 2020). Additional case reports in POI also describe pregnancies (Sfakianoudis et al., 2019) and live births (Hsu et al., 2020) after PRP injection.</p>		
<b>(Rosario and Anderson, 2021)</b>	Review	Novel approaches to fertility restoration in women with premature ovarian insufficiency					Research on improving the fertility of women with POI surrounds the potential value of stem cells, potentially in combination with other poorly defined treatments such as injection of platelet-rich plasma, and in investigating the applicability of in vitro activation protocols, both physical and chemical. While the use of animal models shows some evidence of efficacy, the clinical data on such treatments are largely very preliminary and often from poorly or uncontrolled observations.	Narrative review
<b>(Cakiroglu et al., 2020)</b>	Cohort study	Women (N=311; age 24-40) diagnosed with POI based on ESHRE criteria	intraovarian injection of autologous platelet rich plasma	(none, before and after study)	ovarian reserve AMH/AFC/FSH  IVF outcome parameters	<p>Increased AFC and AMH, serum FSH did not change significantly.</p> <p>23 (7.4%) conceived spontaneously 87 (27.8%) had no antral follicles and no further treatment</p> <p>201 (64.8%) developed antral follicle(s) and attempted IVF: 82 (26.4% of total) developed embryos; 25 of these preferred to cryopreserve, 57 underwent ET resulting</p>	in women with POI, intraovarian injection of autologous PRP might be considered as an alternative experimental treatment option	Included in review (Pellicer et al., 2023)



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
						in 13 pregnancies (22.8% per transfer, 4% of total).  In total, 25/311 (8.0%) achieved livebirth/sustained implantation, another 25 (8.0%) cryopreserved embryos.		
<b>Oocyte donation</b>								
<b>(Oyesanya et al., 2009).</b>	Cohort study	353 consecutive infertile women with premature ovarian failure or diminished ovarian function.	IVF-ET with the use of oocyte sharing (n=220)	IVF-ET with the use of altruistic egg donation (n=133).	CPR Sec outcomes: E2 dosage, endometrial thickness, fertilization, embryo quality, and rates of embryo cleavage, transfer, and implantation, positive b-hCG, and biochemical, ectopic, and multiple pregnancy	No statistically significant difference in clinical pregnancy rates (28.18% vs. 30.08%; OR 0.91 [0.49–1.67]; RR 1.07 [0.69–1.65]; adjusted OR 0.95 [0.51–1.78])	The prognosis with use of shared oocytes is similar to that with altruistic donors.	compares CPR of altruistic egg donation with egg sharing
<b>(Sung et al., 1997).</b>	Cohort study	228 consecutive oocyte recipients (age ≤40y.o. FSH>18mU/ml, failure to respond to OS)	N=66 unrelated donors	N=13 sisters	Cancellation rate PR Nr of eggs retrieved Nr of embryos Abortion rate	Uncancelled group: Group I: N=62; group II: n=9  Group I: PR 35.5% Ab. Rate 22.7% Group II: PR 36.4% Ab Rate 25.0%  Sign higher cancellation rate with sister eggs (4/13 [30.8%] vs 4/66[6.1%])  No sign diff. In eggs retrieved, embryos and pregnancy rate and abortion rate	Egg donation by sister of POI patient: these donors have a significant higher cancellation rate, but if they pursue there are no significant differences in outcome	Important info for sisters of POI patients who may be willing to donate eggs for their sister.
<b>(O'Donnell et al., 2012).</b>	RCT	34 (17 completed) POI range of aetiologies (same study as for blood pressure)	Physiological E/P 12 months, cross-over	Pharmacological E/P	Uterine vol/blood flow/endometrial thickness	Physiological E/P gave slightly thicker endometrium, others not significant	Physiological E/P may be better	Surrogate outcomes
<b>(Critchley et al., 1992).</b>	Observational study	10 patients with POI following abdominal irradiation in childhood  22 POI (no radiation)	abdominal irradiation in childhood	no radiation	Uterine length  Uterine blood flow  Endometrial thickness	Sign less; 4.1 cm (2SE 0.8) vs 7.3 (2SE 0.6)  Not detectable in most irradiated women  No increase in 3/10 women	Uterine musculature and blood flow are irreversibly affected by high dose irradiation in childhood.	



Ref.	Study Type	Patients	Intervention / Control	Diagnostic test	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Larsen et al., 2000),</b>	Case report	3 patients Egg donation after TBI and BMT for malignancy in childhood			Uterine volume / size  Endometrial thickness in treatment cycle  Outcome	reduced in all 3 cases  6-9mm  Case 1 Threatened prem labour at 29/40, GDM at 33/40, LSCS at 37/40 contractions and mild PET Case 2 Vaginal bleeding at 10/40, miscarriage at 17/40 Case 3 One unsuccessful egg donation cycle		Outcome of treatment or pregnancy
<b>(Foudila et al., 1999)</b>	Cohort study	18 women with Turner's syndrome	Oocyte donation (mean of 1.8 embryos per transfer)  28 fresh + 25 frozen ETs		Pregnancy	Clinical pregnancy rate per fresh ET was 46%, and implantation rate 30%, for frozen ET 28 and 19%.  20 clinical pregnancies 40% ended in miscarriage.  All deliveries were c-section	Pregnancy and implantation rates after oocyte donation were high in women with Turner's syndrome, but the risk of cardiovascular and other complications is high. Careful assessment before and during follow-up of pregnancy are important. Transfer of only one embryo at a time to avoid the additional complications caused by twin pregnancy is recommended.	
<b>(Bodri et al., 2006)</b>	Cohort study	21 women with Turner's syndrome  Age: 33.1± 1.8 years	30 Oocyte donation cycles with fresh ET  Median (range) of 2 embryos transferred per cycle (range: 1-4)		clinical outcome and obstetrical complications	17 pregnancies (57%), of which 12 were clinical (40%). The IR and OPR were 22% (15/68) and 30% (9/30), respectively. Premature delivery was observed in 50% (4/8) pregnancies and intrauterine growth retardation in 55.5% (5/9) of the fetuses. Hypertensive disorders occurred in 5/8 pregnancies (3 pre-eclampsias)	Turner's syndrome patients achieve acceptable pregnancy rates after oocyte donation. A high rate of pregnancy-associated hypertensive disorders was observed which have led to a high rate of prematurity and IUGR	
<b>(Alvaro Mercadal et al., 2011),</b>	Cohort study	23 women with Turner's syndrome	49 Oocyte donation cycles, 45 fresh + 10 frozen ETs  Median (range) of 2 embryos transferred per cycle (range: 1-4)		clinical outcome and obstetrical complications	18 pregnancies, 10 deliveries (9 singletons and 1 pair of twins), 3 miscarriages and 5 biochemical pregnancies. The CPR per ET was 24.4% in fresh cycles and 20% in frozen cycles.  Complications of pregnancy occurred in 5 of 10 pregnancies (50%): 3 premature deliveries because of pregnancy-induced hypertensive	Pregnancy rates after oocyte donation in patients with TS are comparable with those previously published. These was a high risk of pregnancy hypertensive disorders and a high risk of low birthweight.	



Ref.	Study Type	Patients	Intervention / Control	Diagnostic test	Outcome measures	Effect size	Authors conclusion	Comments
						disorders. The mean birthweight (g) ( $\pm$ SD) for singletons and twins was $2728 \pm 577$ and $2335 \pm 318$ , resp. Four babies were below the 10th percentile. No cardiac complications in any of the pregnant women.		
(Yaron <i>et al.</i> , 1996).	Cohort study	53 patients with POI undergoing oocyte donation.  7 Turner's syndrome (45,X) - 22 ET cycles, 15 Turner variants (mosaics, deletions, or isochromosomes) - 36 ET cycles  31 POI with normal karyotype) - 69 ET cycles.	127 Oocyte donation ET cycles  All patients were treated with E2 valerate 6 mg/d until oocytes became available; then P 100 mg/d was added. Oocyte donors were healthy women < 34 years who underwent IVF themselves.		CPR  Biochemical pregnancy  early abortions  delivery rates	Turner's syndrome patients vs POI  - significantly higher rate of biochemical pregnancies (22.7% vs 4.3%) - lower CPR (22.7% vs 33.3%) - a significantly higher rate of early abortions (60% vs 8.7%)  significantly lower rate of deliveries per pregnancy (20.0% vs 73.1%)	Patients with a complete or partial deficiency of an X chromosome have reduced PRs and an increase in early implantation failure after oocyte donation.	
(Bryman <i>et al.</i> )	Cohort study	482 Swedish women with Turner syndrome	27 (47%) used their own oocytes (23 spontaneous, 3 IVF, 1 IUI)  30 (53%) oocyte donation		Pregnancy rate and outcomes	Pregnancies occurred in 57 (12%) of 482 women  67 deliveries (68 babies)-liveborn rate of 54%.  Spontaneous pregnancies occurred mainly in women with 45,X/46,XX mosaicism,  miscarriages were less frequent after OD: OR 0.43 (95% CI 0.17-1.04)		

65

66 *Evidence to recommendations*

QUESTION	What fertility interventions are effective?
RECOMMENDATION	<b>Women with POI should be informed that there are no interventions that have been reliably shown to increase ovarian activity and natural conception rates.</b>
Desirable effects	Of all interventions evaluated in women with POI, none have been shown to improve the chances of natural conception. These interventions include administration of estrogens, gonadotrophins or corticosteroids, in vitro activation of follicles, administration of mesenchymal stem cells and injection of platelet rich plasma into the ovary.
Undesirable effects	Interventions may be associated with risks, which are not well documented.
Certainty of evidence	Low (⊕⊕⊕⊕) (observational data only, small studies for most interventions, for others small RCTs are available)
Values	In general, treatments unsupported with any data of efficacy should not be offered
Balance of effects	Strong recommendation in favor of information provision



Resource use, equity, acceptability and feasibility	Not relevant as the recommendation recommends against the interventions.
Subgroup considerations (if applicable)	Not relevant

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QUESTION RECOMMENDATION	What fertility interventions are effective? <b>Women with POI should be informed that oocyte donation is an established option to achieve pregnancy after a diagnosis of POI.</b>
Desirable effects	The efficacy of oocyte donation to achieve a pregnancy/live birth in women with POI is shown in observational studies. Oocyte donation is the only possible treatment option currently available for women with POI to establish pregnancy.
Undesirable effects	There are some obstetrics risks associated with pregnancies after oocyte donation, and there may be additional risks related to the etiology of POI. In addition, when oocytes are donated from family, the genetic contexts may need to be considered.
Certainty of evidence	Low (⊕⊕○○) (observational data only in POI, but indirect evidence of efficacy of oocyte donation pregnancy in general)
Values	
Balance of effects	Given the risks and ethical/psychological complications, a recommendation for oocyte donation in all POI women was not considered appropriate, and it was agreed to merely state that Oocyte donation is an established option for fertility in women with POI.
Resource use, equity, acceptability and feasibility	There are some limitations on the availability of oocytes through oocyte donation in different countries, as well as some restrictions on who can use donated oocytes to achieve pregnancy.
Subgroup considerations (if applicable)	Not relevant

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QUESTION RECOMMENDATION	What fertility interventions are effective? <b>Women with non-iatrogenic POI and considering assisted reproduction using oocytes donated by their sister should be informed that this includes shared genetic risk and carries a higher risk of ovarian stimulation cycle cancellation.</b>
Desirable effects	There are known benefits of oocyte donation by a sister, such as availability of a donor/donor gametes, shorter waiting lists, kinship, costs,...
Undesirable effects	There are some data (small observational study) showing higher cycle cancellation rates in sisters of women with POI when they engage in oocyte donation. Furthermore, there may be (unknown) genetic factors underlying the POI diagnosis, which may be shared between sisters.
Certainty of evidence	Low (⊕⊕○○) (observational data only in POI, but indirect evidence of efficacy of oocyte donation pregnancy in general)
Values	
Balance of effects	It is recommended to inform women considering oocyte donation from sisters allowing them to balance the desirable and undesirable outcomes as part of the decision-making process.
Resource use, equity, acceptability and feasibility	There are some limitations on the availability of oocytes through oocyte donation in different countries, as well as some restrictions on who can use donated oocytes to achieve pregnancy.
Subgroup considerations (if applicable)	Only relevant for women considering oocyte donation from sisters

70



## 71 V.2. Fertility preservation

### 72 PICO QUESTION – ARE THERE TECHNIQUES AVAILABLE FOR FERTILITY 73 PRESERVATION IN WOMEN WITH POI?

74

<b>Population</b>	Patients diagnosed with premature ovarian insufficiency Patients at risk of POI
<b>Interventions</b>	stem cells and biomaterials Platelet-Rich Plasma in vitro activation Ovarian tissue cryo Ovarian suppression Oocyte cryopreservation Embryo cryopreservation
<b>Control</b>	
<b>Outcomes</b>	Fertility Fertility preservation Prevention of POI

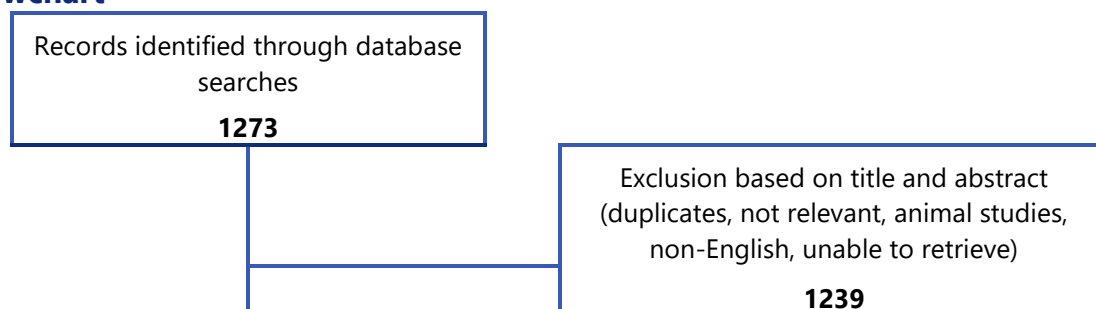
75

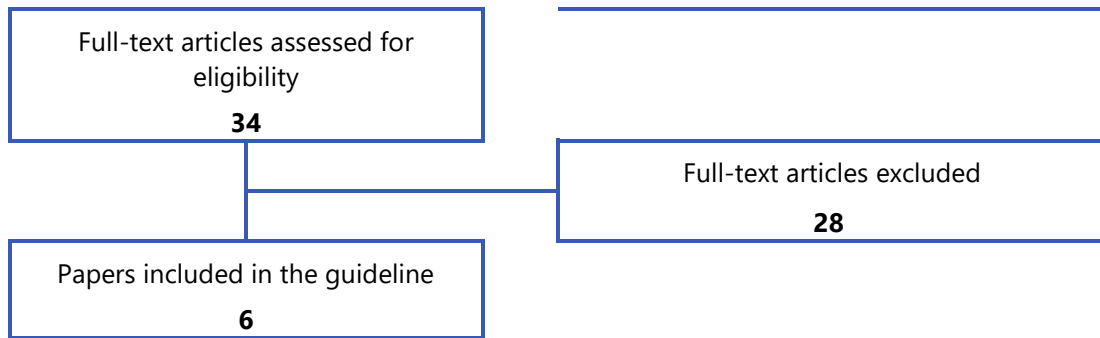
### 76 Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("Oocyte cryopreservation" OR "Oocyte freezing" OR "Egg cryopreservation" OR "Egg freezing" OR "oocyte banking" OR "Oocyte vitrification" OR "egg vitrification" OR "Embryo cryopreservation" OR "embryo freezing" OR "Embryo slow freezing" OR "Embryo vitrification" OR "Cryopreservation"[Mesh] OR "Cryopreservation" OR "frozen embryo transfer" OR "ovarian tissue cryopreservation" OR ("ovarian tissue" AND "surgery") OR "ovarian tissue transplantation" OR "ovarian tissue freezing" OR "ovarian cortex cryopreservation" OR ("Gonadotropin-Releasing Hormone Agonist" OR "GnRH agonists" OR Triptorelin OR buserelin OR goserelin OR diphereline OR "leuprolide acetate" OR GnRHa) AND ("ovarian suppression" OR "ovarian protection" OR chemotherapy)) OR "Platelet-Rich Plasma"[Mesh] OR "Platelet-Rich Plasma" OR "PRP" OR "Platelet Rich Plasma" OR "stem cell" OR "Stem Cell Transplantation"[Mesh] OR "in vitro activation")

77 Literature search was limited to the period between 01/01/2014 and 26/01/2024. Studies and data published prior  
78 to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of  
79 newer data, the studies and data published prior to 01/01/2014 were retained.

### 80 Flowchart





81

82 **Evidence**

83 *Evidence table*

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Lau et al., 2009)</b>	retrospective study	Young TS:  28 complete / partial absence of one X chrom (13 45,X; 9 mosaic karyotypes; 6 karyotypes containing isochromosome or ring X chrom.  6 (21%) spontaneous puberty 14 (14%) identified as potential candidates for FP.	fertility preservation  Criteria for FP: (i) spontaneous menarche; (ii) confirmation by US of the presence of at least one normal ovary;  serum FSH below 40 IU/l.		Feasibility	One patients underwent an ovarian stimulation protocol of GnRH-agonist down-regulation followed by recombinant FSH and HMG stimulation. Two metaphase-II-stage oocytes were aspirated and vitrified.  Another patient conceived spontaneously at the age of 24 years.		
<b>(Balen et al., 2010)</b>	Case report	young woman with mosaic Turner syndrome	fertility preservation + oocyte genetics				This case provides some reassurance for the validity of this approach.	
<b>(Borgstrom et al., 2009)</b>	Case series	57 TS Girls, aged 8–19.8 yr,	ovarian tissue freezing for FP			Ovarian biopsy was feasible in 47 of the 57 girls. In 15 of the 57 girls (26%), there were follicles in the tissue piece analyzed histologically. 6/7 girls (86%) with mosaicism, 6/22 (27%) with structural chromosomal abnormalities, and 3/28 with karyotype 45X (10.7%) had follicles.  8/13 girls (62%) with spontaneous menarche	Signs of spontaneous puberty, mosaicism, and normal hormone concentrations were positive and statistically significant but not exclusive prognostic factors as regards finding follicles	



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
						<p>had follicles, and 11/19 girls (58%) who had signs of spontaneous puberty had follicles.</p> <p>The age group 12–16 yr had the highest proportion of girls with follicles.</p> <p>Normal FSH and AMH for age and pubertal stage were more frequent in girls with follicles</p>		
<b>(Mamsen et al., 2019)</b>	Retrospective case–control study	<p>15 Girls and young women (5–22yrs) with Turner syndrome who underwent ovarian tissue cryopreservation</p> <p>42 controls (1–25yrs) – OTC for cancer</p>			Follicle density (follicles/mm <sup>3</sup> ), morphology, and health	<p>Follicles were found in 60% of the biopsies (9 of 15) from TS ovaries. In 78% of the ovaries (7 of 9) with follicles, the follicle density was within the 95% CI of the control group. There was a high rate of abnormal follicle morphology. Six follicle-specific proteins were expressed similarly in TS and control ovaries. However, apoptosis and zona pellucida protein expression were found to be abnormal in TS. Turner syndrome follicle fluid from small antral follicles had lower concentrations of estrogen and testosterone and higher concentrations of AMH than controls. Thirty-one cumulus oocyte complexes were collected from one patient and cultured for 48 hours in vitro, resulting in five metaphase II oocytes (maturation rate 16%, degeneration rate 19%).</p>	The benefits of OTC may be limited to a highly selected group of TS mosaic patients in whom a sizeable pool of normal follicles is present at OTC.	
<b>(Mamsen et al., 2018)</b>	Case series	6 pre-pubertal girls with galactosemia	cryopreservation of ovarian tissue (OTC)	NA		<p>morphological normal follicles and follicle densities within the 95% CI of controls. No follicles were detected in the ovary from an 11.7-year-old girl with galactosemia. Expression of AMH, GDF-9, BMP-15, and PAPP-A appeared similar in follicles from girls with galactosemia and controls.</p>	Young girls with galactosemia maintain follicles in early childhood and fertility cryopreservation may be considered. The pathophysiology of galactosemia leading to an accelerated follicle loss is unknown and it is currently	



Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
							unknown to what extent transplanted ovarian tissue can sustain fertility in adult life.	
(Grynberg et al., 2020)	Case report	36-year-old amenorrheic patient with autoimmune POI (serum antiperoxidase, anti-21-hydroxylase, and anti-ovary antibodies)  Serum FSH (21.0 and 36.3 mIU/mL) and LH (35.0 and 60.0 mIU/mL) levels taken 4 weeks apart were around the menopausal range  serum AMH was low (0.76 and 0.65 ng/mL), total AFC remained unexpectedly normal (24 and 22).	Two cycles of IVM of immature oocytes aspirated from the remaining antral-stage follicles after HCG priming,  (After unsuccessful ovarian stimulation using recombinant FSH (300 IU/day for 10 days))	NA	Obtention of immature oocyte capable of maturing in vitro in a context of acute ovarian dysfunction	IVM lead to 6 and 10 cumulus-oocyte complexes and 4 and 8 metaphase II oocytes.  After ICSI, 8 cleavage-stage embryos were frozen. When the patient presented in the clinic 1 year later for reutilization of the embryos, thyroid and adrenal functions were controlled with levothyroxine and hydrocortisone. Endometrium was primed with 17β-estradiol (2 mg/day, vaginally) for 14 days. Progesterone (600 mg/day, vaginally) was subsequently combined with E2. Two embryos were thawed and further transferred into the uterus. The patient became pregnant and uneventfully delivered two babyboys at term.	First pregnancy and live birth achieved using IVM for FP in a woman diagnosed with autoimmune POI	

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85 **Evidence to recommendations**

QUESTION RECOMMENDATION + GOOD PRACTICE POINT	WHAT THERAPIES ARE EFFECTIVE FOR FERTILITY PRESERVATION AND /OR PREVENTION OF POI? <b>For iatrogenic causes of POI, fertility preservation can be considered prior to treatment.</b> <b>The guideline group recommends that fertility preservation is discussed with women at risk of POI. In most women with POI, there is no opportunity for fertility preservation as the follicle pool is depleted.</b>
Desirable effects	Data on the effectiveness of fertility preservation interventions are not available in terms of pregnancy. Still, these interventions (oocyte and/or ovarian tissue cryopreservation) are established fertility preservation methods in patients with other indications.
Undesirable effects	Oocyte and/or ovarian tissue cryopreservation are considered to be safe (based on indirect data).
Certainty of evidence	Evidence is largely indirect, as there are data from studies in POI.
Values	Strong emphasis was put on providing individual and appropriate information on the relevance and usefulness of fertility preservation.



Balance of effects	Strong recommendation to discuss the option of fertility preservation in women at risk of POI and strong recommendation against offering it to women with established POI.
Resource use, equity, acceptability and feasibility	There may be some issues with access to fertility preservation counselling and treatments. Moreover, offering ovarian tissue cryopreservation may not be feasible in all centres.
Subgroup considerations (if applicable)	There is a difference in efficacy in women at risk of POI and women with established POI, with a possible (theoretical) benefit for the former and no benefit for the latter. These subgroups were separately mentioned in the recommendation.

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89 **V.3. Pregnancy**

90 **KEY QUESTION: WHAT ARE THE OBSTETRIC RISKS ASSOCIATED WITH**  
 91 **POI?**

<b>Population</b>	POI Pregnant Specifically for egg donation – spontaneous pregnancy
<b>Interventions</b>	
<b>Control</b>	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Complications, risks</li> <li>• Still birth</li> <li>• Gestational growth</li> <li>• Pre-eclampsia</li> <li>• Consequences for underlying autoimmune diseases</li> <li>• Multifetal pregnancy</li> <li>• OHSS</li> <li>• Fetal morbidity</li> <li>• Maternal morbidity</li> <li>• aortic rupture during pregnancy</li> <li>• transmitting the premutation and of transmission of the full mutation</li> </ul> <p>cervical incompetence, placenta praevia, placenta accreted, placenta recreted, down syndrome, aneuploidy, gestational diabetes, congenital fetal abnormalities, uterine rupture, postpartum hemorrhage, late miscarriage, mid trimester loss, high risk pregnancy</p>

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93 **Search strings**

<b>Database</b>	<b>Search String</b>
<b>PUBMED</b>	(("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (pregnant OR pregnancy) NOT ("egg donation" OR "oocyte donation" OR "Oocyte Donation"[Mesh]) AND (Complication OR risk OR "Still birth" OR stillbirth OR "Stillbirth"[Mesh] OR "Gestational growth" OR "Fetal Growth Retardation"[Mesh] OR Pre-eclampsia OR "Pre-Eclampsia"[Mesh] OR eclampsia OR "Eclampsia"[Mesh] OR "autoimmune" OR "Multifetal pregnancy" OR "Pregnancy, Multiple"[Mesh] OR OHSS OR "Ovarian hyperstimulation syndrome" OR "Ovarian Hyperstimulation Syndrome"[Mesh] OR "morbidity" OR "aortic rupture" OR "cervical incompetence" OR "placenta praevia" OR "Placenta Previa"[Mesh] OR "placenta accreted" OR "Placenta Accreta"[Mesh] OR "placenta recreted" OR "down syndrome" OR aneuploidy OR "Aneuploidy"[Mesh] OR "gestational diabetes" OR "Diabetes, Gestational"[Mesh] OR "fetal abnormalities" OR "uterine rupture" OR "Uterine Rupture"[Mesh] OR "postpartum hemorrhage" OR "Postpartum Hemorrhage"[Mesh] OR "late miscarriage" OR "Abortion, Spontaneous"[Mesh] OR "mid trimester loss" OR "high risk pregnancy" OR "Pregnancy, High-Risk"[Mesh] OR "Pregnancy Complications"[Mesh] OR "Obstetric Labor Complications"[Mesh])) OR (("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (pregnant OR pregnancy) AND ("egg donation" OR "oocyte donation" OR "Oocyte Donation"[Mesh]) AND (Complication OR risk OR "Still birth" OR stillbirth OR "Stillbirth"[Mesh] OR "Gestational growth" OR "Fetal Growth Retardation"[Mesh] OR Pre-eclampsia OR "Pre-Eclampsia"[Mesh] OR eclampsia OR "Eclampsia"[Mesh] OR "autoimmune" OR "Multifetal pregnancy" OR "Pregnancy, Multiple"[Mesh] OR OHSS OR "Ovarian hyperstimulation syndrome" OR "Ovarian Hyperstimulation Syndrome"[Mesh] OR "morbidity" OR "aortic rupture" OR "cervical incompetence" OR "placenta praevia" OR "Placenta Previa"[Mesh] OR "placenta accreted" OR "Placenta Accreta"[Mesh] OR "placenta recreted" OR "down syndrome" OR aneuploidy OR "Aneuploidy"[Mesh] OR "gestational diabetes" OR "Diabetes,

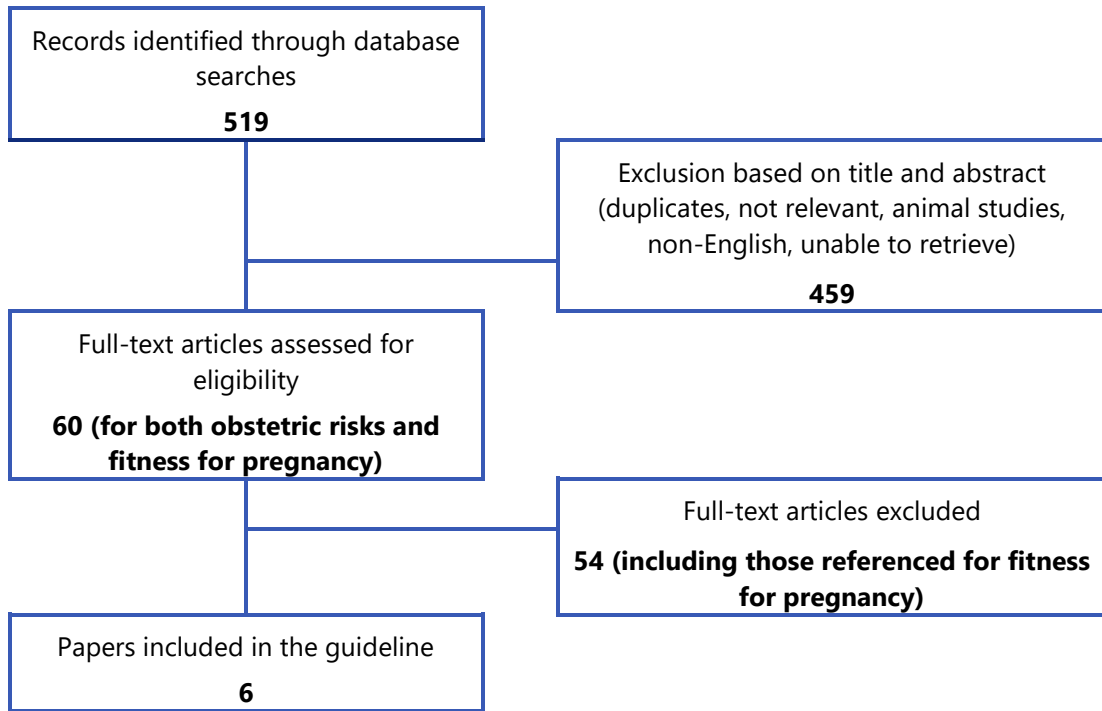


Gestational"[Mesh] OR "fetal abnormalities" OR "uterine rupture" OR "Uterine Rupture"[Mesh] OR "postpartum hemorrhage" OR "Postpartum Hemorrhage"[Mesh] OR "late miscarriage" OR "Abortion, Spontaneous"[Mesh] OR "mid trimester loss" OR "high risk pregnancy" OR "Pregnancy, High-Risk"[Mesh] OR "Pregnancy Complications"[Mesh] OR "Obstetric Labor Complications"[Mesh])

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95 Literature search was limited to the period between 01/04/2014 and 26/01/2024. Studies and data  
 96 published prior to 01/04/2014 were assessed in the development of the POI Guideline 2015. Where still  
 97 relevant, and in absence of newer data, the studies and data published prior to 01/04/2014 were  
 98 retained.

99 **Flowchart**



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101 **Evidence**

102 *Evidence table*

Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>After idiopathic POI</b>								
(van Kastere n and Schoemaker, 1999)	REVIEW	52 case reports (pregnancy or return of ovulation in POI)  8 observational studies (number of POI patients that had			Chance of pregnancy  Change of livebirth	In the observational studies, 4.8% of all women became pregnant, in the uncontrolled studies 18%, and in the controlled studies 1.5%. Overall, 6.3% of all women conceived after diagnosis.		



Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
		become pregnant)  9 uncontrolled studies reported the number of patients that became pregnant in association with a specific intervention  7 controlled trials				Data on 112 pregnancies were available. 3 pregnancies were terminated on request, 19 miscarriages, 1 stillbirth at term, 1 tubal pregnancy, and 5 ongoing. Thus, 104 pregnancies resulted in the birth of 86 healthy children (three twin pregnancies). We did not find any reports on congenital malformations or chromosomal aberrations such as trisomy 21		
<b>(Weghofer et al., 2007)</b>	Retrospective, case-control study	20 women with prematurely declining ovarian function (not POI) and 20 age-matched controls (women with age-appropriate ovarian function)	IVF cycles and PGT (FISH for Chr X,Y, 13, 16, 18, 21, 22)		mean number of oocytes  embryonic aneuploidy rates  pregnancies (per ET)  miscarriages	Lower in PDOF (ns) (10.0 ± 0.4 vs 13.0 ± 7.1)  258 embryos; PDOF 52.6%, Controls: 52.2%  43% vs 47%  50% vs 13%	PDOF is not characterized by an increased aneuploidy rate	
<b>After cancer treatment</b>								
<b>See ESHRE Guideline on Female Fertility Preservation (Anderson et al., 2020).</b>								
<b>For oocyte donated pregnancies</b>								
<b>(Storgard et al., 2017)</b>	Systematic review	women who conceived after oocyte donation  included studies; 22 cohort studies, including 4 national cohort register studies, and 13 ASRM/SART annual reports	oocyte donation	Natural conception or IVF	adjusted OR (AOR)  hypertensive disorders of pregnancy,  pre-eclampsia  gestational diabetes  cesarean section  postpartum hemorrhage	OD vs IVF (singleton)  2.30 (95% CI, 1.60–3.32) (5 studies)  2.11 (95% CI, 1.42–3.15) (n=6)  1.33 (95% CI, 0.71–2.50) (n=7)  2.20 (95% CI, 1.85–2.60)  2.40 (95% CI, 1.49–3.88) (n=3)	- higher risk of HDP in singleton/ multiple OD vs IVF (GRADE+++) - Higher risk of PE in singleton/ multiple OD vs in IVF and SC (GRADE+++) - No higher risk of gestational diabetes in OD (GRADE++) - Higher risk of CS in singleton OD vs singleton	



Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
					preterm birth  low birth weight  small for gestational age	1.75 (95% CI, 1.39–2.20)  1.53 (95% CI, 1.16–2.01) (n=3)  1.14 (95% CI, 0.83–1.56) (n=4)	IVF and SC (GRADE+++)  - Higher risk of postpartum haemorrhage in OD singleton vs IVF singleton (GRADE++)  - higher risk of PTB in singleton OD vs singleton IVF and SC (GRADE+++)  - higher risk of LBW in singleton OD vs IVF and SC (GRADE+++)  No higher risk of SGA (GRADE+++)	
<b>(Keukens et al., 2022)</b>	Systematic review	pregnancies resulting from oocyte donation, natural conception or IVF  literature search was performed using PubMed, EMBASE and CINAHL, OpenGrey and GreyNet from January 1980 through July 2020  7089 OD, 1139 540 NC and 72 742 IVF pregnancies			Pre-eclampsia (prevalence) (%; 95% CI)  Severe PE:  OD vs NC:  OD vs IVF	OD: 15.7 (11.3–20.6) NC: 3.1 (2.1–4.2) IVF: 5.3 (4.0–6.8)  OD: 5.7 (3.3–8.6) NC: 0.5 (0.4–0.6) IVF: 1.5 (0.3–3.2)  OR 5.09 (95% 4.29-6.04)  OR 2.97 (95% 2.49-3.53)	prevalence of PE after OD  4–5 times higher than after NC  - 2–3 times higher than after IVF	
<b>(Conrad et al., 2022).</b>	Clinical opinion				Preeclampsia risk	O CL vs 1 CL: AOR: 2.73 (1.14-6.49)  Programmed FET vs modified FET-NC: 3.55 (1.20-11.94)	Preeclampsia risk is higher in women who conceived using autologous frozen embryo transfer in a programmed or artificial cycle (absent corpus luteum) than in those who	



Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
							conceived using autologous frozen embryo transfer in - natural cycle (1 corpus luteum)	
<b>{Bowman, 1994 #916}</b>	Review / letter	Oocytes of older women	Oocytes from women ≥35 years	Oocytes from women <35 years	Aneuploidy rates	Aneuploidy rates in oocytes that failed to fertilize were higher in women ≥35 years vs younger women in 2 studies, but not in 3 other studies  No difference in AR in oocytes from stimulated vs natural cycles (1 study)	-	
<b>{Donnefeld, 2002 #927}</b>	Cohort study	93 oocyte donation pregnancies  Mean ages oocyte donors: 27 years (range 20-38.5 years) recipients 43.6 years (range, 25.9-54.3 years)			Aneuploidy risk – age of donor/ recipient	When the age of the donor was used in the determination of aneuploidy risk, there were 9 screen-positive pregnancies (9.7%).  When the age of the ovum recipient was used, there were 76 screen-positive pregnancies (82%), including 9 pregnancies with risks of ≥1 in 10	- the use of the age of the ovum donor in aneuploidy risk calculations significantly reduced the false-positive rate (9.7% vs 82%), produced much more favorable odds of being affected given a positive result (1/9 vs 1/76), and did not affect the detection rate for prenatal diagnosis of aneuploidy.	
<b>In women with Turner Syndrome (TS)</b>								
<b>{Hadnott et al., 2011}.</b>	case series	276 adults with cytogenetically-proven Turner syndrome	Pregnancies  7 spontaneous pregnancies in 5 women  6 ART (OD) pregnancies in 5 women  => 13 pregnancies		fetal and maternal outcomes: Menstrual and obstetric histories, 50-cell karyotypes, and cardiovascular evaluation including aortic diameter	14 live births 1 cerebral palsy – 13 chromosomally and developmentally normal.  Caesarean section in 4/7 spontaneous and 6/6 ART pregnancies.	2% of the cohort experienced spontaneous pregnancies despite high grade X monosomy  - The potential for life-threatening cardiovascular complication	Included in Karnis 2012  Included in Bondy 2014



Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
					measurements.	1 pre-eclampsia in an ART-related twin pregnancy requiring preterm delivery; she has marked but stable aortic dilation years later.	s warrants comprehensive screening prior to conception, single ET, and caution regarding unintentional pregnancies for TS women.	
<b>(Bryman et al., 2011).</b>	Cohort study	482 Swedish women with Turner syndrome	27 (47%) used their own oocytes (23 spontaneous, 3 IVF, 1 IUI)  30 (53%) oocyte donation		Pregnancy rate and outcomes  Miscarriage rate	Pregnancies occurred in 57 (12%) of 482 women  67 deliveries (68 babies)- liveborn rate of 54%.  Spontaneous pregnancies occurred mainly in women with 45,X/46,XX mosaicism  lower among women with TS with oocyte donation, 26%, versus spontaneous/IVF/IUI with own oocytes 45%  OR 0.43 (95% CI 0.17-1.04)	-	Included in Karnis 2012
<b>(Bernard et al., 2016)</b>	Cohort study	480 women with Turner syndrome	27 women (5.6%) had a total of 52 spontaneous pregnancies (SP) with 30 full-term deliveries for 18 women.		predictive factors for SP  Outcomes:	spontaneous menarche and mosaic karyotype  16 pregnancies; <ul style="list-style-type: none"> <li>• 30.8% miscarriage: (15% in the general population)</li> <li>• 2 legal abortion</li> <li>• 3 medical interruption</li> <li>• 1 intrauterine fetal death</li> <li>• 30 delivery at term</li> </ul> C-section; 46.7% versus 21% (P<0.001)  Hypertensive disorders: 4(13.3%), incl 2 PE	-	



Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments																																																																																																																																		
						No aortic root dilatation or aortic dissection																																																																																																																																				
<b>(Birkebaek et al., 2002)</b>	Cohort study	410 women with Turner syndrome			Fertility and pregnancy outcome	<p>33 women, one with 45,X, 27 with mosaicism and 5 with 46,XX and a structural abnormality of the second X, gave birth to 64 children. (1 autologous IVF, 1 OD)</p> <p>6/25 examined children, including 3 siblings, had chromosomal aberrations. No case of Down's syndrome, 2 children malformations.</p>	- Fertility in women registered with TS is higher than earlier reported. However, only women with 45,X/46,XX mosaicism or 46,XX and structural abnormality of the second X, gave birth to live children after spontaneous pregnancies.	Included in Karnis 2012																																																																																																																																		
<b>(Kalra et al., 2019)</b>	Review	women with Turner syndrome	AMH			It has been proposed that assessment of ovarian reserve in the mosaic group is appropriate, followed by appropriate counseling and pursuit of either ovarian tissue freezing or oocyte cryopreservation. It has been recommended that pre-pubescent girls with Turner syndrome have their serum AMH levels assessed. If within the normal range, it should be repeated, with ovarian tissue cryopreservation considered if there is a consecutive drop in the AMH.	-																																																																																																																																			
<b>{Karnis , 2012 #957}</b>	Review	Women with Turner syndrome			Prevalence of pregnancy complications	<p>Own oocyte pregnancies:</p> <table border="1"> <thead> <tr> <th></th> <th>Number</th> <th>Mean (SD)</th> <th>Median (IQR)</th> <th>Range</th> </tr> </thead> <tbody> <tr> <td>No. of women with Turner syndrome who conceived</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> <tr> <td>No. of pregnancies</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> <tr> <td>No. of live births</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> <tr> <td>No. of miscarriages</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of stillbirths</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of abortions</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of pregnancies lost</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of pregnancies completed</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> <tr> <td>No. of women with Turner syndrome who conceived</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> <tr> <td>No. of pregnancies</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> <tr> <td>No. of live births</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> <tr> <td>No. of miscarriages</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of stillbirths</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of abortions</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of pregnancies lost</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of pregnancies completed</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> </tbody> </table> <p>OD pregnancies:</p> <table border="1"> <thead> <tr> <th></th> <th>Number</th> <th>Mean (SD)</th> <th>Median (IQR)</th> <th>Range</th> </tr> </thead> <tbody> <tr> <td>No. of women with Turner syndrome who conceived</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> <tr> <td>No. of pregnancies</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> <tr> <td>No. of live births</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> <tr> <td>No. of miscarriages</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of stillbirths</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of abortions</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of pregnancies lost</td> <td>0</td> <td>0.0 (0.0)</td> <td>0.0 (0.0-0.0)</td> <td>0-0</td> </tr> <tr> <td>No. of pregnancies completed</td> <td>18</td> <td>30.0 (10.0)</td> <td>28.0 (20.0-36.0)</td> <td>18-48</td> </tr> </tbody> </table>		Number	Mean (SD)	Median (IQR)	Range	No. of women with Turner syndrome who conceived	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	No. of pregnancies	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	No. of live births	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	No. of miscarriages	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of stillbirths	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of abortions	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of pregnancies lost	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of pregnancies completed	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	No. of women with Turner syndrome who conceived	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	No. of pregnancies	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	No. of live births	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	No. of miscarriages	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of stillbirths	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of abortions	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of pregnancies lost	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of pregnancies completed	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48		Number	Mean (SD)	Median (IQR)	Range	No. of women with Turner syndrome who conceived	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	No. of pregnancies	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	No. of live births	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	No. of miscarriages	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of stillbirths	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of abortions	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of pregnancies lost	0	0.0 (0.0)	0.0 (0.0-0.0)	0-0	No. of pregnancies completed	18	30.0 (10.0)	28.0 (20.0-36.0)	18-48	-	
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Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
						birth defect or serious neonatal illness • Own oocyte: 5/44 (11%) OD: 8/118 (7%)		
<b>(Bondy , 2014).</b>	Narrative review	Women with Turner syndrome	Pregnancy + OD		Aortic dissection / Death	 	-	
<b>(Hynes et al., 2020).</b>	Systematic review	Women with Turner syndrome  5 case reports, 2 case series, and 4 retrospective cohort studies			Aortic dissection / Death	14 total reported cases of aortic dissection associated with pregnancy in women with TS.  10 occurred during pregnancy or in the first month postpartum, 3 up to 17 years postpartum, and 1 unspecified time postpartum.  9 deaths occurred.  Majority resulted from oocyte donation, 2 of multiple gestations.  2 women had a documented history of hypertension, and 3 pregnancies were complicated by preeclampsia.  Bicuspid aortic valve and coarctation of the aorta were the most common associated cardiac anomalies. More than half of women had some degree of aortic dilatation. Two women had no identifiable risk factors.	Women with TS who desire pregnancy must be thoroughly counseled regarding the increased risk of aortic dissection during pregnancy and postpartum.  - If women with TS choose to pursue pregnancy, they require rigorous cardiac monitoring each trimester during pregnancy and postpartum.	
<b>(Hagman et al., 2013).</b>	cohort study	106 TS women in 3 Nordic countries (1992-2011)	oocyte donation pregnancies SET in 70.3% MBR: 7.4%		Maternal complications:	122 pregnancies  35%, of which 20.5% (17/117) PE		Included in Bondy 2014 and Hynes 2020



Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
		<p>karyotype was 45,X in 44% of the women</p> <p>10 women (9.4%) had a known cardiac defect before pregnancy.</p>			<p>Hypertensive disorders</p> <p>Cardiovascular complications</p> <p>Placental complications</p> <p>Neonatal complications</p>	<p>2/117 (1.7%), incl 1 aortic dissection and 1 heart regurgitation and left ventricular dilatation</p> <p>5/118 (4.2%); placenta previa (n=2), placenta accreta (n=2) placental abruption (n=1)</p> <p>There were no maternal mortalities.</p> <p>preterm birth rate : 12.3%</p> <p>low birth weight: 17.6%. Perinatal mortality: 2.3%</p> <p>Birth defects: 6.1% incl 5 major defects (3.8%)</p>		
<b>(Shea and Wolfman, 2017)</b>	case report	previously well 32-year-old patient with an 46 X, i(Xq) karyotype	Pregnancy after oocyte donation			severe postpartum depression with psychotic features in a patient with Turner syndrome, which presented at 4 weeks after the birth of her first child via egg donation		

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## Evidence to recommendations

QUESTION	What are the obstetric risks associated with POI?
RECOMMENDATION	<b>Women should be reassured that natural pregnancies after idiopathic POI or most forms of chemotherapy do not show any higher obstetric or neonatal risk than in the general population.</b>
Desirable effects	
Undesirable effects	
Certainty of evidence	Moderate – significant available evidence
Values	
Balance of effects	Strong recommendation in favor of information provision
Resource use, equity, acceptability and feasibility	
Subgroup considerations (if applicable)	Not relevant



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QUESTION	What are the obstetric risks associated with POI?
RECOMMENDATION	<b>Oocyte donation pregnancies are high risk and should be managed in an appropriate obstetric unit. Women and their partners should be encouraged to disclose the origin of their pregnancy to their obstetric team.</b>
Desirable effects	Oocyte donation is a valid option to achieve pregnancy in women with POI (see above)
Undesirable effects	Oocyte donation pregnancies have been shown to be associated with specific pregnancy complications, such as Preeclampsia and preterm birth (Storgaard <i>et al.</i> , 2017) (Keukens <i>et al.</i> , 2022)
Certainty of evidence	Low to moderate (cfr Storgaard 2017)
Values	Oocyte donation can be applied, but specific obstetric care is recommended to monitor patients and prevent complications
Balance of effects	Strong recommendation for specific care to monitor and prevent complications
Resource use, equity, acceptability and feasibility	Additional resources will be needed.
Subgroup considerations (if applicable)	Not relevant

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QUESTION	What are the obstetric risks associated with POI?
RECOMMENDATION	<b>Pregnancies occurring after radiation to the uterus are at high risk of obstetric complications and should be managed in an appropriate obstetric unit.</b>
Desirable effects	
Undesirable effects	Pregnancies in women who have received radiation to the uterus are at high risk of obstetric complications
Certainty of evidence	Low – only observational data
Values	
Balance of effects	Strong recommendation for specific care to monitor and prevent complications
Resource use, equity, acceptability and feasibility	Additional resources will be needed.
Subgroup considerations (if applicable)	Not relevant

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QUESTION	What are the obstetric risks associated with POI?
RECOMMENDATION	<b>Pregnancies in women with Turner Syndrome are at high risk of obstetric and non-obstetric complications and should be managed in an appropriate obstetric unit with cardiologist involvement.</b>
Desirable effects	
Undesirable effects	Pregnancies in TS women are at high risk of obstetric complications, including aortic dissection which is life-threatening
Certainty of evidence	Low – only observational data, consistent evidence for complications
Values	
Balance of effects	Strong recommendation for specific care to monitor and prevent complications



Resource use, equity, acceptability and feasibility	Additional resources will be needed.
Subgroup considerations (if applicable)	Not relevant

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112 **SUMMARY TABLE THE PREVALENCE OF COMPLICATIONS IN PREGNANCIES IN WOMEN WITH TURNER SYNDROME-**  
 113 **A PREGNANCIES WITH OWN OOCYTES**  
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	Pregnancies with own oocytes			
	(Hadnott <i>et al.</i> , 2011)	(Bryman <i>et al.</i> , 2011).	(Bernard <i>et al.</i> , 2016)	(Birkebaek <i>et al.</i> , 2002)
Women with TS (N)-	5	27	27	33 <sup>3</sup>
Unassisted / IVF / IUI	5 / 0	23 / 3 / 1	27	32 / 1
Nr of Pregnancies	7	82	52	61
Deliveries (children)	7 (7)	36 (37)	30 (30)	61 (64)
<b>Pregnancy complications</b>				
Multiple pregnancy	0/7	1/82	0/52	
Miscarriage		37/82 (45)	16/52 (30.8)	
Legal abortion / Medical interruption		8/82 (10)	5/52 (9.6)	
Extrauterine pregnancy		1/82 (1.2)		
Intrauterine foetal death			1/52 (1.9)	
Stillbirth				
<b>Maternal complications</b>				
Aortic dissection	0	1	0/30	
Other cardiovascular complications				
⇒ Maternal death		0		
Pregnancy-associated hypertensive disorders (PAHD)	0		4/30 (13.3)	
Pre-eclampsia	0		2/30 (6.7) (included in PAHD)	
Gestational diabetes	0		1/30 (3.3)	
Intrahepatic cholestasis of pregnancy			1/30 (3.3)	
C-section	4/7 (57.1)	17/27 (63)	14/30 (46.7)	
<b>Neonatal complications</b>				
Placental complications				
Perinatal mortality				
Preterm delivery (<37wks)	0			
Low birth weight (<2500g)	0			
Chromosomal anomalies				
Birth defects	1/7 <sup>4</sup>	4 <sup>5</sup>	0	
Abnormal Karyotype			2 TS /11 girls tested	6 /25 tested <sup>6</sup>
Other adverse neonatal outcomes				0

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<sup>3</sup> This includes 1 patient pregnant after Oocyte donation for which the results/data could not be excluded.

<sup>4</sup> cerebral palsy

<sup>5</sup> five (7%) had a birth defect or a serious illness. These were cerebral paresis (n=1), neuropsychological disorder (n=1), coarctation of the aorta (n=1), cleft lip and palate (n=1), and congenital tumour (n=1). Four of these five children were born after spontaneous pregnancies.

<sup>6</sup> Two children had karyotype of 46,Xdel(X)(p22.1)mat, and one child a karyotype of 47XX,del(X)(p22.1)mat. All three were siblings. One child with congenital hydrocephalus had the karyotype 46,Xdel(X)(p21.2)mat. One child with ambiguous genitalia had the karyotype 45,X/ 46,XY, and one child had a normal variant.



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**SUMMARY TABLE THE PREVALENCE OF COMPLICATIONS IN PREGNANCIES IN WOMEN WITH TURNER SYNDROME- B PREGNANCIES WITH DONATED OOCYTES**

	Pregnancies with donated oocytes					
	(Hadnott <i>et al.</i> , 2011)	(Bryman <i>et al.</i> , 2011).	{Chevalier, 2011 #2419}	(Foudila <i>et al.</i> , 1999)	(Bodri <i>et al.</i> , 2006)	(Hagman <i>et al.</i> , 2013)
Women with TS (N)	5	30		18	21	106
Unassisted / IVF / IUI						
Nr of Pregnancies	6	42	82	20	17	
Deliveries (children)	6 (7)	31 (31)	71	11 (12) (1 ongoing)	7 (8) (1 ongoing)	122 (131)
<b>Pregnancy complications</b>						
Multiple pregnancy	1/6	0/42		1/20		13/122
Miscarriage		11/42 (26)		8/20 (40)	8/17 (47)	
Legal abortion / Medical interruption		0				
Extrauterine pregnancy		0				
Intrauterine foetal death					1/17 (5.6)	
Stillbirth						1/131 (0.8)
<b>Maternal complications</b>						
Aortic dissection	0		2/93 (2.2)			1/117 (0.8)
Other cardiovascular complications						1/117 (0.8) <sup>7</sup>
⇒ Maternal death			2			0
Pregnancy-associated hypertensive disorders (PAHD)	0		31/82 (37.8)	6/18 (33)	5/8 (62.5)	17/117 (14.5)
Pre-eclampsia	1 (twin pregnancy)		17/82 (20.7) (included in PAHD)	2/18 (11) (included in PAHD)	3/8 (37.5) (included in PAHD)	24/117 (20.5)
Gestational diabetes	0/6		3/82 (3.6)			11/117 (9.4)
Intrahepatic cholestasis of pregnancy			1/82 (1.2)			8/117 (6.8)
C-section	6/6 (100)	24/30 (80)	58/71 (81.7)	11/11 (100)	7/7 (100)	100/122 (82.0)
<b>Neonatal complications</b>						
Placental complications				1/11 (twin)		5/118 (4.2)
Perinatal mortality						3/131 (2.3)
Preterm delivery (<37wks)	2		28/73 (38.3) <sup>8</sup>		4/8 (50)	15/122 (12.3)
Low birth weight (<2500g)	4/7					23/131 (17.6)
Chromosomal anomalies	0					
Birth defects		1				8/131 (6.1%) <sup>9</sup>
Abnormal Karyotype						
Other adverse neonatal outcomes			7/87			

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<sup>7</sup> heart regurgitation and left ventricular dilatation.

<sup>8</sup> ≤35 wg

<sup>9</sup> Of which 5/131 (3.8) were considered serious birth defects



## KEY QUESTION: HOW SHOULD FITNESS FOR PREGNANCY BE ASSESSED IN WOMEN WITH POI?

<b>Population</b>	POI Seperate searches for Turner and chemotherapy
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• Echocardiogram</li> <li>• Counseling: transmitting the premutation and of transmission of the full mutation</li> <li>• preimplantation genetic testing for the FMR1 premutation</li> <li>• cardiac tests (MRI)</li> <li>• uterine assessment (endometrium development, uterine abnormalities)</li> <li>• uterine artery Doppler</li> <li>• pre-pregnancy/pre-conception screening</li> </ul>
<b>Control</b>	
<b>Outcomes</b>	fitness for pregnancy prevention complication intra-uterine growth restriction retardation/ IUGR / small for dates pregnancy induced hypertension / PIH/ hypertension and pregnancy preeclampsia/ PET /preeclamptic toxemia aortic root dissection and pregnancy

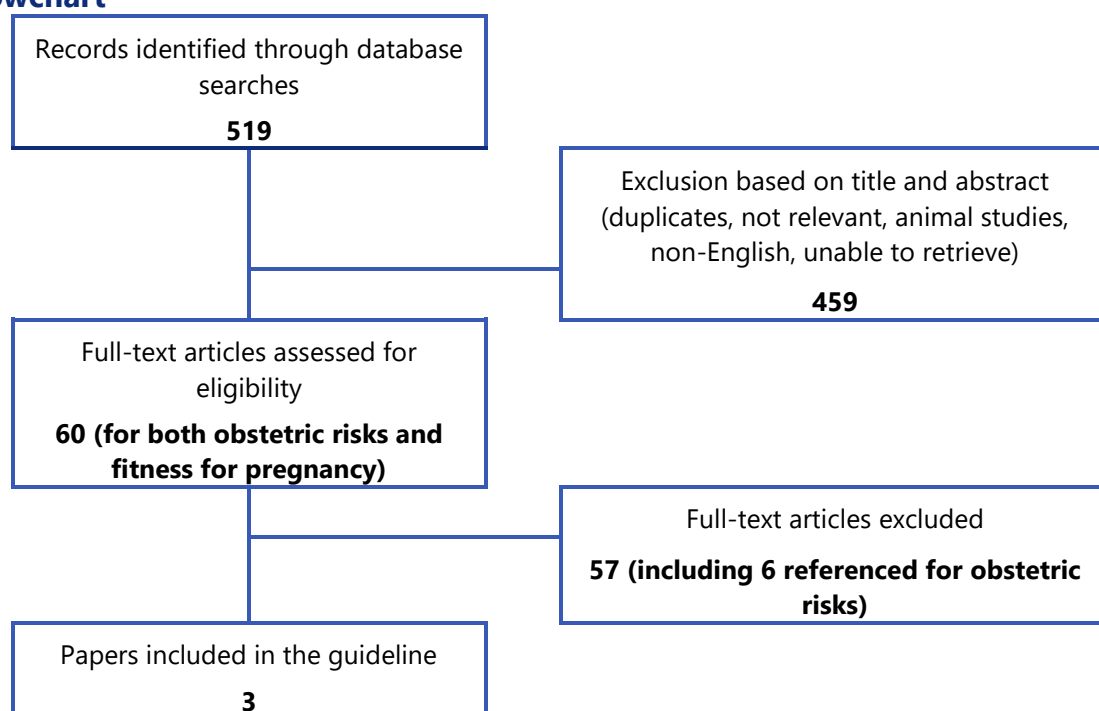
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ((("pre-pregnancy screening" OR "pre-conception screening" OR "fitness for pregnancy" OR "prevention of pregnancy complications") OR ((screening OR prevention) AND (pregnancy) AND ("intra-uterine growth restriction" OR "Intrauterine Growth restriction" OR "Intrauterine Growth Retardation" OR "Intra-uterine Growth Retardation" OR "Fetal Growth Retardation"[Mesh] OR IUGR OR "small for dates" OR "pregnancy induced hypertension" OR PIH OR "Gestational Hypertension" OR Pregnancy-Induced Hypertension OR "Hypertension, Pregnancy-Induced"[Mesh] OR (hypertension NEAR pregnancy) OR "Pre Eclampsia" OR "Pregnancy Toxemia" OR Preeclampsia OR "preeclamptic toxemia" OR "Pre-Eclampsia"[Mesh] OR "aortic root dissection")) OR ((Echocardiogram OR "Echocardiography"[Mesh] OR Counseling OR "Counseling"[Mesh] OR "Genetic Counseling"[Mesh] OR PGD OR "Genetic Testing"[Mesh] OR "preimplantation genetic testing" OR "cardiac test" OR "Heart Function Tests"[Mesh] OR MRI OR "Magnetic Resonance Imaging" OR "Magnetic Resonance Imaging"[Mesh] OR "uterine assessment" OR "endometrium development" OR "uterine abnormalities" OR "uterine artery Doppler") AND (Screening OR prevention OR fitness) AND (pregnancy)) OR ((Anthracycline OR doxorubicin OR trastuzumab OR radiotherapy OR "breast cancer") AND (cardiac OR cardiovascular) AND (pregnancy OR pregnant)))

Literature search was limited to the period between 01/04/2014 and 26/01/2024. Studies and data published prior to 01/04/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/04/2014 were retained.



## Flowchart



## Evidence

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Nolan et al., 2020)</b>	systematic review	Cancer Patients – during or soon after pregnancy  6 studies consisting of 2,016 pregnancies, predominantly in childhood cancer survivors, were included			incidence of left ventricular (LV) systolic dysfunction or heart failure (HF) during or soon after pregnancy in cancer survivors and evaluated the impact of history of cancer therapeutics-related cardiac dysfunction (CTRCD).	33 cardiac events.  Incidence of LV dysfunction or HF with pregnancy: 1.7% (95% CI 0.9% to 2.7%)  If history of CTRCD 28.4% (95% CI: 14.6% to 43.9%) If no history of CTRCD; 0.24% (95% CI: 0% to 0.81%)  With CTRCD history; OR 47.4 (95% CI: 17.9 to 125.8).	Overall, low incidence but women with a history of CTRCD had a 47.4-fold higher odds of experiencing pregnancy-related LV dysfunction or HF compared to those without	
<b>(Bansal et al., 2022)</b>	Narrative Review	childhood, adolescent, and young adult cancer survivors who are achieving survival to their prime reproductive year			maternal cardiovascular risk and outcomes of pregnancy	In female cancer survivors with normal cardiac function before pregnancy, the incidence of new heart failure during pregnancy is low. In survivors with cardiotoxicity prior to pregnancy, the risk of heart failure during and immediately after pregnancy is much higher. We recommend cardiomyopathy surveillance with echocardiography before pregnancy for all female		



						survivors treated with anthracyclines and chest radiation. Survivors with cardiotoxicity prior to pregnancy should be cared for by an expert multidisciplinary team, including obstetrics, cardiology, anesthesia, and specialized nursing, among others.	
<b>(Ehrhardt et al., 2023).</b>	Systematic review and updated recommendations	Survivors of childhood, adolescent, and young adult cancer, previously treated with anthracycline chemotherapy (including mitoxantrone) or radiotherapy in which the heart was exposed,				<p>Cardiomyopathy surveillance is reasonable before pregnancy or in the first trimester for female survivors of CAYA cancer at moderate and high risk cancer treated with anthracyclines or chest-directed radiotherapy (moderate-quality evidence, moderate recommendation)</p> <p>Continuing cardiomyopathy surveillance is reasonable during pregnancy for survivors of CAYA cancer treated with any dose of anthracyclines or chest-directed radiotherapy who had a history of previous left-ventricular systolic dysfunction that has resolved, even in the presence of a normal baseline ejection fraction, in the first trimester (moderate-quality evidence, moderate recommendation)</p>	
<b>(Felker et al., 2000)</b>	Cohort study	1230 patients with unexplained cardiomyopathy				During a mean follow-up of 4.4 years, 417 patients died and 57 underwent cardiac transplantation.	Doxorubicin-induced cardiomyopathy was associated with a poor survival rate compared to other causes in a study of 1230 patients with cardiomyopathy, although these cases were not pregnancy related
<b>(Bar et al., 2003).</b>	Cohort study	40 women treated with doxorubicin for childhood cancer  37 women (72 pregnancies) completed follow-up.			Pregnancy outcome	<p>Pregnancy outcome was favorable in the 29 women with fractional shortening values of <math>\geq 30\%</math> before pregnancy, and their myocardial function was sustained. In 8 women with fractional shortening of <math>&lt; 30\%</math> before pregnancy, pregnancy outcome was less favorable; a 19% decrease in fractional shortening was observed after pregnancy, and this finding was not significant (<math>P = .08</math>).</p>	<p>Pregnancy outcome in women who received doxorubicin for malignancy in childhood is generally favorable. However, those with baseline left ventricular dysfunction should be considered at increased risk for worse pregnancy outcome and further deterioration in myocardial function.</p>



Turner Syndrome							
(Matura et al., 2007)	Cohort study	166 adult volunteers with TS (average age, 36.2 years) who were not selected for cardiovascular disease and 26 healthy female control subjects.	Ascending and descending aortic diameters were measured by magnetic resonance imaging at the right pulmonary artery.		Aortic Dilatation and Dissection	Ascending and descending aortic diameters were measured by magnetic resonance imaging at the right pulmonary artery. TS women were on average 20 cm shorter, yet average aortic diameters were identical in the 2 groups. Ascending aortic diameters normalized to body surface area (aortic size index) were significantly greater in TS, and approximately 32% of TS women had values greater than the 95th percentile of 2.0 cm/m <sup>2</sup> . Ascending diameter/descending diameter ratios also were significantly greater in the TS group. During approximately 3 years of follow-up, aortic dissections occurred in 3 women with TS, for an annualized rate of 618 cases/100,000 woman-years. These 3 subjects had ascending aortic diameters of 3.7 to 4.8 cm and aortic size indices > 2.5 cm/m <sup>2</sup> .	

## Evidence to recommendations

QUESTION	How should fitness for pregnancy be assessed in women with POI?
RECOMMENDATION	<b>Women presenting for oocyte donation who are suspected of having POI should be investigated for the aetiology of POI prior to oocyte donation.</b>
Desirable effects	Investigations for the aetiology could highlight risk factors that would need to be managed before or during pregnancy
Undesirable effects	Oocyte donation pregnancies appear to be at higher risk of obstetric complications, especially in women with POI and a history of chemotherapy and/or cardiac irradiation, or women with TS.
Certainty of evidence	NA
Values	Same as for investigating the cause of POI, see above
Balance of effects	
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	

QUESTION	How should fitness for pregnancy be assessed in women with POI?
RECOMMENDATION	<b>A cardiologist should be involved in care of women considering pregnancy who have received anthracyclines and/or cardiac irradiation. Comprehensive cardiac screening and appropriate counselling by both a maternal-fetal medicine specialist and cardiologist with expertise in managing women with Turner Syndrome is recommended prior to planning a pregnancy, especially if oocyte or embryo donation is considered.</b>
Desirable effects	Prevention of complications
Undesirable effects	Oocyte donation pregnancies appear to be at higher risk of obstetric complications, especially in women with POI and a history of chemotherapy and/or cardiac irradiation, or women with TS.
Certainty of evidence	Observational data on complications
Values	
Balance of effects	



Resource use, equity, acceptability and feasibility  
Subgroup considerations (if applicable)

QUESTION	How should fitness for pregnancy be assessed in women with POI?
RECOMMENDATION	<b>In addition to usual antenatal screening, women with POI should have their cardiometabolic and thyroid function assessed prior to pregnancy.</b>
Desirable effects	Although no evidence was found on the effectiveness of any intervention prior to pregnancy in POI, the guideline group recommends consideration of a general assessment for all women prior to oocyte donation, and a specific assessment based on additional risk factors, especially a history of chemotherapy and/or cardiac irradiation, or in women with TS.
Undesirable effects	
Certainty of evidence	Observational data on complications
Values	
Balance of effects	
Resource use, equity, acceptability and feasibility	
Subgroup considerations (if applicable)	Turner Syndrome

QUESTION	How should fitness for pregnancy be assessed in women with POI?
RECOMMENDATION	<b>Pregnancy in some women can be of such high risk that HCPs may consider oocyte donation pregnancy to be life threatening and therefore inappropriate.</b>
Desirable effects	NA
Undesirable effects	Oocyte donation pregnancies appear to be at higher risk of obstetric complications, especially in women with POI and a history of chemotherapy and/or cardiac irradiation, or women with TS.
Certainty of evidence	Observational data on complications
Values	
Balance of effects	
Resource use, equity, acceptability and feasibility	
Subgroup considerations (if applicable)	Oocyte donation pregnancies



## VI. POI and musculoskeletal health

### VI.1. Skeletal health

#### KEY QUESTION - WHAT ARE THE CONSEQUENCES OF POI FOR BONE HEALTH?

<b>Population</b>	Patients diagnosed with premature ovarian insufficiency (different etiologies)
<b>Interventions</b>	/
<b>Control</b>	/
<b>Outcomes</b>	Bone density, Bone mineral density Osteoporosis, Osteopenia Bone loss, risk, Fractures Bone geometry, Bone quality, Long bones growth, Bone turnover metabolism/remodelling, Stature growth

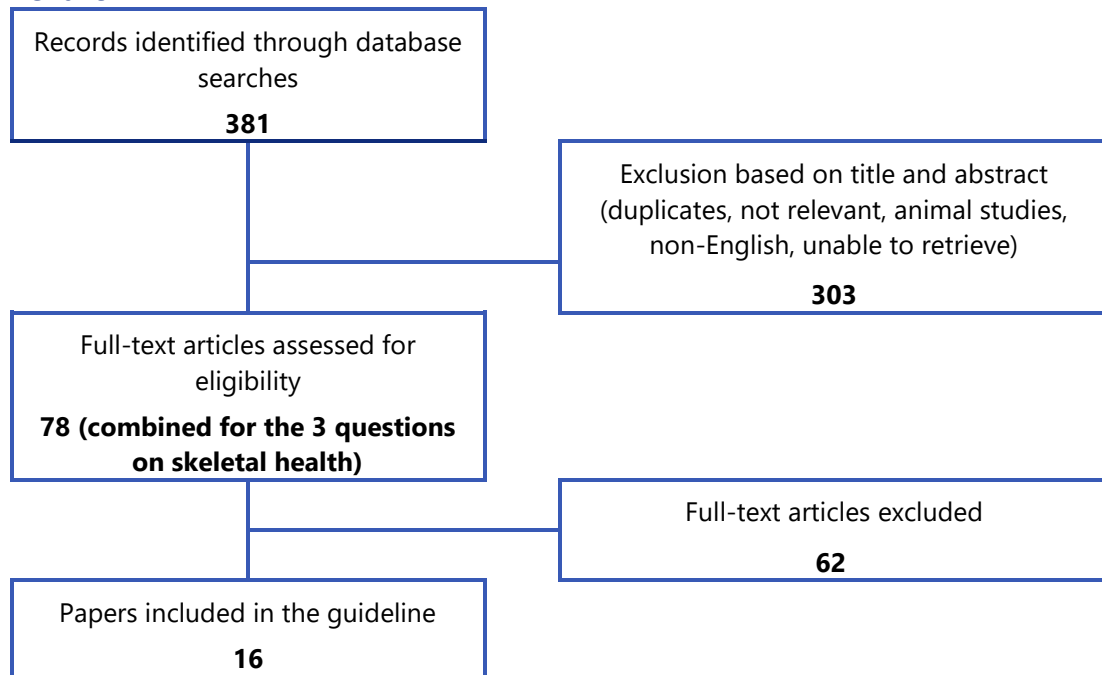
#### Search strings

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Literature search was limited to the period between 01/01/2014 and 26/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

*Summary of Findings Table*

Not applicable



Evidence table – FRACTURE

REF	Study Design <sup>10</sup>	Describe population (cause of POI)	Duration of follow-up: mean (range)	POI PARTICIPANTS				CONTROLS			FRACTURE												
				n=? (for POI)	n=? For whole cohort (if it includes those > 40 years)	Mean age (years)	Age range used in study (years)	Describe population	n = ? (control group)	Mean age (years)	Age range used in study (years)	Total Fractures POI (mean SD or n or %)	Total fractures control (mean SD or n or %)	Comment	Fragility fractures POI (mean SD or n or %)	Fragility Fractures Control (mean SD or n or %)	Type of fracture 1) hip 2) vertebral 3) pelvis 4) long bones 5) ribs 6) other	Mean SD age at fracture POI	Mean SD age at fracture Control	Include relative risk/hazard ratio or Y/N depending on study design and available information	Comment		
(Dutta et al., 2016)	8	Hypergonadotropic Hypogonadism		20		32.5 (9.7)			n = 223 (control group)			1 (5%)											
(Wasserman et al., 2018)	8	TS		711			Divided to 2 groups <25y = 12.4 (6.1); >25 years 43.5 (12.1)		231	<25 years 13.7 (6.2); >25 years 47.34 (13.6)		41,80 %	39,40 %	< 25 years 103 (29.0%) vs 24 (29.6%) control p 0.91; > 25 years 180 (57.7%) vs 64 (46.4%) p 0.03	No difference between TS and controls in clinically significant fragility fractures (no other data); < 25 years upper extremity 53% vs 48%, P = .45; 25-44 years and ≥45 years, the proportion of fractures at any skeletal site between women with TS and controls did not differ.							≥25 years TS were more likely to report at least one fracture in their lifetime than controls (P = .03). ≥25 years who discontinued ERT compared to those who continued ERT, there was a significant difference in fracture prevalence (67.4% vs 47.7% P = .003);	
(Cardona Attard et al., 2019)	8	TS and POI		67	267+67	28.1 (Age at diagnosis 16 (0.1-32))	17.4-52.7	TS	267	34.3 (Age at diagnosis 10 (0-.5))	15-70.9	TS n = 72 (30.7%); POI n = 22 (32.8%) P 0.737			Vertebral fractures TS 4(3.6%) POI 1 (2.3%) p vale 0.694; Hip TS = 3(2.7%) POI 0(0%); Proximal humerus TS 5(4.5%) POI 0(0%); Clavicle and ribs TS			1+2+4+5					

<sup>10</sup> 1. Randomised trial 2. Non-randomised trial 3. Pre-test post-test 4. Controlled before and after study 5. Interrupted time series study 6. ITS w repeated measures 7. Case study/series 8. Cross-sectional study 9. Repeated cross-sectional study 10. Cohort study 11. Case-control study



															7(6.3%) POI 3 (7%) p0.869					
(Viuff <i>et al.</i> , 2020)	10	TS		1156		Age of diagnosis 15 (0-85)		115577			n = 103				n = 103					IRR 1.8 (CI 1.4–2.3)
(Samad <i>et al.</i> , 2022).	10	Normal karyotype POI; Spontaneous 40%; latrogenic 60%	6 years for Longitudinal component	60		34 (29-38)		Age+BMI matched	60	34 (30-38)	s-POI = 20%; i-POI = 17%	8%	p = 0.275	1	2		s-POI = 24.0 (9-34); i-POI = 29.5 (16-50)	28 (21-37)		

Evidence table – OSTEOPOROSIS (Tscore -2.5 or less or fragility fracture)

REF	Describe population (cause of POI)	n=? (for POI)	n=? <sup>11</sup>	Mean age (years)	Age range used in study	BMI	Any other comorbidities Y/N	Comment	Describe population	n = 723 (control group)	Mean age (years)	Age range used in study (years)	Any other comorbidities Y/N	Comment	POI LS BMD	POI Femoral neck BMD(mean SD or MD)	POI total hip BMD (mean SD or MD)	Control LS (mean SD or MD)	Control FN (mean SD or MD)	Control Total hip (mean SD or MD)	Comment	POI osteoporosis Incidence	Control Osteoporosis incidence	POI Osteoporosis Prevalence	Control osteoporosis prevalence	Include relative risk/hazard ratio/odds ratio or Y/N depending on study design and available information	Comment
Kortoglou-Alsey 2014	TS and surgical menopause Groups divided divided age < 30 years vs age > 30	54		27,9	16-38										T-score < 30 years -1.84 ± 1.47 vs > 30 years -1.06 ± 0.93 p = 0.021		T-score < 30 years -0.83 ± 1.13 vs > 30 years -1.07 ± 1.15 p = 0.489										

<sup>11</sup> For whole cohort (if it includes those > 40 years)











(Shea <i>et al.</i> , 2021).	8	NR	2010-2015		374	9837	34.8 (0.125)								Y	14.26% smokers	55.70%				
(Samad <i>et al.</i> , 2022).	10	Normal karyotype POI; Spontaneous 40%; Iatrogenic 60%	2005-2018	6 years for Longitudinal component	60		34 (29-38)					Age+BMI matched	60	34 (30-38)					13%		
(Vogt <i>et al.</i> , 2022)	8	Idiopathic 45%; Iatrogenic 55%	2013-2016		168	6870	Idiopathic = 28.7 (7.3); Iatrogenic = 33.2 (4.9)														
(Dhakate <i>et al.</i> , 2023)	10	Idiopathic	2018-2021		70		32.5+/-7					Age matched + normal menstruation with BGL < 7.8 mmol and TSH < 10 MIU/L	70	32.7+/-6.9							



*Evidence to recommendations*

QUESTION RECOMMENDATIONS	WHAT ARE THE CONSEQUENCES OF POI FOR BONE HEALTH? <b>Women with POI and HCPs should be aware that POI is associated with abnormal bone microarchitecture and reduced bone mineral density. It is suggested that HCPs inform women that POI may be associated with an increased risk of osteoporosis and fracture later in life.</b>
Desirable effects	The effect of POI on bone is among the most clearly established adverse consequences of the condition. Women with POI have been shown to have reduced BMD, abnormal bone microarchitecture and possibly an increased risk of fracture later in life.
Undesirable effects	
Certainty of evidence	Observational data (low quality for BMD, very low for fracture)
Values	Informed patients
Balance of effects	Recommendation for providing information to support uptake of prevention measures
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	NA



## PICO QUESTION: WHAT ARE THE TREATMENT OPTIONS FOR BONE PROTECTION AND IMPROVEMENT?

<b>Population</b>	Patients diagnosed with premature ovarian insufficiency (different etiologies)
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• Nonpharmacologic interventions</li> <li>• Exercise – regular weight-bearing and muscle-building exercise / physical activity, yoga , tai chi / sport</li> <li>• Smoking cessation</li> <li>• calcium and vitamin D / Vitamin supplement cholecalciferol or calcidiol</li> <li>• calcium salts/ Dietary Supplement</li> <li>• Pharmacologic interventions</li> <li>• Bone anti-resorptives: alendronate, risedronate, ibandronate, zoledronic acid, raloxifene, bazedozifene, HRT</li> <li>• Bone forming agents:</li> <li>• Strontium ranelate, teriparatide</li> <li>• For women under corticosteroids:</li> <li>• Alendronate, risedronate, strontium ranelate, teriparatide</li> <li>• Monitoring of pharmacologic treatment</li> </ul>
<b>Control</b>	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Maintaining/improving:bone mineral density (BMD)-osteoporosis</li> <li>• bone quality</li> <li>• fracture risk</li> <li>• incidence of fracture</li> </ul>

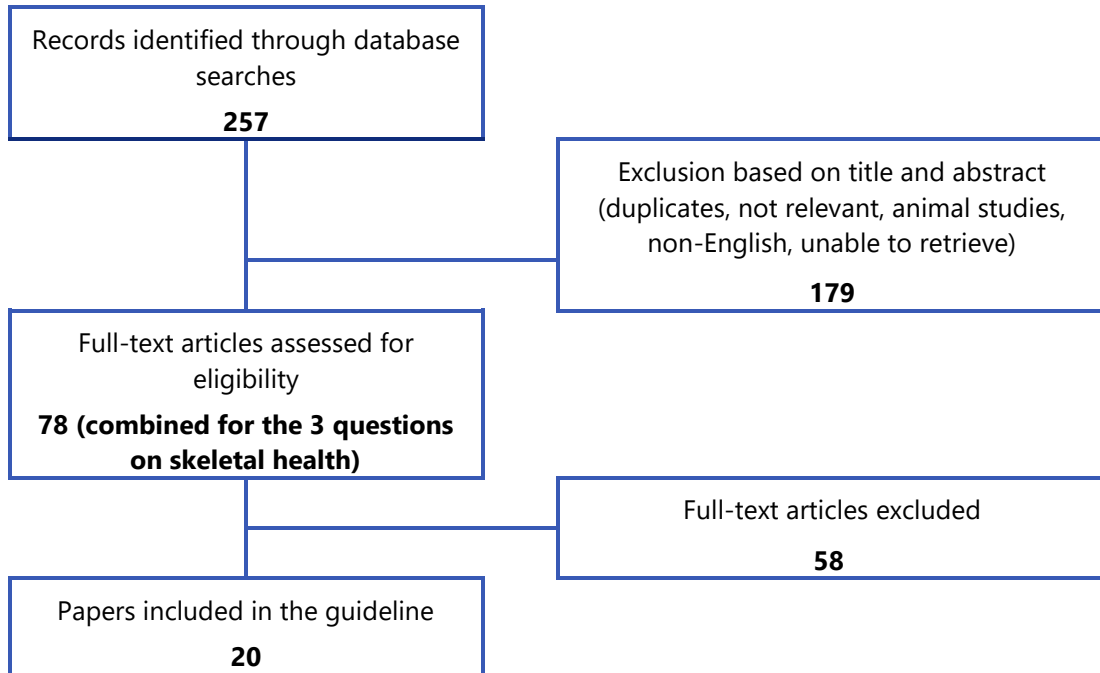
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<b>COCHRANE</b>	

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## Flowchart





## Evidence

### Summary of Findings Table

Not applicable

### Evidence table - Non-pharmacological approaches

Evaluated outcomes; Any Fractures, Fragility, Traumatic, Spinal bone density, Hip bone density, Osteoporosis, Osteopenia, P1NP, CTX (included below only if reported)

Ref.	PARTICIPANTS			CONTROLS		NON PHARMACOLOGICAL						OUTCOMES	
	Describe population (cause of POI)	n=? (for POI)	Mean age (years)	Describe population	Mean age (years)	% or N POI treated with Calcium	Comment type dose duration	% or N Controls treated with Calcium	Comment type dose duration	% or N POI treated with Vitamin D	Comment type dose duration		Other
<b>(Popat et al., 2014)</b>	POI divided into Estradiol+progestin +placebo (EPP) vs Estradiol+progestin+testosterone (EPT)	EPP group n = 72; EPT n= 70	EPP 33 (5.2); EPT 31.3 (5.8)	Healthy, nonpregnant, regularly menstruating women	30.1(7.3)	100%	Calcium carbonate oral supplementation (two tablets of 0.650 g/d, 520 mg elemental calcium/d)						<p>Spinal bone density POI Mean SD not statistically different at any time point between the EPT group and the EPP group (P&gt;.56). Specific values NR</p> <p>Spinal bone density mean difference At 3 years Intervention vs Control LS [1.02 (0.11) vs 1.01 (0.11) g/cm<sup>2</sup>, P .8].</p> <p>Hip bone density POI Mean SD mean BMD of 0.015 g/cm<sup>2</sup> &gt; placebo group (95% confidence interval 0.005– 0.034)</p> <p>Hip bone density mean difference At 3 years Intervention vs Control FN [0.80 (0.12) vs 0.80 (0.11) g/cm<sup>2</sup>, P .95]</p>
<b>(Tsubur ai et al., 2018)</b>	TS; divided into low bone mass, normal bone mass	52	Low bone mass = 31.9 ± 6.1; Normal bone mass 32.5 ± 7.3	TS who maintained ovarian function	28.6 ± 8.1							Eldecalcitol (ELD) and ERT for 12 months	<p>Spinal bone density POI Mean SDPre ELD treatment 0.710 ± 0.056 g/cm<sup>2</sup> vs. 12 months post ELD p &lt; 0.001</p> <p>Osteoporosis POI mean SDT score pre treatment -2.61 ± 0.49; 6 months post tx -2.45 ± 0.58 p value &lt;0.05; 12 months post tx 2.41 ± 0.54 p value &lt;0.54</p> <p>Osteoporosis mean differenceZ score pre tx -2.62 ± 0.55; 6 months post tx -2.46 ± 0.63, 12 months post tx -2.37 ± 0.57 P value &lt; 0.05</p> <p>P1NPPOI mean SD Low bone mass = 63.5 ± 27.4 vs normal bone mass 49.0 ± 21.4 vs.control 35.4 ± 9.0 µg/mL; p = 0.012)</p>







<p><b>(Cartwright et al., 2016)</b></p>	<p>Rando mised trial</p>	<p>Spontaneous POI treated n = 30 (15 in each HT and COCP, untreated n = 29</p>	<p>n = 30</p>	<p>40.5(34.8, 42.7)</p>				<p>Time since diagnosis of POI Months 9 (5, 28)</p>	<p>n=29 (15 compl eted study)</p>					<p>21</p>	<p>HRT n = 12; Estradiol 2 mg daily + levonorgestrel 75 mcg .</p>			<p>HRT n = 9 COCP ethinyloe stradiol 30 mcg and levonorg estrel 150 mcg</p>	<table border="1"> <thead> <tr> <th></th> <th>6 Months</th> <th>12 Months</th> <th>24 Months</th> </tr> </thead> <tbody> <tr> <td>Lumbar spine</td> <td></td> <td></td> <td></td> </tr> <tr> <td>HRT vs COCP</td> <td>0.011 (-0.014 - 0.034)</td> <td>0.042 (0.012 - 0.072)</td> <td>0.052 (0.022 - 0.082)</td> </tr> <tr> <td>HRT vs treatment total spine BMD</td> <td>P = 0.008</td> <td>P = 0.004</td> <td>P = 0.001</td> </tr> <tr> <td>COCP vs treatment total spine BMD</td> <td>0.012 (0.004 - 0.020)</td> <td>0.012 (0.004 - 0.020)</td> <td>0.009 (-0.003 - 0.009)</td> </tr> <tr> <td>P = 0.011</td> <td>P = 0.011</td> <td>P = 0.008</td> </tr> <tr> <td>Total hip</td> <td></td> <td></td> <td></td> </tr> <tr> <td>HRT vs COCP</td> <td>-0.011 (-0.031 - 0.009)</td> <td>-0.021 (-0.041 - 0.017)</td> <td>-0.031 (-0.051 - 0.014)</td> </tr> <tr> <td>HRT vs treatment total hip BMD</td> <td>P = 0.12</td> <td>P = 0.004</td> <td>P = 0.001</td> </tr> <tr> <td>COCP vs treatment total hip BMD</td> <td>0.024 (0.004 - 0.044)</td> <td>0.017 (0.004 - 0.030)</td> <td>0.009 (0.001 - 0.016)</td> </tr> <tr> <td>P = 0.004</td> <td>P = 0.004</td> <td>P = 0.004</td> </tr> <tr> <td>Forearm neck</td> <td></td> <td></td> <td></td> </tr> <tr> <td>HRT vs COCP</td> <td>0.004 (-0.034 - 0.044)</td> <td>0.027 (-0.004 - 0.057)</td> <td>0.010 (-0.014 - 0.033)</td> </tr> <tr> <td>HRT vs treatment forearm neck BMD</td> <td>P = 0.29</td> <td>P = 0.004</td> <td>P = 0.001</td> </tr> <tr> <td>COCP vs treatment forearm neck BMD</td> <td>-0.044 (-0.058 - 0.030)</td> <td>-0.011 (-0.049 - 0.026)</td> <td>-0.002 (-0.010 - 0.006)</td> </tr> <tr> <td>P = 0.004</td> <td>P = 0.001</td> <td>P = 0.001</td> </tr> <tr> <td>HRT vs treatment forearm neck BMD</td> <td>-0.044 (-0.058 - 0.030)</td> <td>-0.011 (-0.049 - 0.026)</td> <td>-0.002 (-0.010 - 0.006)</td> </tr> <tr> <td>P = 0.004</td> <td>P = 0.001</td> <td>P = 0.001</td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th></th> <th>6 Months</th> <th>12 Months</th> <th>24 Months</th> </tr> </thead> <tbody> <tr> <td>CTX</td> <td></td> <td></td> <td></td> </tr> <tr> <td>HRT vs COCP</td> <td>-0.01 (-0.015 - 0.005)</td> <td>-0.04 (-0.046 - 0.006)</td> <td>-0.07 (-0.076 - 0.006)</td> </tr> <tr> <td>HRT vs treatment CTX</td> <td>P = 0.001</td> <td>P = 0.001</td> <td>P = 0.001</td> </tr> <tr> <td>COCP vs treatment CTX</td> <td>0.012 (0.008 - 0.016)</td> <td>0.011 (0.007 - 0.015)</td> <td>0.012 (0.007 - 0.016)</td> </tr> <tr> <td>P = 0.001</td> <td>P = 0.001</td> <td>P = 0.001</td> </tr> <tr> <td>FPNP</td> <td></td> <td></td> <td></td> </tr> <tr> <td>HRT vs COCP</td> <td>0.12 (0.08 - 0.16)</td> <td>0.12 (0.08 - 0.16)</td> <td>0.12 (0.08 - 0.16)</td> </tr> <tr> <td>HRT vs treatment FPNP</td> <td>P = 0.001</td> <td>P = 0.001</td> <td>P = 0.001</td> </tr> <tr> <td>COCP vs treatment FPNP</td> <td>0.12 (0.08 - 0.16)</td> <td>0.12 (0.08 - 0.16)</td> <td>0.12 (0.08 - 0.16)</td> </tr> <tr> <td>P = 0.001</td> <td>P = 0.001</td> <td>P = 0.001</td> </tr> </tbody> </table>		6 Months	12 Months	24 Months	Lumbar spine				HRT vs COCP	0.011 (-0.014 - 0.034)	0.042 (0.012 - 0.072)	0.052 (0.022 - 0.082)	HRT vs treatment total spine BMD	P = 0.008	P = 0.004	P = 0.001	COCP vs treatment total spine BMD	0.012 (0.004 - 0.020)	0.012 (0.004 - 0.020)	0.009 (-0.003 - 0.009)	P = 0.011	P = 0.011	P = 0.008	Total hip				HRT vs COCP	-0.011 (-0.031 - 0.009)	-0.021 (-0.041 - 0.017)	-0.031 (-0.051 - 0.014)	HRT vs treatment total hip BMD	P = 0.12	P = 0.004	P = 0.001	COCP vs treatment total hip BMD	0.024 (0.004 - 0.044)	0.017 (0.004 - 0.030)	0.009 (0.001 - 0.016)	P = 0.004	P = 0.004	P = 0.004	Forearm neck				HRT vs COCP	0.004 (-0.034 - 0.044)	0.027 (-0.004 - 0.057)	0.010 (-0.014 - 0.033)	HRT vs treatment forearm neck BMD	P = 0.29	P = 0.004	P = 0.001	COCP vs treatment forearm neck BMD	-0.044 (-0.058 - 0.030)	-0.011 (-0.049 - 0.026)	-0.002 (-0.010 - 0.006)	P = 0.004	P = 0.001	P = 0.001	HRT vs treatment forearm neck BMD	-0.044 (-0.058 - 0.030)	-0.011 (-0.049 - 0.026)	-0.002 (-0.010 - 0.006)	P = 0.004	P = 0.001	P = 0.001		6 Months	12 Months	24 Months	CTX				HRT vs COCP	-0.01 (-0.015 - 0.005)	-0.04 (-0.046 - 0.006)	-0.07 (-0.076 - 0.006)	HRT vs treatment CTX	P = 0.001	P = 0.001	P = 0.001	COCP vs treatment CTX	0.012 (0.008 - 0.016)	0.011 (0.007 - 0.015)	0.012 (0.007 - 0.016)	P = 0.001	P = 0.001	P = 0.001	FPNP				HRT vs COCP	0.12 (0.08 - 0.16)	0.12 (0.08 - 0.16)	0.12 (0.08 - 0.16)	HRT vs treatment FPNP	P = 0.001	P = 0.001	P = 0.001	COCP vs treatment FPNP	0.12 (0.08 - 0.16)	0.12 (0.08 - 0.16)	0.12 (0.08 - 0.16)	P = 0.001	P = 0.001	P = 0.001
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<p><b>(Cleemann et al., 2017)</b></p>	<p>Rando mised trial - Double blind</p>	<p>TS on high dose 4mg estradiol vs low dose 2mg estradiol</p>	<p>20</p>		<p>19.2 ±2.5</p>			<p>age match ed</p>	<p>34</p>	<p>18.4 ±2.7</p>			<p>100%; n = 10 high dose; n = 10 low dose</p>	<p>Low-dose (LD) oral 2 mg 17B- estradiol/day; High- dose (HD) group oral 4 mg 17B- estradiol/day</p>	<p>LD 4.4± 1.5 vs HD 4.7± 1.4 years</p>		<p>Spinal bone density mean difference BMD (total, spine and arm/radius UD) were similar among TS and controls (data not shown)</p> <p>mean difference TS vs Control (at baseline) BMDhip: TS vs C: 0.88 ± 0.14 g/cm<sup>3</sup> vs 0.95 ± 0.10 g/cm<sup>3</sup>, P = 0.037; BMDarm/radius1/3: TS vs C: 0.62 ± 0.05 g/cm<sup>3</sup> vs 0.66 ± 0.05 g/cm<sup>3</sup>, P = 0.009"</p> <p>"P1NP, POI mean SD P1NP; CTX and bALP measured yearly; no significant differences in the treatment groups except for bALP, HD group had a significantly higher level throughout the study period; Specific data not shown"</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>B</th> <th>Std. Error</th> <th>Significant variables</th> <th>P</th> </tr> </thead> <tbody> <tr> <td rowspan="2">CTX</td> <td>-0.1756</td> <td>0.0140</td> <td>BMD<sub>total</sub></td> <td>&lt;0.0005</td> </tr> <tr> <td>0.0116</td> <td>0.0040</td> <td>Former estrogen</td> <td>0.0106</td> </tr> <tr> <td rowspan="2">bALP</td> <td>0.0089</td> <td>0.0070</td> <td>Spontaneous puberty</td> <td>0.0119</td> </tr> <tr> <td>-0.0067</td> <td>0.0117</td> <td>BMD<sub>total</sub></td> <td>0.0051</td> </tr> <tr> <td rowspan="2">P1NP</td> <td>2.2408</td> <td>0.9000</td> <td>Spontaneous puberty</td> <td>0.0148</td> </tr> <tr> <td>0.8238</td> <td>0.1608</td> <td>Former estrogen</td> <td>0.0154</td> </tr> <tr> <td rowspan="2">BMD<sub>total</sub></td> <td>-0.1716</td> <td>0.0186</td> <td>BMD<sub>total</sub></td> <td>&lt;0.0005</td> </tr> <tr> <td>11.3572</td> <td>1.7542</td> <td>Spontaneous puberty</td> <td>0.0051</td> </tr> <tr> <td rowspan="2">BMD<sub>arm</sub></td> <td>-0.1716</td> <td>0.0186</td> <td>BMD<sub>arm</sub></td> <td>&lt;0.0005</td> </tr> <tr> <td>11.3572</td> <td>1.7542</td> <td>Spontaneous puberty</td> <td>0.0051</td> </tr> </tbody> </table> <p>Legend Multiple linear regression models in Turner syndrome between carboxy-terminal collagen crosslinks (CTX), bone specific alkaline phosphatase (bALP) and pro-collagen 1 amino terminal pro-peptide (P1NP). The background variables bone mineral density at randomization (BMD<sub>total</sub>), body surface area (BSA), body mass index (BMI), duration of estrogen treatment before randomization (former estrogen), and spontaneous puberty were included in the models.</p> <p>Muscle mass POI mean SD Lean body mass (LBM) there was a significant effect of the interaction between time and treatment (P=0.0290)</p>	Outcome	B	Std. Error	Significant variables	P	CTX	-0.1756	0.0140	BMD <sub>total</sub>	<0.0005	0.0116	0.0040	Former estrogen	0.0106	bALP	0.0089	0.0070	Spontaneous puberty	0.0119	-0.0067	0.0117	BMD <sub>total</sub>	0.0051	P1NP	2.2408	0.9000	Spontaneous puberty	0.0148	0.8238	0.1608	Former estrogen	0.0154	BMD <sub>total</sub>	-0.1716	0.0186	BMD <sub>total</sub>	<0.0005	11.3572	1.7542	Spontaneous puberty	0.0051	BMD <sub>arm</sub>	-0.1716	0.0186	BMD <sub>arm</sub>	<0.0005	11.3572	1.7542	Spontaneous puberty	0.0051																																																														
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<b>(Cardona Attard et al., 2019)</b>	Cross-sectional study	TS and POI	67	267+67	28.1 (Age at diagnosis 16 (0.1-32))	17.4-52.7				TS	267	34.3 (Age at diagnosis 10 (0-.5))	15-70.9	97% of POI and 87.6% of TS	NR	Age at start of ERT in primary amenorrhoea (y) TS = 14.0 (9.0 - 35.0) POI = 16.0 (13.0 - 23.0)			Spinal bone density POI Mean SD HRT group = -1.1 [-4.3 - 2.7] vs Non HRT group = -1.4 [-3.4 - 2.2], P = .031; Bisphosphonate group (-2.7 [-3.4 - -0.6] vs no bisphosphonate group -1.1[-4.3 - 2.7], P = <.001)
<b>Gazarra 2020</b>	Cohort study	NR	119		30+/-9.24				POI with no HRT	20				119	Low-dose HT group (0.625 mg CE or 1 mg E2) = 92; high-dose HT group (1.25mg CE or 2mg E2) = 45; tibolone 2.5 mg = 8	NR	n = 45	Spinal bone density POI Mean SD Continues use for 2 years BMD: COC = +2.5% +/-6.5%; High dose = +1.8% = +/-9.9%; Low dose = -1.3% +/-11.5%; Tibolone = -2.2%+/-5.3%; Untreated=-3.3%+/-5.4%  "Spinal bone density mean difference Adjusted mean differences COC = 0.0; Low dose = 0.0024 (-0.046 to -0.002) P 0.03; High dose -0.003 (-0.025 to 0.020) P 0.824; Tibolone = 0.026 (-0.072 to 0.021) P 0.277; No treatment = 0.032 (-0.062 to -0.003) P 0.031  Hip bone density POI Mean SD Continues use for 2 years BMD total femur COC = +2.4% +/- 4.6%; High dose = +0.9%+/-5.8%; Low dose = 2.2%+/-3.3%; Tibolone = 0.02%+/-0.02%  Hip bone density mean difference Femoral neck Adjusted mean differences COC = 0.000; Low dose = -0.020 (-0.047 to 0.007) P 0.143; High dose = -0.006 (-0.026 to 0.015) P0.593; Tibolone 0.022 (-0.018 to 0.062) P 0.282; No treatment = -0.015 (-0.053 to 0.024) P 0.455  Hip bone density p-value Total femur Adjusted mean differences COC = 0.000; Low dose = -0.029 (-0.046 to -0.012) P 0.001; High dose -0.012 (-0.026 to 0.002) P 0.100; Tibolone 0.012 (-0.012 to 0.035); P 0.328; No difference = 0.009 (0.029 to 0.011) P 0.357 Adjusted for age, BMI, Hormone therapy duration	
<b>(Fante et al., 2020)</b>	Cross-sectional study	NR; 18.67% karyotype alteration	150		34.30 (8.58)				Age and BMI matched with	150	34		n= 114 HT users vs non users n = 36	n= 27 1mg estradiol or 0.625 mg CEE+progestogens, n= 55 were using 2 mg		0	21	Spinal bone density POI Mean SD TS and controls (data not shown).	



									regular menstrual cycles						estradiol or 1.25 mg CEE + progestogens, n = 11 were using tibolone			Muscle mass POI mean SD Questionnaire: Pelvic floor distress inventory (PFDI-20) and Kings Health Questionnaire (KHQ) and vaginal palpation for pelvic floor assessment  Muscle mass mean difference prevalence UI HT users 22.81%, non-HT users 41.67% (P=0.03); POP 7.89% vs 13.89% (P > 0.05); FI 6.14% vs 13.89% (P > 0.05).
<b>(Ha et al., 2020)</b>	Cohort study	Iatrogenic post allogeneic hematopoietic stem cell transplant	234		30	19-40								n = 170; 73%	43.5% = estradiol 2mg with cyclical progesterone; 31.8% = estradiol 2mg and dydrogesterone; 24.7% = oestradiol 2mg and cyproterone			Spinal bone density mean difference 1 year post HRT BMD LS gain = 4.16 ± 4.39% vs 2.61 ± 7.50%, P = .033; 2 years post HRT 5.42 ± 5.86% vs 3.80 ± 6.00%, P = .047  Hip bone density mean difference 1 year post HRT Total hip 1.22 ± 5.04% (no p value); 2 years post HRT 2.57 ± 4.27% (no p value)  HRT initiation before and after 12 months = LS BMD 6.31 ± 3.89% vs 3.10 ± 4.94%, P = .013; Total hip BMD 3.35 ± 3.99% vs 1.39 ± 3.94%, P = .002
<b>(Podfigurna et al., 2020)</b>	Cohort study	Idiopathic	132		31.86+/-7.75			Healthy with regular menstrual cycles	17	23.21 ± 5.86			100%	Oral 2 mg 17-β-estradiol and 10 mg dydrogesterone	Mean 12 months	100%	BMD [g/cm <sup>2</sup> ] 1.088 ± 0.14 (before treatment) vs 1,109 ± 0.14 (after treatment) P < 0.001  Osteoporosis frequency (x/n) or % or N Post HRT 1.69%  Osteopenia frequency (x/n) or % or N Post HRT = 42.37%  Osteopenia mean difference T score difference = -0.75 ± 1.17 vs -0.59± 1.22 (p<0.001); Z score difference -0.75 ± 1.12 vs -0.49 ± 1.11 p <0.001	
<b>(Viuff et al., 2020)</b>	Cohort study	TS	1156		Age of diagnosis 15 (0-85)			Age matched	115577				n=329	41% to 95 % = oral HRT, 7% to 22% = transdermal HRT			19% to 78%	Fragility RR or OR HR 0.37 (CI 0.14–0.99) HRT-Treated 45,X vs. HRT Nontreated 45,X  Osteoporosis RR or OR HR 1.2 (CI 0.4–3.3) HRT-Treated 45,X vs. HRT Nontreated 45,X
<b>(Samad et al., 2022)</b>	Cohort study	Normal karyotype POI; Spontaneous 40%; Iatrogenic 60%	60		34	29-38		Age+BMI matched	60	24 (30-38)			Total =81%	s-POI = 67%; i-POI = 78%;			COCP s-POI 33%; i-POI 12%	Hip bone density POI Mean SD Interrupted HRT = FN-BMD (-0.020g/cm <sup>2</sup> (95% CI: -0.037, 0.0030), p=0.025)
<b>(Dhakate et al., 2023)</b>	Cohort study	Idiopathic	70		32.5+/-7			Age matched with normal menstruation with BGL < 7.8	70				61,40%	0.625 mg-1.25 mg CEE (day 1 to 25) +10 mg MPA	12(0-24)	0%		Osteopenia POI mean SDZ score < -2 at LS: 51.9% in non HRT users vs 25.6% in HRT users  Osteopenia p-value 0,04





### Evidence to recommendations

QUESTION	WHAT ARE THE TREATMENT OPTIONS FOR BONE PROTECTION AND IMPROVEMENT?
RECOMMENDATION	<b>Osteoporosis risk factors should be identified and addressed at POI diagnosis and during ongoing care.</b>
Desirable effects	There are a number of modifiable risk factors associated with fracture risk that have been identified or are relevant to women with POI and advice regarding these modifiable risk factors should be provided.
Undesirable effects	NA – for assessment and information provision
Certainty of evidence	NA
Values	Providing information and addressing knowledge gaps may facilitate positive bone health related behaviours.
Balance of effects	NA
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	NA

QUESTION	WHAT ARE THE TREATMENT OPTIONS FOR BONE PROTECTION AND IMPROVEMENT?
GOOD PRACTICE POINT	<b>The guideline group recommends that women with POI should be encouraged to adopt a healthy lifestyle (including weight-bearing exercise, healthy diet, avoiding smoking, and maintaining normal body weight) to optimize bone health.</b>
Justification	There are a number of modifiable risk factors associated with fracture risk that have been identified or are relevant to women with POI and advice regarding these modifiable risk factors should be provided. Providing information and addressing knowledge gaps may facilitate positive bone health related behaviours.

QUESTION	WHAT ARE THE TREATMENT OPTIONS FOR BONE PROTECTION AND IMPROVEMENT?
RECOMMENDATION	<b>Dietary supplementation of calcium and vitamin D may be required in women with inadequate vitamin D status and/or calcium intake and may be of benefit in women with low bone mineral density.</b>
Desirable effects	
Undesirable effects	
Certainty of evidence	Observational data, no high quality RCTs
Values	
Balance of effects	Bone health/prevention of fracture vs side-effects of treatment
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	Addressed in the recommendation

QUESTION	WHAT ARE THE TREATMENT OPTIONS FOR BONE PROTECTION AND IMPROVEMENT?
RECOMMENDATION	<b>HT is recommended to maintain bone density and prevent osteoporosis.</b>  <b>A daily dose of hormone replacement therapy (HRT) containing no less than 2 mg oral estradiol or 100 µg transdermal estradiol, or equivalent, is suggested to optimize bone mineral density.</b>



	<p><b>Delayed initiation and non-adherence of hormone therapy should be avoided.</b></p> <p><b>If the combined oral contraceptive is used, then a continuous or extended regimen is recommended to provide continuous estrogen therapy and avoid bone loss.</b></p>
Desirable effects	HRT in postmenopausal women increases BMD and reduces fracture risk. Estrogen replacement appears to have similar beneficial effects on BMD in POI of all causes although fracture data are lacking. A dose of at least 2 mg estradiol or 100 µg transdermal patch is associated with gains in BMD. Evidence suggests that sequential COC use is inferior to HRT with continuous estrogen and that continuous COC is the preferred option if the COC is used. Non-adherence to HRT is associated with reductions in bone density and increased risk of osteoporosis. Current data suggest no benefit for bone health with the addition of testosterone therapy to HRT.
Undesirable effects	
Certainty of evidence	Observational data, no high quality RCTs
Values	
Balance of effects	Bone health/prevention of fracture vs side-effects of treatment
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	NA

QUESTION	WHAT ARE THE TREATMENT OPTIONS FOR BONE PROTECTION AND IMPROVEMENT?
RECOMMENDATION	<b>Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies to women desiring pregnancy.</b>
Desirable effects	
Undesirable effects	
Certainty of evidence	Observational data, no high quality RCTs
Values	
Balance of effects	Bone health/prevention of fracture vs side-effects of treatment
Resource use, equity, acceptability and feasibility	
Subgroup considerations (if applicable)	Addressed in the recommendation



## PICO QUESTION: HOW SHOULD BONE HEALTH BE MONITORED IN WOMEN WITH POI?

<b>Population</b>	Patients diagnosed with premature ovarian insufficiency (different etiologies)
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• dual energy X-ray absorptiometry (DXA)</li> <li>• Fracture Risk Assessment Tool (FRAX)</li> <li>• bone quality and bone turnover markers</li> <li>• calcium and PTH serum levels</li> <li>• C-Terminal telopeptides of type I-collagen (CTx) (resorption, deformation marker)</li> <li>• tartrate resistant-acid phosphatase (TRAP),</li> <li>• markers of bone resorption,</li> <li>• bone alkaline phosphatase</li> <li>• vitamin D deficiency</li> </ul>
<b>Control</b>	•
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• bone health / bone mineral density / bone density / BMD</li> <li>• osteoporosis / osteoarthritis</li> <li>• fracture risk / incidence of fracture / T-score</li> </ul>

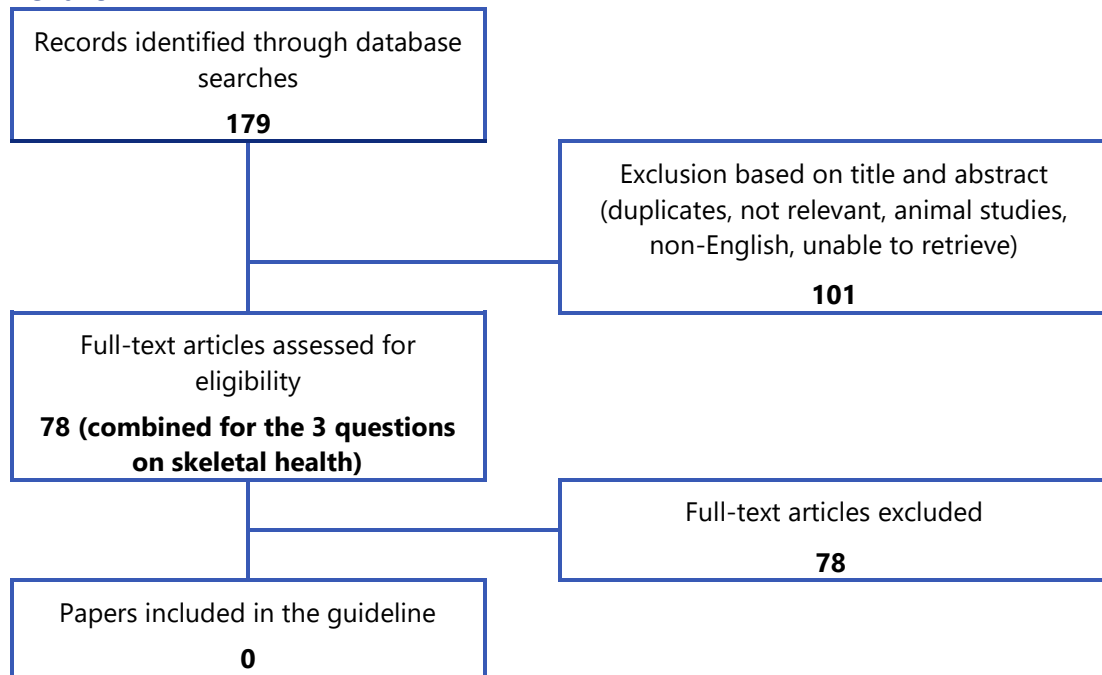
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failue" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("dual energy X-ray absorptiometry" OR DXA OR "Absorptiometry, Photon"[Mesh] OR "Fracture Risk Assessment Tool" OR FRAX OR "bone turnover marker" OR "calcium level" OR "PTH level" OR "parathyroid hormone level" OR CTx OR "resorption marker" OR "bone formation marker" OR "tartrate resistant-acid phosphatase" OR TRAP OR "bone resorption marker" OR "bone alkaline phosphatase" OR BAP OR "vitamine D" OR osteocalcin OR "tartrate resistant acid phosphatase" OR "bone-specific alkaline phosphatase" OR collagen OR procollagen)
<b>COCHRANE</b>	

Literature search was limited to the period between 01/01/2014 and 26/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Not applicable

### Evidence to recommendations

QUESTION RECOMMENDATION GOOD PRACTICE POINT	HOW SHOULD SKELETAL HEALTH BE MONITORED IN WOMEN WITH POI? <b>Where available, measurement of bone mineral density using dual x-ray absorptiometry (DXA) at diagnosis of POI is recommended for all women. If bone mineral density is normal and adequate systemic HT is commenced and adhered to, the value of a repeated DXA scan within 5 years is low. Bone mineral density using DXA should be reassessed every 1–3 years, based on individual risk factors, in women with POI who have osteoporosis or low bone density..</b>
Desirable effects	Based on the evidence that women with POI have reduced BMD (see section VI.1. Skeletal health), BMD measurement should be considered at POI diagnosis. Dual-Energy X-ray Absorptiometry (DXA) is the most reliable assessment for BMD and the amount of ionising radiation used is very small. The optimal interval at which DXA should be repeated is uncertain and intervals of several years may be required based on the limitations of DXA for measuring small changes in BMD. However, repeat BMD testing should be considered in the setting of initial lower BMD, suspected increased rate of bone loss, and where the results will influence management, i.e. change in treatment. As in older postmenopausal women, bone turnover markers may be useful to assess response or adherence to treatment, but evidence is limited in POI.
Undesirable effects	NA



Certainty of evidence	Observational data only
Values	Resource use vs impact of testing
Balance of effects	International guidance was considered with regard to the optimal interval at which DXA should be repeated. When there is an indication, such as suspected increased rate of bone loss, or where the results will influence management, repeated DXA is recommended
Resource use, equity, acceptability and feasibility	Significant
Subgroup considerations (if applicable)	NA

QUESTION	HOW SHOULD SKELETAL HEALTH BE MONITORED IN WOMEN WITH POI?
GOOD PRACTICE POINT	<b>The guideline group recommends that a decrease in bone mineral density should prompt review of HT and potential factors contributing to bone loss. Referral to a specialist may be required.</b>
Justification	Follow up of monitoring, which in absence of evidence could only be formulated as a GPP



## VI.2. Muscle health

### PICO QUESTION: WHAT ARE THE CONSEQUENCES OF POI FOR MUSCLE HEALTH?

<b>Population</b>	POI
<b>Interventions</b>	
<b>Control</b>	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• lean mass</li> <li>• body composition</li> <li>• muscle mass</li> <li>• muscle</li> <li>• sarcopenia</li> <li>• muscle function</li> <li>• muscle hypertrophy</li> </ul>

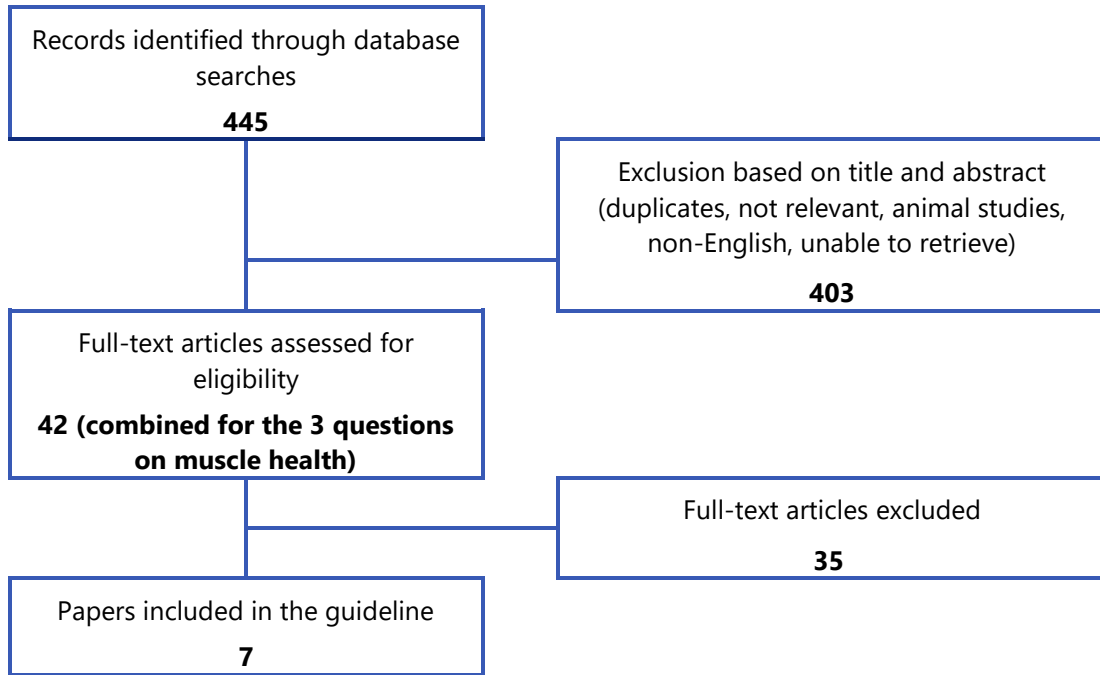
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("lean mass" OR "Body Composition"[Mesh] OR "Body Composition" OR "muscle mass" OR "Muscle" OR "Muscles"[Mesh] OR "Muscle Strength"[Mesh] OR "Satellite Cells, Skeletal Muscle"[Mesh] OR "sarcopenia" OR "Sarcopenia"[Mesh] OR "Muscular Atrophy"[Mesh] OR "muscle function" OR "muscular function" OR "Muscle Hypertrophy")

Literature search was performed on 26/01/2024.



## Flowchart





## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref	Study Design	POI					Controls					Muscle health parameters																																										
		population (cause of POI)	n=? (for POI)	Mean age POI (years)	Age range used in study (years)	Co morbidities Y/N	Comment	Describe population	n = ? (control group)	Mean age controls (years)	Method used to analyse (DXA/BIA/CT/MRI)	Total muscle mass POI mean (SD)	Total muscle mass control mean (SD)	ALM	POI Muscle mass/Composition/Echogenicity/Compressibility	Controls Muscle mass/Composition/Echogenicity/Compressibility	Prevalence	Muscle function																																				
<b>Soucek 2015</b>	Cross-sectional study	TS n = 23 pubertal induction; n = 13 spontaneous puberty; n = 19 prepubertal	60	13.7±4.5	4.7-21.7 years	Y	Autoimmune thyroiditis on treatment N = 13	Healthy	432		Leonardo Mechanograph* Ground Reaction Force Platform; measurements fmax = muscle force; pmax = muscle power; data available for n = 57							<p>Table 3. Muscle function parameters measured by isometric, isometric or by ground reaction force platform.</p> <table border="1"> <thead> <tr> <th></th> <th>Mean (SD)</th> <th>P value</th> </tr> </thead> <tbody> <tr> <td>F<sub>max</sub> (N)</td> <td>134 (60)</td> <td>0.001</td> </tr> <tr> <td>f<sub>max</sub> (N/kg)</td> <td>40.2 (19.2)</td> <td>0.001</td> </tr> <tr> <td>Peak Power (W)</td> <td>231 (101)</td> <td>0.017</td> </tr> <tr> <td>Peak Power (W/kg)</td> <td>71.6 (35.8)</td> <td>0.001</td> </tr> <tr> <td>Peak Power (W/kg)</td> <td>71.6 (35.8)</td> <td>0.001</td> </tr> <tr> <td>Peak Power (W/kg)</td> <td>71.6 (35.8)</td> <td>0.001</td> </tr> <tr> <td>Peak Power (W/kg)</td> <td>71.6 (35.8)</td> <td>0.001</td> </tr> <tr> <td>Peak Power (W/kg)</td> <td>71.6 (35.8)</td> <td>0.001</td> </tr> <tr> <td>Peak Power (W/kg)</td> <td>71.6 (35.8)</td> <td>0.001</td> </tr> <tr> <td>Peak Power (W/kg)</td> <td>71.6 (35.8)</td> <td>0.001</td> </tr> <tr> <td>Peak Power (W/kg)</td> <td>71.6 (35.8)</td> <td>0.001</td> </tr> </tbody> </table>		Mean (SD)	P value	F <sub>max</sub> (N)	134 (60)	0.001	f <sub>max</sub> (N/kg)	40.2 (19.2)	0.001	Peak Power (W)	231 (101)	0.017	Peak Power (W/kg)	71.6 (35.8)	0.001	Peak Power (W/kg)	71.6 (35.8)	0.001	Peak Power (W/kg)	71.6 (35.8)	0.001	Peak Power (W/kg)	71.6 (35.8)	0.001	Peak Power (W/kg)	71.6 (35.8)	0.001	Peak Power (W/kg)	71.6 (35.8)	0.001	Peak Power (W/kg)	71.6 (35.8)	0.001	Peak Power (W/kg)	71.6 (35.8)	0.001
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<b>Luo 2018</b>	Case-control study	Idiopathic	240	31.58 ± 6.83			Age and BMI matched healthy women and Peri/postmenopausal	260+260	Peri-M=45.50 ± 3.54; Post M=50.14 ± 3.78; Normal =31.32 ± 6.62					Anthropometry; Mobility evaluation system Strength of Left lower limb SRL(weight) = 1.19 ± 0.25; Strength of right lower limb SRL(weight)=1.22 ± 0.25; muscle distributing coefficient of lower limbs (MD) = 0.81 ± 0.09	Perim: Strength of Left lower limb SRL(weight) = 1.15 ± 0.23; Strength of right lower limb SRL(weight)=1.19 ± 0.26; muscle distributing coefficient of lower limbs (MD) = 0.86 ± 0.10; PostM: Strength of Left lower limb SRL(weight) = 1.08 ± 0.22; Strength of right lower limb SRL(weight)=1.12 ± 0.25; muscle distributing coefficient of lower limbs (MD) = 0.87 ± 0.10; Normal: Strength of Left lower limb SRL(weight) = 1.24 ± 0.22; Strength of right lower limb SRL(weight)=1.27 ± 0.22; muscle distributing coefficient of lower limbs (MD) = 0.84 ± 0.10 [P values for all 0.000]																																							
<b>Fante 2020</b>	Cross-sectional study	NR; 18.67% karyotype alteration	150	34.30 (8.58)			Age and BMI matched with regular menstrual cycles	150	34	Questionnaire: Pelvic floor distress inventory (PFDI-20) and Kings Health Questionnaire (KHQ) and vaginal palpation for pelvic floor assessment						POI prevalence 27.33% Urinary incontinence (UI), 9.33% pelvic organ prolapse (POP), and 8% Faecal incontinence (FI) vs control group 37.33% UI, 8% POP, and 4%FI; P > 0.05																																						
<b>Cho 2021</b>	Cross-sectional study	Cause NR	45	Age of menopause < 40 years mean age not given; age of assessment for this group 77.2±4.2			Premature menopause and post menopausal groups	40-44 (n=89); 45-54 (n=552); ≥55 (n=79)	30		Age-adjusted body composition and physical function by age of natural menopause																																											
<b>Freitas 2021</b>	Case-control study	Normal Karyotype POI on HT for at least 12 months	70	36.33 ± 7.51 years			Age and BMI matched healthy	70	36.27 ± 7.30 years	DXA	Lean mass (LM) 36 053 ± 4771 vs 36844 ± 4557 p value 0.250; LM% 56.97 ± 7.62 vs																																											



											57.97 ± 8.30 P = 30							
<b>Samad 2022</b>	Cohort study	Normal karyotype POI; Spontaneous 40%; Iatrogenic 60%	60	34 (29-38)				Age+BMI matched	60	34 (30-38)	DXA		ALM (g) or ASM POI mean (SD) ALM s-POI = 15891.00 (14063.50, 17247.00); ALM i-POI = 16952.00 (14613, 19029.50)  ALM (g) or ASM Control mean (SD) ALM = 19627.50 (17718.00, 21360.00) p < 0.001  ALM/ H2 POI mean(SD) s-POI = 6172.69 (5472.46, 6638.57); i-POI = 6154.71 (5645.69, 7100.59) ALM/ H2 Controls mean (SD) 7077.83 (6452.79, 7740.68) p < 0.001					
<b>Li 2023</b>	Cross-sectional study	Spontaneous	59	37 (32, 38)				Premenoapusal	57	37 (32, 38)	DXA	Total skeletal muscle (TSM): 33.85 ± 4.08 vs 36.43 ± 3.56, P < 0.001; TSM/weight: 0.63 [0.59, 0.65] vs 0.64 [0.61, 0.67], P = 0.02	ALM (g) or ASM POI mean (SD) ASM: 14.62 ± 2.08 vs 15.97 ± 1.78, P < 0.001; ASM/height2: 5.71 ± 0.64 vs 6.15 ± 0.62, P < 0.001; ASM/weight: 0.27 [0.25, 0.28] vs 0.28 [0.27, 0.29], P = 0.002; ASM/BMI: 0.68 ± 0.07 vs 0.73 ± 0.06, P = 0.001; TSM: 33.85 ± 4.08 vs 36.43 ± 3.56, P < 0.001; TSM/weight: 0.63 [0.59, 0.65] vs 0.64 [0.61, 0.67], P = 0.02  Prevalance of low muscle mass POI vs control ASM/height2 <5.4 kg/m2 32.20% vs 8.77%, χ2 = 9.70, P = 0.00.					



*Evidence to recommendations*

QUESTION RECOMMENDATION	WHAT ARE THE CONSEQUENCES OF POI FOR MUSCLE HEALTH? <b>It is suggested that HCPs inform women that POI may be associated with reduced muscle mass, strength, and performance, which may increase the risk of sarcopenia.</b>
Desirable effects	POI may be associated with reduced muscle mass, strength, and performance
Undesirable effects	NA
Certainty of evidence	Observational data only
Values	Informed patients
Balance of effects	Focus on information provision
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	NA



## PICO QUESTION: WHAT ARE THE TREATMENT OPTIONS FOR MUSCLE PROTECTION AND IMPROVEMENT?

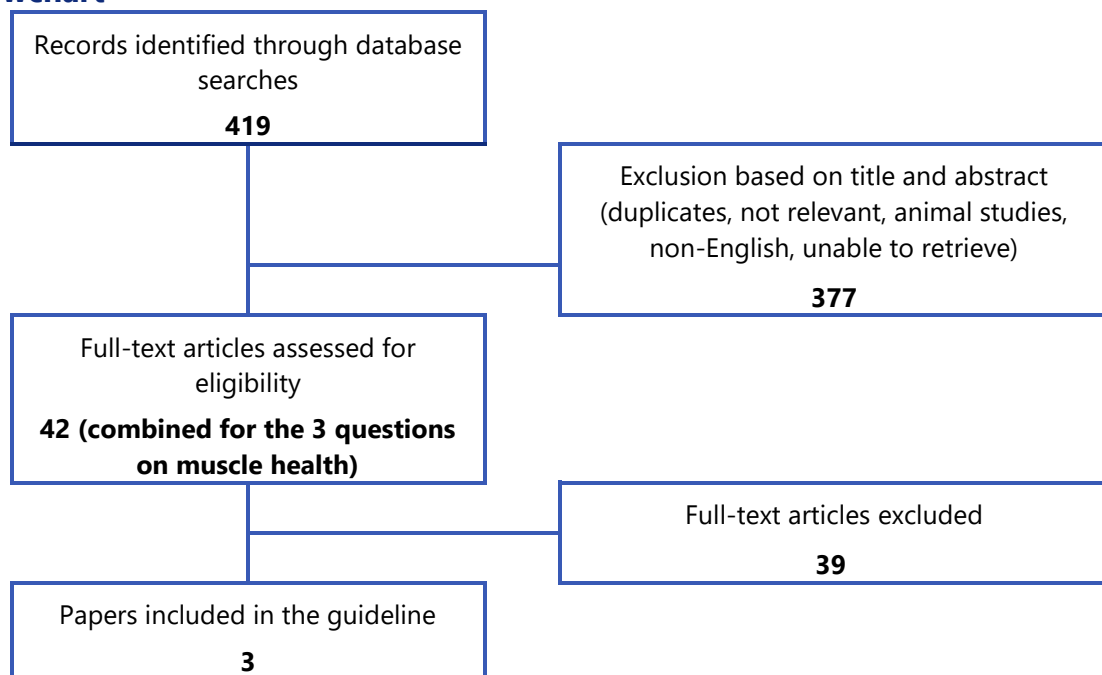
<b>Population</b>	POI
<b>Interventions</b>	<ul style="list-style-type: none"> <li>Resistance training / exercise</li> <li>Estrogen</li> </ul>
<b>Control</b>	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>lean mass</li> <li>body composition</li> <li>muscle mass</li> <li>muscle</li> <li>sarcopenia</li> <li>muscle function</li> <li>muscle hypertrophy</li> </ul>

### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (Exercise OR "weight-bearing" OR "muscle-building" OR "physical activity" OR "Resistance training" OR "sport" OR "Exercise"[Mesh] OR estrogen OR estradiol OR HRT OR "hormone replacement therapy") AND ("lean mass" OR "Body Composition"[Mesh] OR "Body Composition" OR "muscle mass" OR "Muscle" OR "Muscles"[Mesh] OR "Muscle Strength"[Mesh] OR "Satellite Cells, Skeletal Muscle"[Mesh] OR "sarcopenia" OR "Sarcopenia"[Mesh] OR "Muscular Atrophy"[Mesh] OR "muscle function" OR "muscular function" OR "Muscle Hypertrophy")

Literature search was performed on 26/01/2024.

### Flowchart





## Evidence

### Summary of Findings Table

Not applicable

### Evidence table - Hormone therapy

Ref.	Study Design	PARTICIPANTS						CONTROLS					HRT				OUTCOMES																																									
		Describe population (cause of POI)	n=? (for POI)	n=? For whole cohort (if it includes those > 40 years)	Mean age (years)	Any other co-morbidities Y/N	Comment	Describe population	n=? (control group)	Mean age (years)	Age range used in study (years)	Any other co-morbidities Y/N	% or N POI treated with HRT	Comment type dose	Comment duration	% or N Controls treated with HRT		% or N POI treated with COC																																								
<b>(Cleemann et al., 2017)</b>	Randomised trial - Double blind	TS on high dose 4mg estradiol vs low dose 2mg estradiol	20		19.2 ±2.5			age matched	34	18.4±2.7			100%; n = 10 high dose; n = 10 low dose	Low-dose (LD) oral 2 mg 17β-estradiol/day; High-dose (HD) group oral 4 mg 17β-estradiol/day	LD 4.4±1.5 vs HD 4.7±1.4 years			<p>Muscle mass POI mean SD Lean body mass (LBM) there was a significant effect of the interaction between time and treatment (P=0.0290)</p> <table border="1"> <thead> <tr> <th></th> <th>Tumor syndrome</th> <th>Controls</th> <th>P*</th> </tr> </thead> <tbody> <tr> <td>No.</td> <td>20</td> <td>34</td> <td></td> </tr> <tr> <td>Age (years)</td> <td>19.2 ± 2.5</td> <td>18.4±2.7</td> <td>0.3</td> </tr> <tr> <td>Height (cm)</td> <td>158.0±6.9</td> <td>167.7±6.6</td> <td>&lt;0.0001</td> </tr> <tr> <td>Weight (kg)</td> <td>57.1±11.3</td> <td>59.8±7.7</td> <td>0.4</td> </tr> <tr> <td>BMI (kg/m<sup>2</sup>)</td> <td>23.2±8.8</td> <td>20.4±2.5</td> <td>0.001</td> </tr> <tr> <td>BSA (m<sup>2</sup>)</td> <td>1.45±0.18</td> <td>1.64±0.13</td> <td>&lt;0.0001</td> </tr> <tr> <td>LBM (kg)</td> <td>34.4±5.9</td> <td>41.2±5.2</td> <td>&lt;0.0001</td> </tr> <tr> <td>Fat (%)</td> <td>42.6±7.3</td> <td>22.5±3.9</td> <td>0.06</td> </tr> <tr> <td>Fat (%)</td> <td>29.3±6.3</td> <td>23.0±4.1</td> <td>&lt;0.0001</td> </tr> </tbody> </table> <p>*P values determine by unpaired t-test</p> <p>Legend Age, height, weight, body mass index (BMI), body surface area (BSA), lean body mass (LBM), fatness (FM) and fat percentage (Fat %) in Tumor syndrome and age-matched controls at the baseline visit.</p>		Tumor syndrome	Controls	P*	No.	20	34		Age (years)	19.2 ± 2.5	18.4±2.7	0.3	Height (cm)	158.0±6.9	167.7±6.6	<0.0001	Weight (kg)	57.1±11.3	59.8±7.7	0.4	BMI (kg/m <sup>2</sup> )	23.2±8.8	20.4±2.5	0.001	BSA (m <sup>2</sup> )	1.45±0.18	1.64±0.13	<0.0001	LBM (kg)	34.4±5.9	41.2±5.2	<0.0001	Fat (%)	42.6±7.3	22.5±3.9	0.06	Fat (%)	29.3±6.3	23.0±4.1	<0.0001
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<b>(Fante et al., 2020)</b>	Cross-sectional study	NR; 18.67% karyotype alteration	150		34.30 (8.58)			Age and BMI matched with regular menstrual cycles	150	34		n = 114 HT users vs non users n = 36	n= 27 1mg estradiol or 0.625 mg CEE+progestogens, n= 55 were using 2 mg estradiol or 1,25 mg CEE + progestogens, n = 11 were using tibolone		0	21	<p>Muscle mass POI mean SD Questionnaire: Pelvic floor distress inventory (PFDI-20) and Kings Health Questionnaire (KHQ) and vaginal palpation for pelvic floor assessment</p> <p>Muscle mass mean difference prevalence UI HT users 22.81%, non-HT users 41.67% (P=0.03); POP 7.89% vs 13.89% (P &gt; 0.05); FI 6.14% vs 13.89% (P &gt; 0.05).</p>																																									
<b>(Li et al., 2023a)</b>	Cross-sectional study	Spontaneous	59		37 (32, 38)			Premenoapusal	57	37 (32, 38)		74.58% of POI (n=44)	NR				<p>Muscle mass POI mean SD Total skeletal mass (TSM) TSM/weight 0.62 (0.58, 0.65) vs 0.63 (0.60, 0.65) p value = 0.88</p> <p>Appendicular lean (skeletal) mass (ALM or ASM) POI mean SD Non HT users vs HT users; ASM,kg 14.73 ± 1.81 vs 14.58 ± 2.19 p = 0.51; ASM/height 5.75 ± 0.68 vs 5.69 ± 0.63 p value 0.77; ASM/weight 0.27 (0.25, 0.28) vs 0.27 (0.25, 0.28) p value 0.94; TSM, kg 34.00 ± 3.36 vs 33.80 ± 4.33 p value 0.87</p>																																									





*Evidence to recommendations*

QUESTION	WHAT ARE THE TREATMENT OPTIONS FOR MUSCLE PROTECTION AND IMPROVEMENT?
GOOD PRACTICE POINT	<b>The guideline group recommends that women with POI should be encouraged to adopt a healthy lifestyle (including healthy diet, physical activity, avoiding smoking, and maintaining normal body weight) to aid muscle health.</b>
Justification	Evidence suggests that lifestyle interventions and HRT in non-POI populations may benefit muscle mass, strength, and performance. Advice regarding modifiable risk factors should be provided.

QUESTION	WHAT ARE THE TREATMENT OPTIONS FOR MUSCLE PROTECTION AND IMPROVEMENT?
RECOMMENDATION	<p><b>HCPs may consider prescribing resistance exercise for women with POI and impaired muscle parameters as resistance exercise increases muscle mass, strength and performance in other populations, although specific evidence in women with POI is lacking.</b></p> <p><b>It is suggested that HCPs inform women with POI that HRT prescribed for other indications may also benefit muscle health.</b></p> <p><b>The effect of other interventions, including testosterone therapy, on muscle health in women with POI is uncertain and therefore they should not be offered.</b></p>
Desirable effects	Studies of interventions for muscle health in women with POI are limited and inconclusive. Evidence suggests that lifestyle interventions and HRT in non-POI populations may benefit muscle mass, strength, and performance.
Undesirable effects	
Certainty of evidence	Very low evidence, scarce data
Values	Interventions not supported by data should not be offered.
Balance of effects	Focus on exercise (low undesirable effects) or treatments prescribed for other indications. Interventions not supported by data should not be offered.
Resource use, equity, acceptability and feasibility	YES
Subgroup considerations (if applicable)	NA



## PICO QUESTION: HOW SHOULD MUSCLE HEALTH BE MONITORED IN WOMEN WITH POI?

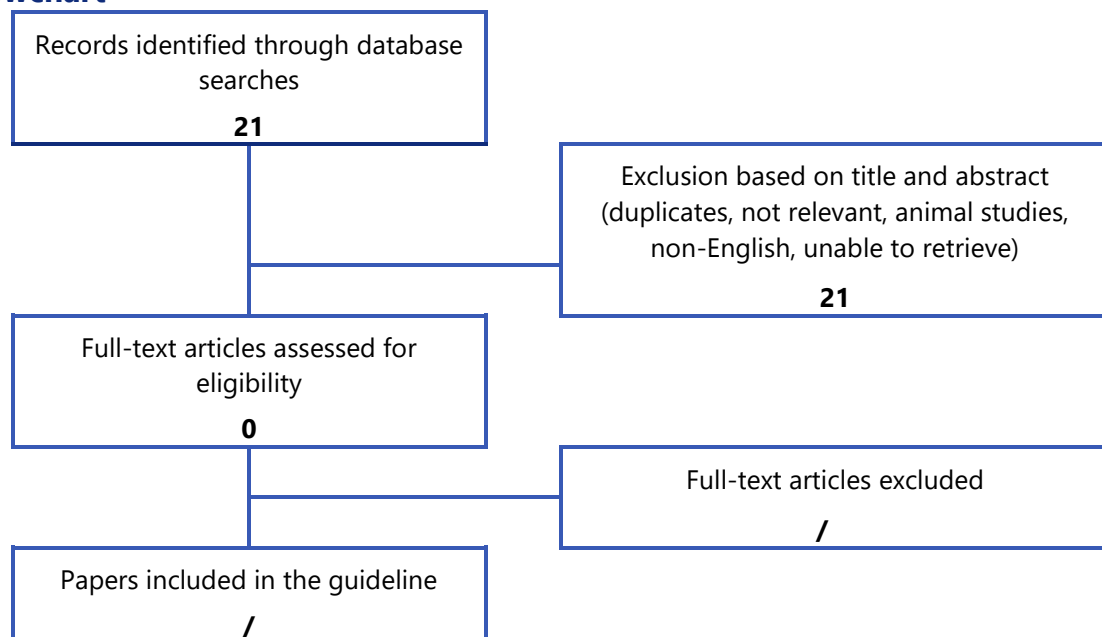
<b>Population</b>	POI
<b>Interventions</b>	dual energy X-ray absorptiometry (DXA)
<b>Control</b>	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• lean mass</li> <li>• body composition</li> <li>• muscle mass</li> <li>• muscle</li> <li>• sarcopenia</li> <li>• muscle function</li> <li>• muscle hypertrophy</li> </ul>

### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("dual energy X-ray absorptiometry" OR DXA OR "Absorptiometry, Photon"[Mesh]) AND ("lean mass" OR "Body Composition"[Mesh] OR "Body Composition" OR "muscle mass" OR "Muscle" OR "Muscles"[Mesh] OR "Muscle Strength"[Mesh] OR "Satellite Cells, Skeletal Muscle"[Mesh] OR "sarcopenia" OR "Sarcopenia"[Mesh] OR "Muscular Atrophy"[Mesh] OR "muscle function" OR "muscular function" OR "Muscle Hypertrophy")

Literature search was performed on 26/01/2024.

### Flowchart







## Evidence

### *Summary of Findings Table*

Not applicable

### *Evidence table*

Not applicable

### *Evidence to recommendations*

QUESTION	How should muscle health be monitored in women with POI?
GOOD PRACTICE POINT	<b>The guideline group recommends that HCPs consider screening for sarcopenia at POI diagnosis.</b>
Justification	Recommendations for screening, diagnosis and monitoring of sarcopenia exist for older populations; however, the best tools and relevant cut-off values for women with POI are lacking. DXA assessment of bone density provides osteoporosis risk stratification and information regarding muscle mass. Emerging evidence indicates that POI may have an adverse effect on muscle health which has implications for cardiometabolic and bone health. Optimal strategies for assessing, monitoring, and managing muscle health in women with POI are unknown..



## VII. POI and cardiometabolic health

### PICO QUESTION: WHAT ARE THE CONSEQUENCES OF POI FOR THE CARDIOVASCULAR SYSTEM?

<b>Population</b>	POI
<b>Interventions</b>	
<b>Control</b>	
<b>Outcomes</b>	Cardiovascular risk Rupture of the aorta Aortic dilatation Blood pressure Hypertension Congenital heart disease low-density lipoprotein (LDL) cholesterol high-density lipoprotein (HDL) cholesterol myocardial infarction, cerebrovascular disease, arteriosclerosis, cholesterol monitoring, endothelial dysfunction

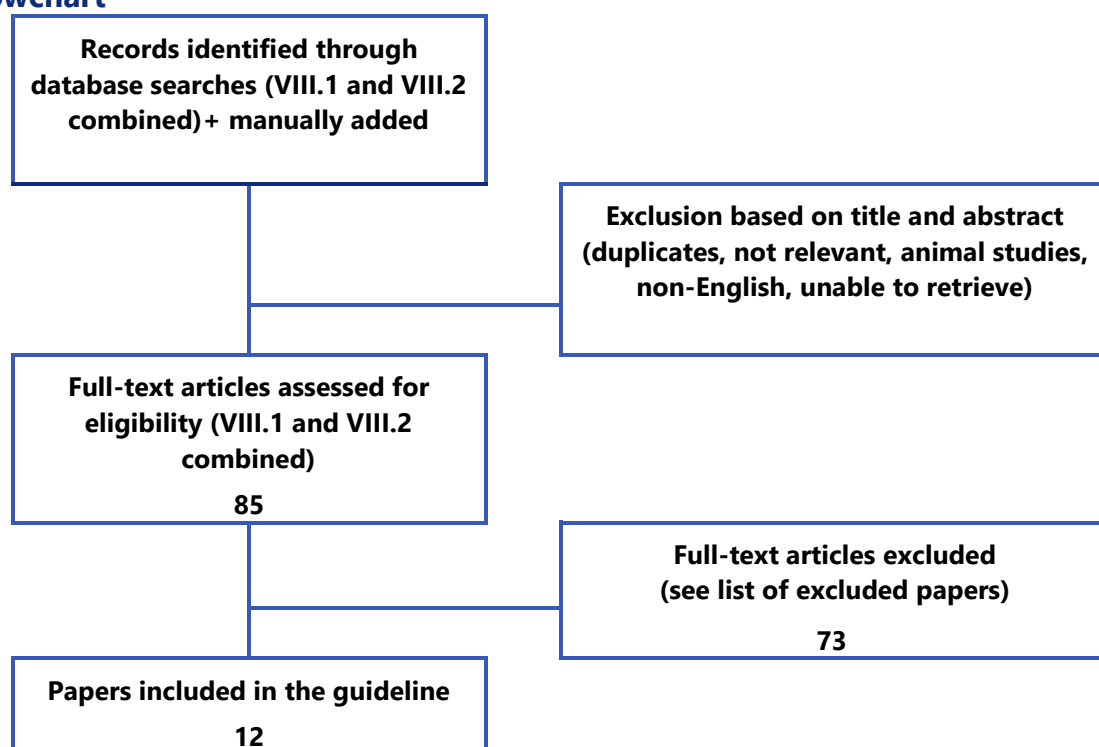
### Search strings

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<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("Cardiovascular risk" OR "Rupture of the aorta" OR "aortic rupture" OR "Aortic Rupture"[Mesh] OR "Aortic dilatation" OR "Blood pressure" OR "Blood Pressure"[Mesh] OR "Hypertension" OR "Hypertension"[Mesh] OR "Congenital heart disease" OR "Heart Diseases"[Mesh] OR CHD OR "low-density lipoprotein cholesterol" OR LDL OR "high-density lipoprotein cholesterol" OR HDL OR cholesterol OR "Cholesterol"[Mesh] OR "Cholesterol, HDL"[Mesh] OR "Cholesterol, LDL"[Mesh] OR "myocardial infarction" OR "Myocardial Infarction"[Mesh] OR "cerebrovascular disease" OR "Basal Ganglia Cerebrovascular Disease"[Mesh] OR arteriosclerosis OR "Atherosclerosis"[Mesh] OR "endothelial dysfunction")

Literature search was limited to the period between 01/01/2014 and 19/12/2023. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Cardiovascular disease (CVD) and mortality</b>								
(Muka <i>et al.</i> , 2016).	meta-analyses	310329 women (derived from 32 observational studies)	EM	control	risk for CAD, CVD mortality and CAD mortality	women with early menopause had an increased risk for CAD, CVD mortality and CAD mortality compared to women who had menopause after the age of 45 years (RR 1.50; 95% CI 1.28 to 1.76, RR 1.19; 95% CI 1.08 to 1.31, and RR 1.11; 95% CI 1.03 to 1.20, respectively)		
(Zhu <i>et al.</i> , 2019).	meta-analyses	15 observational studies	EM/POI	control	cardiovascular disease event	women with POI and early menopause had a substantially increased risk of a non-fatal		



						cardiovascular disease event before the age of 60 years, but not after age 70 years, as compared with women who had menopause at the usual age of 50-51 years		
<b>(Lee et al., 2023)</b>	Study	1,159,405 Korean postmenopausal women	POI	Control (UAM)	Stroke	increased risk of myocardial infarction (HR 1.40; 95% CI 1.31 to 1.50), ischemic stroke (HR 1.24; 95% CI 1.17 to 1.31), and all-cause mortality (HR 1.19; 95% CI 1.14 to 1.24)		
<b>(Yuk et al., 2023).</b>	Study	135,575 women aged 40-49 years	POI	Control (UAM)	Stroke (median follow-up 7.9 years)	risk of stroke was significantly higher in women with early hysterectomy before 45 years of age (HR 1.31; 95% CI 1.12 to 1.53)		
<b>(Hassan et al., 2024)</b>	systematic review		hysterectomy with bilateral oophorectomy before the age of 45		Stroke CVD	an increased risk of stroke (HR 1.20; 95% CI 1.10 to 1.31) and CVD (HR 1.18; 95% CI 1.11 to 1.25)		
<b>(Liu et al., 2023).</b>	meta-analysis	20 cohort studies,	POI or early menopause (at age 40-45 years)	women with menopause at age > 45 years	CHD Stroke	higher risk for coronary heart disease (CHD), ischemic and haemorrhagic stroke and total cardiovascular event		
<b>Cardiovascular effects of spontaneous and surgical POI</b>								
<b>(Farland et al., 2023).</b>			hysterectomy along with any oophorectomy (unilateral or bilateral) has also been			associated with an increased risk of CVD		
<b>(Honigberg et al., 2019).</b>	Cohort	144,260 postmenopausal women	POI	control	Cardiovascular effects	POI was independently associated with increased risk for a composite cardiovascular outcome, that included CAD, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism  The hazard ratio (HR) was 1.36 for non-iatrogenic POI and 1.87 for surgical premature menopause  Risk of hypertension, diabetes and hyperlipidaemia was greater in women with surgical POI versus spontaneous POI		
<b>Cardiovascular disease risk factors</b>								



<b>(Liu et al., 2023).</b>	meta-analysis	20 cohort studies,	POI or early menopause (at age 40-45 years)	women with menopause at age > 45 years	Metabolic effects	higher risk of type 2 diabetes (RR 1.32; 95% CI 1.08 to 1.62 and RR 1.17; 95% CI 1.09 to 1.36, respectively), and hyperlipidaemia (RR 1.21; 95% CI 1.05 to 1.39 and RR 1.17; 95% CI 1.02 to 1.33, respectively), compared with women with usual age menopause		
<b>(Cai et al., 2022).</b>	meta-analysis	21 case-control studies	1573 women with POI	1762 controls	Metabolic effects	women with POI had significantly higher waist circumference, total cholesterol, LDL-C, triglycerides, and fasting glucose		medium quality
					Hypertension	No significant difference in systolic or diastolic blood pressure between women with POI or controls was reported in 6 studies (n=273 POI patients and 480 controls)		
<b>(Jin et al., 2023).</b>	cross-sectional study		118 Chinese women with POI	151 age-matched controls	Metabolic effects	women with POI have significantly increased triglyceride levels, fasting glucose and insulin and HOMA-IR		
<b>(Honigberg et al., 2019).</b>	Cohort	144,260 postmenopausal women	POI	control	Metabolic effects	Secondary outcomes : an increased risk (models adjusted for age, race/ethnicity, BMI, and the prevalent hypertension, hyperlipidaemia, and type 2 diabetes) of incident type 2 diabetes and hyperlipidaemia in women with spontaneous or surgical POI compared with women at usual age of menopause; greater risk observed with surgical POI		
					Hypertension	Incident hypertension was increased in women with spontaneous (HR 1.43; 95%CI 1.24 to 1.65) or surgical (HR 1.93; 95% CI 1.37 to 2.74) POI		

**Turner Syndrome**

Section updated based on the recent paper of (Gravholt et al., 2023)

*Evidence to recommendations*

QUESTION	WHAT ARE THE CONSEQUENCES OF POI FOR THE CARDIOVASCULAR SYSTEM?
RECOMMENDATION	<b>Women with POI should be advised that they are at increased risk of cardiovascular disease, including coronary artery disease, heart failure, and stroke.</b>



Desirable effects	Women with POI are at greater risk of hypertension, diabetes and hyperlipidaemia and endothelial dysfunction contributing to premature atherosclerosis. They further show increased cardiovascular morbidity and mortality regardless of the cause of the ovarian insufficiency.
Undesirable effects	
Certainty of evidence	Observational data
Values	Focus on information provision and advice
Balance of effects	
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	NA

QUESTION RECOMMENDATION	WHAT ARE THE CONSEQUENCES OF POI FOR THE CARDIOVASCULAR SYSTEM? <b>All women diagnosed with Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease, especially prior to and during pregnancy.</b>
Desirable effects	Morbidity and mortality are increased in patients with TS compared with the general population, predominately due to an increased risk of cardiovascular disease including congenital heart disease.
Undesirable effects	
Certainty of evidence	Observational data - complications
Values	Focus on information provision and prevention
Balance of effects	
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	Especially important for women prior to and during pregnancy.



## PICO QUESTION : IS ESTROGEN REPLACEMENT CARDIO-PROTECTIVE?

<b>Population</b>	POI
<b>Interventions</b>	Oestrogen replacement therapy HRT OR "hormone replacement therapy")
<b>Control</b>	
<b>Outcomes</b>	Cardio-protective" Cardiovascular risk /problems Rupture of the aorta Aortic dilatation Blood pressure Hypertension Congenital heart disease Endothelial elasticity low-density lipoprotein (LDL) cholesterol high-density lipoprotein (HDL) cholesterol myocardial infarction, cerebrovascular disease, atherosclerosis, cholesterol monitoring, endothelial dysfunction

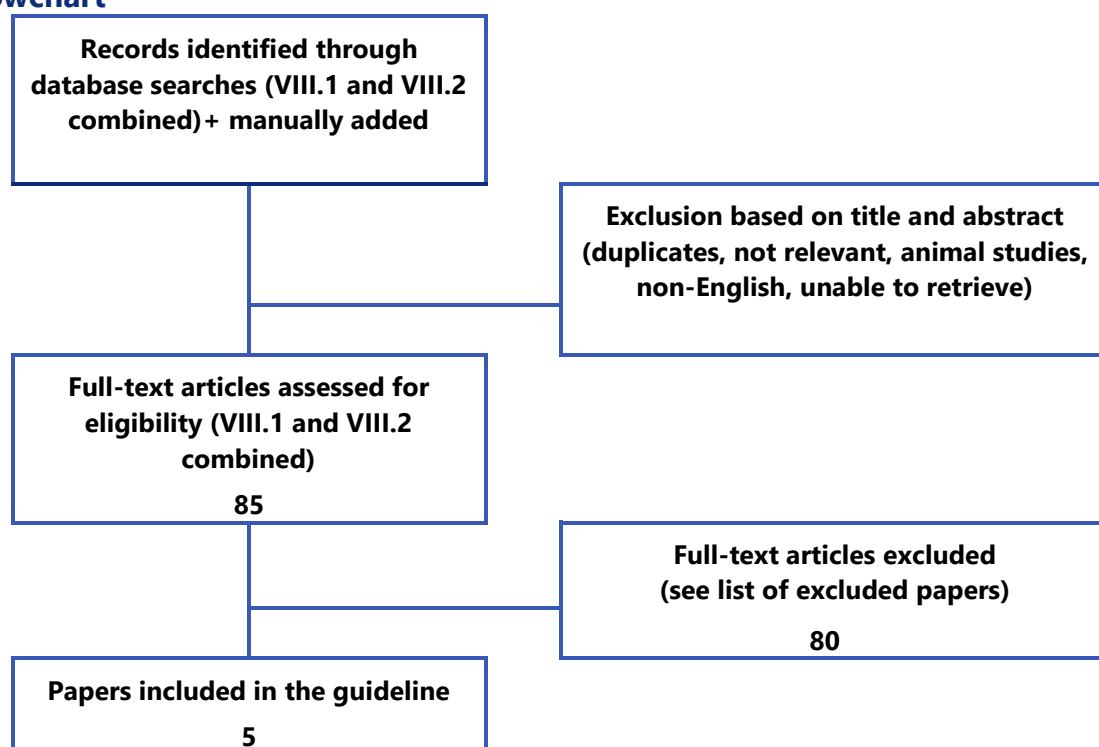
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhoea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (estrogen OR estradiol OR oestrogen OR "Estrogen Replacement Therapy"[Mesh] OR "Estrogen Replacement Therapy" OR HRT OR "hormone replacement therapy" OR "hormone therapy" OR "Hormone Replacement Therapy"[Mesh] ) AND ("Cardio-protective" OR "Cardiovascular problems" OR "Endothelial elasticity" OR "Cardiovascular risk" OR "Rupture of the aorta" OR "aortic rupture" OR "Aortic Rupture"[Mesh] OR "Aortic dilatation" OR "Blood pressure" OR "Blood Pressure"[Mesh] OR "Hypertension" OR "Hypertension"[Mesh] OR "Congenital heart disease" OR "Heart Diseases"[Mesh] OR CHD OR "low-density lipoprotein cholesterol" OR LDL OR "high-density lipoprotein cholesterol" OR HDL OR cholesterol OR "Cholesterol"[Mesh] OR "Cholesterol, HDL"[Mesh] OR "Cholesterol, LDL"[Mesh] OR "myocardial infarction" OR "Myocardial Infarction"[Mesh] OR "cerebrovascular disease" OR "Basal Ganglia Cerebrovascular Disease"[Mesh] OR atherosclerosis OR "Atherosclerosis"[Mesh] OR "endothelial dysfunction")

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## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Effect of estrogen therapy on CVD outcomes</b>								
{Lokkegaard, 2006 #577}.	observational	Danish female nurses above 44 years of age in 1993  (n= 19,898)				In menopause after bilateral oophorectomy : 3-fold increase in ischemic heart disease among never users compared to ever users of HT  The effect of HT was most pronounced for the subgroup of current users and among women who started treatment	Generally HT did not reduce the risk except for the early-ovariectomised women, where no increased risk of ischaemic heart disease for HT users was found.	



						within 1 year of menopause.		
<b>(Honigberg et al., 2019).</b>	Cohort	144,260 postmenopausal women	POI	control	Cardiovascular effects	HR for CAD: 3.6 (95% CI 2.3 to 5.5) in surgical menopause 1.8 (95% CI 1.4 to 2.2) in POI 1.2 (95% CI 1.0 to 1.33) with ever use of HRT		
<b>Effect of estrogen therapy on CVD risk factors</b>								
<b>(Burgos et al., 2017)</b>	SR (4 studies)	POI (TS excluded)	HRT		lipid changes	reduction in LDL and increase in triglyceride concentrations with oral HRT on one study (Kalantaridou et al., 2004), no change in one study and inconclusive in the remainder due to methodological issues.		
<b>(Gonçalves et al., 2022)</b>	SR	POI	HRT		lipid changes	reduction in total cholesterol and LDL with HT observed in the largest cohort study (n=2184)		1 RCT and 2 cohort studies
<b>(Christ et al., 2018).</b>	cross-sectional	385 women with POI	estrogen exposure (duration of menstrual function prior to POI diagnosis and HT use) .	NA	CVD risk	Women who reported longer estrogen-free duration had higher CVD risk; every year a woman with POI is without estrogen exposure her risk of CVD events increases by 0.18% to 0.20% (independent of age, ethnicity, smoking)		



						status, and BMI)		
<b>Tumer Syndrome</b>								
(Viuff <i>et al.</i> , 2020).	cohort	1156 females diagnosed with TS from 1960 to 2014  Among 329 45,X women, 44 had never been HRT treated, and 285 had been treated at some point	treated with HRT	Never HRT	mortality, hospitalizations, and medical prescriptions	Comparing HRT treated with nontreated 45,X women, we found a similar mortality (hazard ratio 0.83, 95% confidence interval 0.38-1.79). Among the HRT-treated 45,X women, we found a significantly lower use of antihypertensives, antidiabetics, and thyroid hormones and significantly reduced hospitalization rates for stroke and osteoporotic fractures.	HRT seems to have a beneficial effect on endocrine conditions, hypertension, and stroke in women with 45,X karyotype, with no clear impact on mortality.	

### Evidence to recommendations

QUESTION	Is estrogen replacement cardio-protective?
RECOMMENDATION	HCPs and women should be aware that estrogen therapy has beneficial cardiometabolic effects, which can influence cardiovascular disease risk. Non-use of HT is associated with an increased risk of cardiovascular events and mortality, and HT is therefore recommended until the usual age of menopause.
Desirable effects	Hormone therapy in POI has beneficial effects on plasma lipids, blood pressure, insulin resistance, and vascular endothelial function. Non-use of HT is associated with an increased risk of cardiovascular events and mortality
Undesirable effects	
Certainty of evidence	Observational data only – no long term evidence
Values	Benefits of HT for CV health, but also other benefits (bone)
Balance of effects	Recommendation for HT in women with POI, with a note that in the absence of long-term randomised prospective data, treatment should be individualized and carefully monitored.



Resource use, equity, acceptable and feasible acceptability and feasibility Subgroup considerations (if applicable)	NA
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## PICO QUESTION : SHOULD CARDIOVASCULAR RISK FACTORS BE MONITORED?

<b>Population</b>	POI
<b>Interventions</b>	Monitoring Echocardiography ECG MRI Echo Blood pressure
<b>Control</b>	
<b>Outcomes</b>	Cardiovascular risk Rupture of the aorta Aortic dilatation Blood pressure Hypertension Congenital heart disease

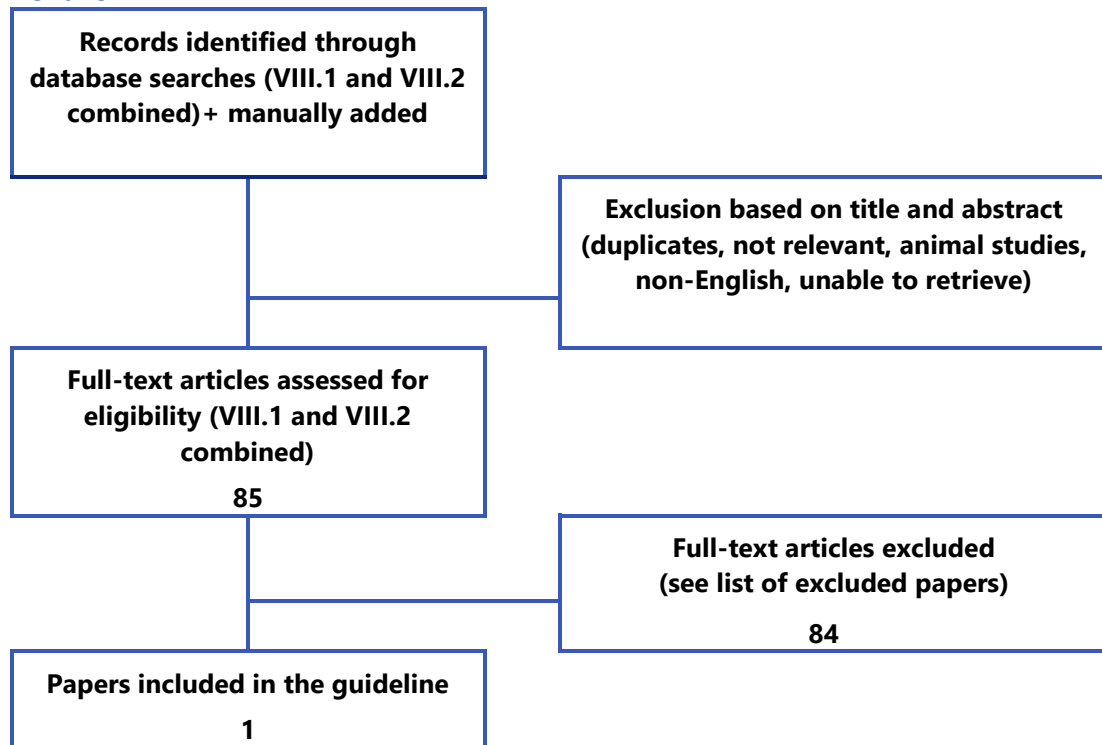
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## Flowchart



## Evidence

### Evidence

#### Summary of Findings Table

Not applicable

#### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
There were no studies evaluating Monitoring interventions on the listed outcomes								
Turner Syndrome								
Section updated based on the recent paper of (Gravholt <i>et al.</i> , 2023)								

#### Evidence to recommendations

QUESTION	SHOULD CARDIOVASCULAR RISK FACTORS BE MONITORED?
GOOD PRACTICE POINT	<p><b>The guideline group recommends that cardiovascular risk should be assessed in women diagnosed with POI.</b></p> <p><b>The guideline group recommends that women with POI should be informed of cardiovascular risk factors that they can modify through lifestyle behavioural change (including avoiding smoking, heart healthy diet, regular physical activity, and maintenance of normal body weight).</b></p>



**The guideline group recommends that all women with POI should have (at least) annual monitoring of blood pressure, weight, and smoking status.**

**The guideline group recommends that all women with POI should have a lipid profile and diabetes screening at diagnosis.**

Justification

There are no validated tools for screening CVD risk in women with POI or Turner Syndrome.

Conventional screening tools are not suitable for women with POI as they are at increased relative risk for cardiovascular disease as compared to age-matched healthy women. Estrogen deficiency at young age adds to the 'lifetime' risk for CVD.

However, screening for cardiovascular risk factors at diagnosis may be indicated as lifestyle measures during pre-menopause improve health in later years.

Women with POI including Turner Syndrome, have an excess of several cardiovascular risk factors, including hypertension, obesity, impaired glucose tolerance, and hyperlipidaemia. Therefore, annual screening for cardiovascular risk factors should be performed, and if present managed appropriately. A heart healthy lifestyle should be discussed including smoking cessation. There are no clear recommendations on BP thresholds or targets for the treatment of hypertension in women with Turner Syndrome, but somewhat lower target values are believed to be desirable.



## VIII. POI and psychological wellbeing

### PICO QUESTION: WHAT ARE THE CONSEQUENCES OF POI ON PSYCHOLOGICAL WELLBEING AND QUALITY OF LIFE?

<b>Population</b>	POI
<b>Interventions</b>	None
<b>Control</b>	
<b>Outcomes</b>	Well being - Quality of life Psychological function Self-esteem - Anxiety Depression - somatization Sensitivity - hostility psychological distress stigma

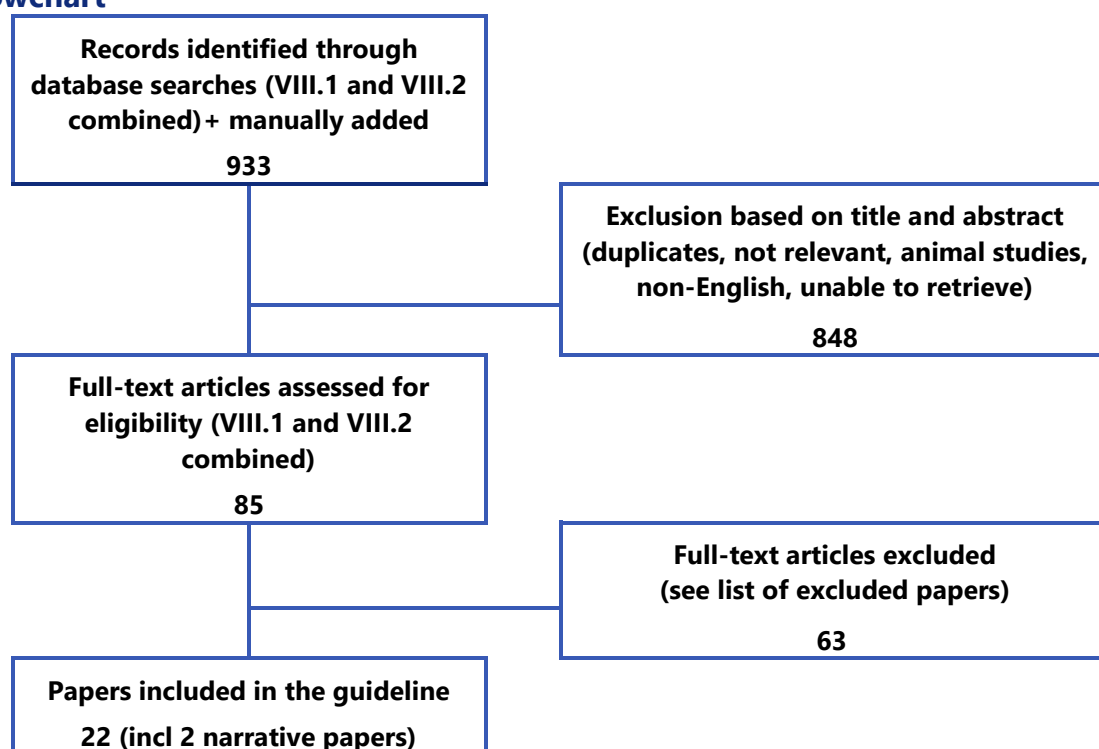
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("Well being" OR "Quality of life" OR "Psychological function" OR Self-esteem OR Anxiety OR Depression OR Somatization OR sensitivity OR hostility OR distress OR stigma OR Satisfaction OR "Quality of Life"[Mesh] OR "Stress, Psychological"[Mesh] OR "Self Concept"[Mesh] OR "Anxiety"[Mesh] OR "Hostility"[Mesh] OR "Social Stigma"[Mesh]) NOT ("Psychological help" OR Counseling OR counselling OR "Psychosocial care" OR Guidance OR "Patient organization" OR Support OR "support group" OR "Peer support" OR "Counseling"[Mesh] OR "Social Support"[Mesh] OR "Peer Group"[Mesh])

Literature search was limited to the period between 01/01/2014 and 04/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
(Li <i>et al.</i> , 2020a)	meta-analysis - six studies	645 women with POI	492 normal-ovarian control subjects under 40 years		HRQoL and physical function	lower overall HRQoL and physical function in women with POI, whereas the impact on psychological and social HRQoL seems to be small. Sexual function is affected, especially lubrication, with a high rate of variability		
(Su <i>et al.</i> , 2023).	Study	Chinese women with POI after HSCT				milder symptoms in comparison with the norm group,		non-specific scales to assess QoL were used
<b>Quality of life and menopausal symptoms</b>								



<b>(Allshouse et al., 2015).</b>	Study	POI-specific support group members			symptoms	symptom scores did not substantially decrease with time since diagnosis or correlate with age at POI diagnosis		many symptoms not adequately captured by the symptom checklist created for age-appropriate postmenopausal women
<b>Quality of life and psychological wellbeing</b>								
<b>(Zilski et al., 2023).</b>	cross-sectional study	134 women with pathogenic BRCA variants	RRSO			RRSO was not associated with significant changes in QoL, but with lower global health status, as compared with an expectant management		
<b>(Steenbeek et al., 2021).</b>	non-randomised controlled trial	BRCA1/2 pathogenic variant carriers  577 women (mean [SD] age, 37.2 [3.5] years) were enrolled: 297 (51.5%) were pathogenic BRCA1 variant carriers and 280 (48.5%) were BRCA2 pathogenic variant carriers.	risk-reducing salpingectomy (RRS) with delayed oophorectomy  394 patients	RRSO  154 patients	Menopause-related quality of life as assessed by the Greene Climacteric Scale, with a higher scale sum (range, 0-63) representing more climacteric symptoms. Secondary outcomes were health-related quality of life, sexual functioning and distress, cancer worry, decisional	Without HRT, the adjusted mean increase from the baseline score on the Greene Climacteric Scale was 6.7 (95% CI, 5.0-8.4; P < .001) points higher during 1 year after RRSO than after RRS. After RRSO with hormone replacement therapy, the difference was 3.6 points (95% CI, 2.3-4.8; P < .001) compared with RRS.	patients have better menopause-related quality of life after RRS than after RRSO, regardless of HRT	TUBA study



					regret, and surgical outcomes.			
					follow-up at 3 and 12 months after surgery			
<b>(Hickey et al., 2021a).</b>	Literature review of qualitative papers					5 qualitative papers were identified relating to interviews with 115 women after RRBSO published between 2000 and 2020. The quality of the papers was moderate. Five different themes were identified related to individual experiences with RRBSO: (1) information needs, (2) psychological impact, (3) psychosexual impact, (4) partner support and (5) hormone replacement therapy (HRT).	Individual experiences of RRBSO were varied and influenced by multiple factors but psychosexual problems were common, often caused significant distress to the women and their partners and were often poorly explained before surgery. Women do not feel adequately prepared for the psychological and sexual side effects of RRBSO. The qualitative data provides invaluable insight into the individual experiences of women and can be used to better help women mitigate the effects of the surgery.	
<b>(Alves-Nogueira et al., 2023)</b>	Review	premenopausal women carrying BRCA1 or BRCA2 mutations			psychosocial impact of the decision-making process		(1) present an updated medical background for RRSO; (2) analyze the psychosocial impact of the decision-making process within a theoretical framework of the Health Belief Model; and (3)	Narrative review



							discuss the role of PPC in such a decision-making process and in post-surgery.	
<b>(Nebgen et al., 2023).</b>								Scoping review and international consensus recommendations
<b>(Kim et al., 2023).</b>	retrospective cohort	945,729 eligible postmenopausal women	female reproductive factors including the age at menarche, age at menopause, parity, duration of oral contraceptive (OC) use, duration of breastfeeding		use of menopausal hormone therapy (MHT), and the occurrence of depression	Compared to women with menopause at the age of 50–54, those with menopause at an earlier age showed an increased risk of depression (aHR of 1.20 for <40 years), and those with menopause at a later age showed a decreased risk of depression (aHR of 0.94 for ≥55 years). Use of MHT was associated with an increased risk of depression (aHR of 1.30 for ≥5 years).	<ul style="list-style-type: none"> <li>• Association between female reproductive factors and depression in postmenopausal women.</li> <li>• Late menarche and early menopause increased the risk of depression.</li> <li>• Oral contraceptive use and menopausal hormone therapy increased the risk.</li> </ul>	
<b>(Ryu et al., 2022)</b>	cross-sectional study	2,232 menopausal women,	25 (1.1%) POI and 114 (5.1%) EM	Usual age menopause	Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9).	The PHQ-9 items that pertained to low self-esteem and suicidal ideation scored higher in women with POI than in those who experienced menopause after 45 years of age. The prevalence of suicidal ideation differed significantly according to age at menopause (POI, 30.0%; EM, 12.7%; menopause, 8.0%; P = 0.016). Logistic regression analysis revealed that POI was significantly associated with suicidal ideation after the adjustment for age, body mass index, and education, household income, and walking levels (OR 4.2; 95% CI 1.0–17.7).	Korean middle-aged women with POI were more likely to have suicidal ideation than those who experienced menopause at 45 years or above, despite not being diagnosed with major depressive disorder.	



<b>(Xi et al., 2023).</b>	systematic review and meta-analyses	women with POI (7 primary studies with 1316 women)			risk of depression and anxiety disorders	Patients with POI were associated with a higher odds of depression and anxiety (depression: OR = 3.33, 95% CI = 2.31–4.81, P < 0.001; anxiety: OR = 4.89, 95% CI = 3.28–7.30, P < 0.001). Subgroup analysis also indicated that patients with POI are at a higher risk of anxiety and depression.	POI appears to be associated with a high risk of depression and anxiety.	All included articles were case-control studies of high quality
<b>(Kotsopoulos et al., 2020),</b>	prospective	women at an elevated risk of ovarian cancer	women with no personal history of cancer or depression  506 matched sets	Controls - matched to a control participant (no oophorectomy) according to year of birth (within 3 years), BRCA mutation type (BRCA1 or BRCA2), and country of residence	self-reported initiation of antidepressant use	Oophorectomy was not associated with more frequent antidepressant use among BRCA mutation carriers (OR = 0.46; 95% CI 0.22-0.96). We observed reductions in the odds of antidepressant medication use among women who underwent oophorectomy before the age of 50 years (OR = 0.33; 95% CI 0.14-0.78) and among those who initiated hormone therapy use after oophorectomy (OR = 0.35; 95% CI 0.14-0.90). Findings were similar when the analysis was based on self-reported depression (rather than antidepressant use).	Although based on a small number of women, these findings suggest that oophorectomy does not increase psychological distress among women at an elevated risk of ovarian cancer.	
<b>(Hickey et al., 2017, Hickey et al., 2021b)</b>	prospective cohort	Women with high risk of ovarian cancer	95 premenopausal women planning RRSO	99 who retained their ovaries	Vasomotor symptoms and menopausal-related quality of life (QoL) were measured by the Menopause-Specific QoL Intervention scale at baseline, 3,	Three months after RRSO hot flush prevalence increased from 5.3% to 56.2% and night sweats from 20.2% to 47.2%. Symptoms did not worsen between 3 and 12 months and remained unchanged in the comparison group (p<0.001). After RRSO, 60% commenced hormone therapy. However, 40% of hormone therapy uses continued to experience vasomotor	Vasomotor symptoms increase by 3 months after RRSO but do not worsen over the next 12 months. Hormone Therapy reduces but does not resolve vasomotor symptoms and may improve QoL, but not to pre-oophorectomy levels.	



					6 and 12 months.	symptoms. After RRSO, 80% of non-hormone therapy users reported vasomotor symptoms. Regardless of hormone therapy use, 86% categorized their vasomotor symptoms as "mild" after RRSO. Following RRSO, Menopause-related QoL deteriorated but was stable in the comparison group (adjusted coefficient = 0.75, 95%CI = 0.55-0.95). After RRSO, QoL was better in hormone therapy users vs non-users (adjusted coefficient = 0.49, 95%CI = 0.20-0.78).		
<b>(Bräuner et al., 2022)</b>	population-based cohort	25188 nurses aged ≥45 years from the Danish Nurse Cohort	women after RRSO for a family history of cancer (n=2002)	age-matched reference group (n=18018)		Compared with nurses with retained ovaries, bilateral oophorectomy was associated with a slightly higher rate of depression (rate ratio [RR], 1.08; 95% confidence interval [CI], 0.95-1.23), but without statistical significance. However, when stratified by age at oophorectomy, compared with nurses with retained ovaries, bilateral oophorectomy at age ≥51 years was associated with higher rates of depression (RR 1.16; 95% CI, 1.00-1.34), but not bilateral oophorectomy at age <51 years (RR 0.86; 95% CI, 0.69-1.07); P value for difference in estimates = 0.02. No association between unilateral oophorectomy and depression was observed.	In this cohort of Danish female nurses, bilateral oophorectomy at age ≥51 years, but not at younger ages, was associated with a slightly higher rate of depression compared with those who retained their ovaries.	
<b>(Ates et al., 2022).</b>	Study	POI	62 women with POI	62 age-matched controls.	sleep disturbances, levels of anxiety, depression and fatigue	poor sleep quality, higher levels of insomnia in women with POI than in controls. Depression was much more prevalent and severe in POI women. Total	Women with POI are more likely to suffer from poor sleep quality, insomnia	Pittsburgh Sleep Quality Index, Insomnia



						anxiety score, the severity of anxiety and fatigue did not differ significantly between the groups. According to the multivariable logistic regression analysis, being married and having POI were associated with worse quality of sleep, and having more children was associated with an increase in depression levels in the whole cohort. Backward analysis showed that when POI status was taken as a reference, married women were at 6.5 fold increased risk of poor sleep quality	and depression than healthy women.	severity index, Epworth Sleepiness Scale, Hospital Anxiety and Depression Scale and Fatigue Severity Scale
<b>(Kundu and Acharya, 2023).</b>		Longitudinal Aging Study in India (LASI), 2017–2018, Wave 1 data. The sample of 31,435 women were aged 45 and above and did not undergo hysterectomy.	POI or EM		insomnia (M1), depression (M2), moderator (W), and cognitive health (Y),	Premature menopause was negatively associated with cognition ( $\beta$ :-0.33; SE:0.12; $p < 0.05$ ), whereas positively associated with insomnia ( $\beta$ :0.18; SE:0.03; $p < 0.001$ ) and depression ( $\beta$ :0.25; SE:0.04; $p < 0.001$ ). There is a moderating effect of smoking or tobacco consumption has a significant moderating effect on the pathways among premature menopause, depression, insomnia and cognition. When the same model was carried out for early menopause (40–44 years), the results were not significant.		moderated multiple mediation model
<b>(Yeganeh et al., 2020)</b>	Study	150 women	digital resource and online surveys to complete before (baseline) and, immediately and 1 month after viewing the resource			Compared to baseline, at 1-month health-related empowerment, 'health directed behavior' scores increased (mean change: +0.13; 95% CI: 0.01-0.24; and $P = 0.03$ ), 'emotional distress' decreased (mean change: -0.15; 95% CI: -0.25 to -0.05; and $P = 0.003$ ) and physical and emotional		



						menopause symptom scores decreased (P = 0.001 and P = 0.02, respectively). Illness perception scores increased at both immediate and 1-month follow-up versus baseline for 'personal control' (P < 0.001 and P = 0.02) and 'coherence' (P = 0.003 and P < 0.001). After viewing the digital resource, more women perceived that hormone therapy decreases heart disease risk, reduces hot flashes, and prevents fractures versus baseline (all P < 0.05). More women correctly answered questions regarding early menopause prevalence (60% vs 35%), cause (46% vs 33%), risk (76% vs 55%), effect of phytoestrogens (60% vs 27%), and osteoporosis prevention (64% vs 44%) at immediate or 1-month follow-up versus baseline (all P < 0.05).	
<b>Quality of life and fertility concerns</b>							
<b>(Driscoll et al., 2016)</b>	Longitudinal study	102 women with POI			personal attributes reflective of vulnerability and resilience were assessed at baseline. Coping strategies were assessed 4 months later and measures of distress and well-being 12 months later.	Confirmatory factor analysis yielded separate, inversely correlated vulnerability and resilience resource factors at baseline, and distress and well-being factors at 12 months. Contrary to predictions, maladaptive and adaptive coping strategies were not bifactorial. Moreover, a single stand-alone strategy, avoidance (i.e., refusing to acknowledge stress), mediated the association between baseline vulnerability and 12-month distress.	For women with POI, interventional studies targeted to reduce avoidance are indicated.



<p><b>(Chu et al., 2021).</b></p>		<p>52 male partners of POI patient (experiment group) and 52 controls (control group)</p>			<p>Anxiety, depression, and marital relationship</p>	<p>Male partners of POI patient experienced greater levels of anxiety (10.96 versus 4.88; <math>P &lt; 0.01</math>) and depression (12.23 versus 5.19; <math>P &lt; 0.01</math>) compared with controls. In addition, they experienced worse marital relationship in several aspects than their counterparts. The findings also demonstrate that most POI patient male partners had inadequate and inaccurate knowledge about their partners' disease, which may be the results of insufficient professional counseling from health-care practitioners. Moreover, their understanding level of the disease was correlated to anxiety (<math>r = -0.64</math>; <math>P &lt; 0.01</math>), depression (<math>r = -0.38</math>; <math>P &lt; 0.01</math>), and communication (<math>r = 0.28</math>; <math>P &lt; 0.05</math>).</p>		
<p><b>(McDonald et al., 2022)</b></p>	<p>Review - 24 articles</p>	<p>Idiopathic POI</p>			<p>health-related quality of life (HR-QoL)</p>	<p>Three interrelated themes affecting HR-QoL in POI emerged from the data synthesis. First, the theme 'diagnostic odyssey' comprised sub-themes of uncertainty, lack of control, knowledge gaps, discontinuous care and negative clinical interactions. The second theme 'isolation and stigma' included sub-themes of guilt, shame, concealment, feeling labeled as infertile, lack of social support and unsympathetic clinicians. The third theme, impaired 'ego integrity' captured sub-themes of decreased sexual</p>	<p>Women with POI have a range of unmet psychosocial needs relating to three interrelated themes: 'diagnostic odyssey', 'isolation and stigma' and impaired 'ego integrity'</p>	



						<p>function, altered body image, psychological vulnerability and catastrophizing.</p> <p>Targets promoting active coping at the individual (n = 2), interpersonal (n = 1) and healthcare system (n = 1) levels were mapped to the TPB to inform development of tailored interventions supporting active coping and improved HR-QoL in POI (i.e. narrative intervention, co-creating patient-facing materials, peer-to-peer support and provider resources).</p>
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*Evidence to recommendations*

QUESTION	WHAT ARE THE CONSEQUENCES OF POI ON PSYCHOLOGICAL WELLBEING AND QUALITY OF LIFE?
RECOMMENDATION	HCPs should be aware that a diagnosis of POI can have a significant impact on psychological wellbeing and quality of life.
Desirable effects	Evidence that a diagnosis of POI can have a significant impact on psychological wellbeing and quality of life
Undesirable effects	
Certainty of evidence	Observational data only, limited number of studies
Values	
Balance of effects	Strong recommendation for awareness
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	NA

QUESTION	WHAT ARE THE CONSEQUENCES OF POI ON PSYCHOLOGICAL WELLBEING AND QUALITY OF LIFE?
GOOD PRACTICE POINT	The guideline group recommends offering assessment of psychological health and quality of life to all women with POI.
Justification	<p>Current evidence suggests that women with POI report lower levels of psychological wellbeing compared to women in the general population. However, it is far from certain whether this constitutes the psychological sequelae of having a chronic condition or is particular to POI per se. Several knowledge gaps in QoL are still present because of the difficulties in investigating the multifaceted impact of a chronic condition that it is very distinct from one woman to another, depending on the stage of life at diagnosis, type of POI, and intrapersonal and interpersonal characteristics able to modulate the psychological impact.</p> <p>Authoritative data are needed to confidently inform service users and providers about the wellbeing trajectories of the key aspects of POI. Meanwhile, the use of doctor- and patient-friendly wellbeing screening tools may prompt discussion and signpost to supportive resources is a crucial aspect of clinical services for long term</p>



medical conditions in general and POI in particular, so that patient distress does not go unnoticed and unmanaged. Many simple and acceptable tools exist to facilitate an effective discussion, and the hope is they can be implemented with the help of women suffering from POI of different aetiologies to guide tailored interventions.



## PICO QUESTION: WHAT ARE THE MANAGEMENT OPTIONS FOR REDUCED QUALITY OF LIFE ASSOCIATED WITH POI?

<b>Population</b>	POI
<b>Interventions</b>	
<b>Control</b>	Psychological help Counseling Psychosocial care Guidance Patient organization Support POF support groups Peer support
<b>Outcomes</b>	Well being - Quality of life Psychological function Self-esteem - Anxiety Depression - somatization Sensitivity - hostility psychological distress stigma

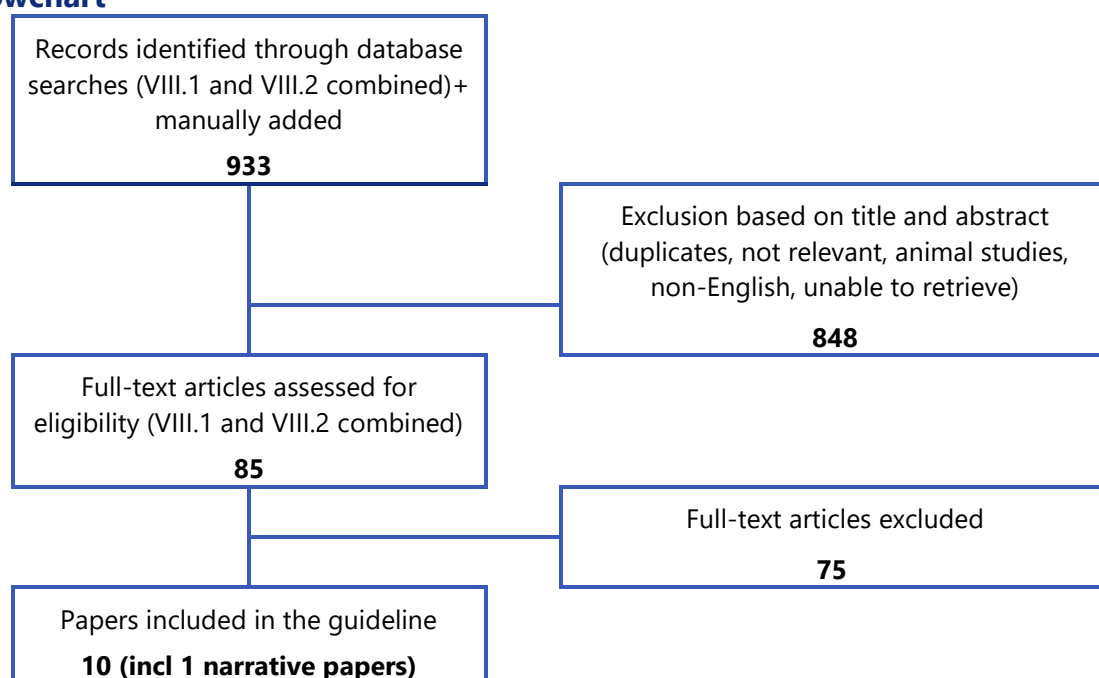
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("Psychological help" OR Counseling OR counselling OR "Psychosocial care" OR Guidance OR "Patient organization" OR Support OR "support group" OR "Peer support" OR "Counseling"[Mesh] OR "Social Support"[Mesh] OR "Peer Group"[Mesh]) AND ("Well being" OR "Quality of life" OR "Psychological function" OR Self-esteem OR Anxiety OR Depression OR Somatization OR sensitivity OR hostility OR distress OR stigma OR Satisfaction OR "Quality of Life"[Mesh] OR "Stress, Psychological"[Mesh] OR "Self Concept"[Mesh] OR "Anxiety"[Mesh] OR "Hostility"[Mesh] OR "Social Stigma"[Mesh])

Literature search was limited to the period between 01/01/2014 and 04/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Medical interventions</b>								
<b>(Gonçalves et al., 2022)</b>	systematic review and meta-analyses	POI 30 reports of 28 studies  total of 4004 POI from diverse aetiologies	3785 received hormone therapies	219 received calcium supplementation, vitamin D, placebo or no treatment		HT was superior to non-treatment, placebo, calcitriol or calcium in preserving BMD in POI. HT was associated with up to 80% reduction in the prevalence of hot flushes and with stability or improvement in the QoL scores. HT induced significant increases in uterine volume and endometrial thickness in POI.		
<b>(Benetti-Pinto et al., 2019).</b>	cross-sectional		61 women diagnosed with POI receiving HT	61 women with preserved ovarian		women with POI receiving HT have poor sleep quality, take longer to fall asleep and have a higher fatigue index		



				function, matched 1:1 for age				
<b>(Menezes et al., 2020)</b>	cross-sectional		61 women diagnosed with POI receiving HT	61 women with preserved ovarian function, matched 1:1 for age	depression, anxiety and stress Instruments: Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Lipp's Stress Symptom Inventory (LSSI).	POI group and control group had a mean of $0.44 \pm 0.92$ and $1.28 \pm 1.38$ children ( $p = 0,001$ ); the total BDI, BAI and LSSI scores were $15.72 \pm 11.68$ and $13.66 \pm 8.44$ ( $p = 0.64$ ); $17.54 \pm 13.16$ and $17.25 \pm 11.05$ ( $p = 0.90$ ), $19.39 \pm 12.08$ and $18.93 \pm 11.21$ ( $p = 0.945$ ). The majority of women did not have depression or presented mild depression, but approximately one-third had moderate-severe undiagnosed depressive or anxiety symptoms. In POI group, depression was positively correlated with the number of children and anxiety. Anxiety and stress were also positively correlated. It was observed that for each point in the BDI, the risk of stress above 20 increased 19.6%, while for each point in the BAI, the risk of greater stress increased 32.4%.	Women with POI receiving HT have indexes of depression, anxiety and stress similar to the population of women with preserved ovarian function.	
<b>(Stuursma et al., 2022).</b>	REVIEW - RCTs	surgically menopausal women and women after BSO  12 studies	SHRT		overall psychological well-being, depression, and anxiety  overall sexual functioning, sexual desire, and sexual satisfaction  short ( $\leq 12$ weeks) or medium term (13-26 weeks).	Estradiol had a beneficial effect on depressed mood on short term 3-6 years after surgery or 2 years (median) after surgery with high heterogeneity (SMD: -1.37, 95%CI: -2.38 to -0.37, $P = .007$ , $I(2) 79\%$ ). Testosterone had a beneficial effect on overall sexual functioning on short to medium term 4.6 years (mean) after surgery (SMD 0.38, 95%CI 0.11-0.65, $I(2) 0\%$ ) and on sexual desire on medium term at least 3-12 months after surgery (SMD 0.38, 95%CI 0.19-0.56, $I(2) 54\%$ ). For most studies, risk of bias was uncertain.	Estradiol may beneficially affect psychological symptoms after surgical menopause or BSO and testosterone might improve sexual desire and overall sexual functioning.	The small number of studies highly varied in nature and bias could not be excluded, therefore our results should be interpreted with great



								caution.
<b>(Vermeulen et al., 2017).</b>	Review		RRSO		quality of life, endocrine symptoms, sexual function, osteoporosis, cardiovascular health, metabolic syndrome, cognitive impairment and safety of hormone replacement therapy	Surgical menopause leads to more menopausal complaints and sexual dysfunction than natural menopause. Overall quality of life is not affected by surgery. In the limited literature, there is no evidence that RRSO leads to more osteopenia in comparison with natural menopause at a young age. Cohort studies show a slight impaired cardiovascular health. Cognitive function decreases later in life in premenopausal oophorectomized women. Short-term hormone replacement therapy seems to decline postmenopausal complaints and does not seem to increase the risk for breast carcinoma in mutation carriers without a personal history of breast carcinoma.	Conclusions are limited by the absence of RCTs. There is growing evidence from observational studies that RRSO may impact negatively on all-cause non-survival endpoints.	
<b>(Diem et al., 2020)</b>	Pooled data from 4 RCTs	1,005 perimenopausal and postmenopausal women with 14 or more VMS/week	escitalopram 10 to 20 mg/d; yoga/aerobic exercise; 1.8 g/d omega-3-fatty acids; oral 17-beta-estradiol 0.5 mg/d; venlafaxine XR 75 mg/d; and cognitive behavioral therapy for insomnia (CBT-I).		Menopause-specific Quality of Life scale and its subscales.	Significant improvements in total Menopause-specific Quality of Life from baseline were observed with estradiol, escitalopram, CBT-I, and yoga, with mean decreases of 0.3 to 0.5 points relative to control. The largest improvement in the vasomotor subscale was observed with estradiol (-1.2 points), with more modest but significant effects seen with escitalopram, yoga, and CBT-I. Significant improvements in the psychosocial subscale were observed for escitalopram, venlafaxine, and CBT-I. For the physical subscale, the greatest improvement was observed for CBT-I and exercise, whereas for the sexual subscale, the	These results suggest that for menopause-related QOL, women have a variety of treatment strategies to choose from and can select an approach based on most bothersome symptoms and individual	



						greatest improvement was observed for CBT-I, with yoga and estradiol demonstrating smaller effects.	preferences.	
<b>Psychological interventions</b>								
<b>(Hunter et al., 2021)</b>	Review		CBT		menopausal symptoms			Narrative
<b>(Ye et al., 2022).</b>	Review	1618 menopausal patients – 14 RCTs	CBT		QoL - menopausal symptoms	CTBT significantly outperformed control groups in terms of reducing hot flushes [g = 0.39, 95% confidence interval (CI) 0.23–0.55, I <sup>2</sup> = 45], night sweats, depression (g = 0.50, 95% CI 0.34–0.66, I <sup>2</sup> = 51), anxiety (g = 0.38, 95% CI 0.23–0.54, I <sup>2</sup> = 49), fatigue, and quality of life. Egger's test indicated no publication bias.		
<b>(Chen et al., 2021)</b>	Review	475 menopausal women  5 RCTs	Mindfulness-based interventions		overall QoL	mindfulness-based intervention groups showed significant improvements in total quality of life and vasomotor and physical quality of life, compared to control groups (standardized mean differences range: from -0.48 to -0.68, all ps < 0.05). After the sensitivity analyses, evidence of heterogeneity remained. Insufficient data prevented conducting a meta-analysis with the sexual subscale of MENQOL or on vasomotor symptoms of menopause.	For menopausal women, mindfulness-based interventions may improve quality of life (except for psychological and sexual subscales).	
<b>(Pyri et al., 2021).</b>	Cohort	62 women with POI randomly allocated into two groups of mindfulness and control.	Mindfulness-based interventions	Control	quality of life, frequency, and intensity of hot flashes were measured before the intervention, immediately, and 3	The scores of quality of life dropped from 95.6 ± 9.77 at baseline to 77.32 ± 7.93 after intervention and 48.32 ± 4.96 at 3-months follow-up in the mindfulness group but rose from 99.5 ± 16.1 at baseline to 100.2 ± 15.33 after intervention, and 102.6 ± 14.9 3-months after it in the control group, P < 0.001. The scores of vasomotor, psychological, physical, and sexual domains also improved significantly in the mindfulness group compared to the control group. The mean of hot flashes in the mindfulness group was 1.30 ±		



					months after it	0.69 and decreased to $1.1 \pm 0.56$ and $0.66 \pm 0.58$ immediately and in 3 months after intervention, respectively. The frequency of hot flashes was $14.74 \pm 10.4$ per week before intervention in the mindfulness group which reduced to $12.38 \pm 8.66$ and $6.74 \pm 6.34$ per week, immediately and 3 months after the intervention, while in the control group, there was an increase in the frequency of hot flashes ( $P < 0.0001$ ).	
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### Evidence to recommendations

QUESTION	What are the Management options for reduced quality of life associated with POI?
RECOMMENDATION	Personalized care, including psychological support, should be accessible to women with POI.
Desirable effects	<p>A personalised care plan that considers how a woman approaches her situation is essential to improve HR-QoL in women with POI. The best methodology to deliver high-quality care is still unclear and should consider both intrinsic and extrinsic factors, including physical health, current and past psychological health, age, parity, personal values and preferences, and access to social resources such as work, education, and supportive relationships.</p> <p>In addition to adequate HT, psychological interventions for problems that are associated with POI can lead to positive benefits on QoL.</p>
Undesirable effects	
Certainty of evidence	Observational data only + Validated, disease specific instruments to measure effectiveness are lacking.
Values	Access to care
Balance of effects	Strong recommendation for making care accessible
Resource use, equity, acceptability and feasibility	An offer of intervention should be based on a thorough and holistic assessment of the presentation, and multi-disciplinary skills may be required.
Subgroup considerations (if applicable)	NA



## IX. POI, sexuality and genitourinary symptoms associated with menopause

### PICO QUESTION: WHAT ARE THE CONSEQUENCES OF POI FOR SEXUALITY?

<b>Population</b>	POI
<b>Interventions</b>	
<b>Control</b>	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Satisfaction with sexual life. sexual fantasies</li> <li>• masturbation frequency. sexual arousal</li> <li>• lubrication</li> <li>• genital pain</li> <li>• desire</li> <li>• frequency of sexual contact</li> <li>• orgasm</li> <li>• sexual debut, identity,</li> <li>• libido</li> <li>• hypoactive sexual desire disorder</li> </ul>

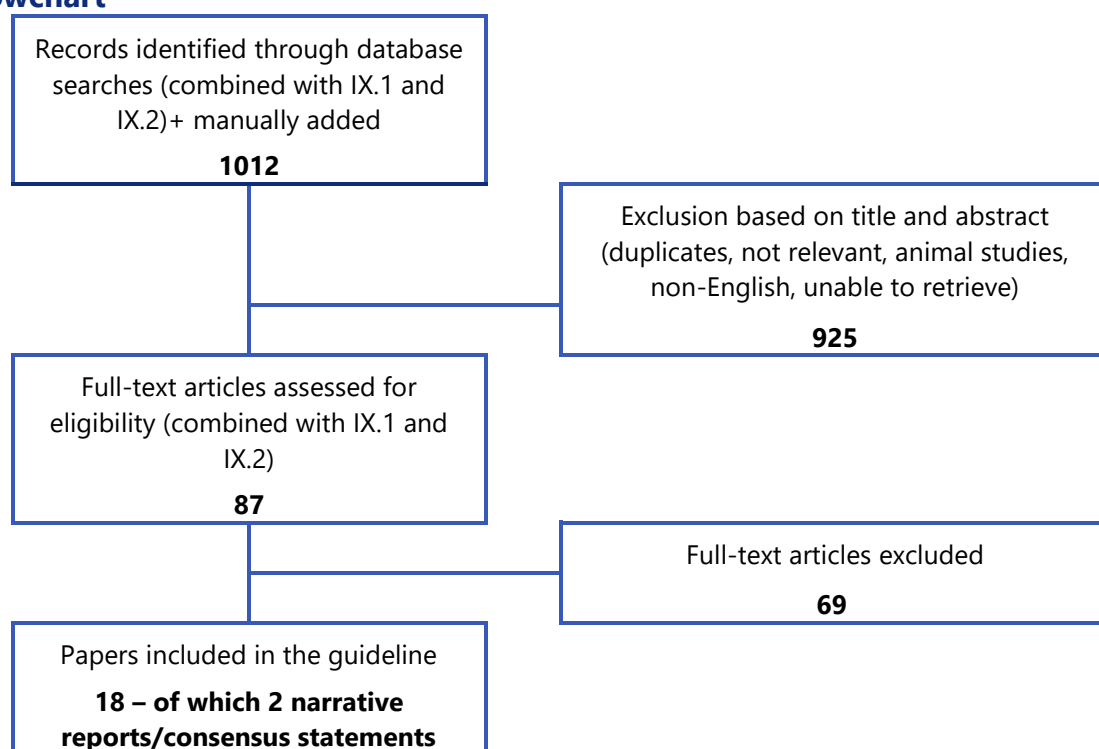
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (sexuality OR "Sexuality"[Mesh] OR "Psychosexual function" OR "Satisfaction with sexual life" OR "sexual fantasies" OR masturbation OR arousal OR lubrication OR "genital pain" OR desire OR "frequency of sexual contact" OR orgasm OR "sexual debut" OR "sexual identity" OR libido OR "hypoactive sexual desire disorder")

Literature search was limited to the period between 01/01/2014 and 19/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Common clinical conditions associated with sexual problems.</b>								
(Simon <i>et al.</i> , 2018a).	Consensus paper							
(Kingsberg and Simon, 2020).	Female Hypoactive Sexual Desire Disorder: A Practical Guide to Causes, Clinical Diagnosis, and Treatment							
<b>Sexual function in women with POI</b>								
(Bildircin <i>et al.</i> , 2020)	cohort	151 women with surgical menopause (SM), 357 women			6-question survey of sexual performance parameters	Demographic features, serum DHEA-S, total testosterone, and FSH levels were found to have statistically significant effects on sexual performance of women ( $p < 0.05$ ). The sexual	significant relationships between several demographic-clinical and hormonal	



		with natural menopause (NM), and 186 perimenopausal women (PM)				function scores for the frequency of sexual desire, coitus, and orgasm were significantly higher in the PM group, whereas vaginal lubrication scores were lower compared to the NM and SM group ( $p < 0.05$ ). In paired comparison of NM and SM, the scores for the frequency of coitus, orgasm, and vaginal lubrication were significantly higher in the SM group, while sexual desire frequency scores were higher in the NM group ( $p < 0.05$ ).	factors. SM was found to not affect female sexual performance, except for sexual desire, more than NM.
<b>(Gulbahar and Akgun Kavurmaci, 2022).</b>	cohort	252 menopausal women			Sexual function - Symptom Check List and the Female Sexual Function Index	menopause women were divided into two equal groups based on the type of menopause (natural vs. iatrogenic). The iatrogenic group was further divided into 3 sub-groups; drug-induced 30 (12%), radiotherapy-induced 18 (7%) and surgical 78 (31%). No significant difference in sexual function between groups were observed with respect to mean scores for desire, arousal, lubrication, orgasm, satisfaction, pain and sexual function ( $p > 0.05$ ).	Our results suggest that sexuality-specific problems during menopause are multifactorial and not solely attributable to biological or psychological factors. Our findings call for comprehensive interventions to address the psychological and biological effects of menopause in order to improve the life quality of women.
<b>(Abadi et al., 2018).</b>	Qualitative study	22 surgical menopausal women			Their experiences of sexual/marital relationship after surgery through in-depth, face-to-face, semi-structured interviews.	An overarching theme entitled "feeling an invisible wall" reflected this experience. It comprised three categories: (1) declined marital intimacy, (2) disarming, and (3) transformation of societal norms into concerns. This study proposed new contextual information about the marital relationship of Iranian women after surgical menopause that was not openly articulated before and which may be applicable for others in such contexts. Women's main concern was the emotional separation because of the sexual consequences of the surgery. Healthcare providers should be aware of women's concerns, which may alter their marital relationship. They must provide individualized care, education, and support for couples to make thoughtful decisions about rebuilding their sexual relationship.	
<b>(Hall et al., 2019).</b>	Study	140 BRCA mutation carriers who elected to undergo a BSO			medical history questionnaire Menopause-Specific Quality of	We included 140 BRCA mutation carriers with an average follow-up of 3.5 years following BSO. Among 93 women who were premenopausal, oophorectomy was	3.5 years after oophorectomy, BRCA mutation carriers experience a significant worsening of menopausal



					Life Intervention questionnaire Sexual Activity Questionnaire prior to surgery and then again approximately one and three years following surgery	associated with an increase in menopausal symptoms (vasomotor, physical) ( $P < 0.001$ ) and a decline in sexual functioning (discomfort, pleasure) ( $P \leq 0.0001$ ), but had no impact on overall QOL ( $P = 0.31$ ). HRT mitigated, but did not eliminate the adverse effects. Women who were postmenopausal at surgery ( $n = 47$ ) experienced an increase in physical symptoms ( $P = 0.03$ ) and a decline in sexual functioning (discomfort) ( $P = 0.004$ ) and in overall QOL ( $P = 0.04$ ).	symptoms and a decline in sexual functioning, particularly among those who underwent surgery prior to natural menopause. The use of HRT mitigated some but not all the effects. Overall, women who were premenopausal at surgery did not experience a decline in their QOL.	
<b>(Kershaw et al., 2021).</b>	meta-analysis	women at high risk of breast/and or ovarian cancer.  21 eligible studies, 10 of which reported sufficient data for meta-analysis.	RRBSO		sexual function	15/21 studies (71%) reported a negative impact of RRBSO on sexual function. Participant numbers ranged from 37 to 1522. Meta-analysis was performed with studies including 3201 patients. This demonstrated that RRBSO has a statistically significant negative impact on sexual function (SMD -0.63, [-0.82, -0.44], $p = 0.03$ ). There was a trend towards reduced sexual pleasure and increased discomfort but this did not reach statistical significance. There was minimal change in the frequency of sex. There was a significant increase in vaginal dryness post-RRBSO (SMD 9.25, [3.66, 14.83], $p < 0.00001$ ). There was no significant difference in sexual function between premenopausal and postmenopausal RRBSO. Hormone replacement therapy (HRT) did not abolish this negative impact.	Sexual function declines post RRBSO, independent of menopausal status. Comprehensive pre-operative counselling regarding anticipated menopausal and sexual symptoms is key to setting realistic patient expectations and minimising post-operative distress. Information and support regarding management of these side effects should be available to all patients.	Most studies were retrospective cohort or observational studies.
<b>(Terra et al., 2023)</b>	study	women with a high familial risk of breast or			long-term sexual functioning	Compared with 48.9% of women in the postmenopausal group, 47.4% of women in the premenopausal group were still sexually active ( $P = .80$ ). Current sexual pleasure scores were the same for women in the premenopausal group and women in the postmenopausal group (mean		



		ovarian cancer + BSO  368 women who were 60 to 70 years old at completion of the questionnaire (226 in the premenopausal group and 142 in the postmenopausal group).				pleasure score, 8.6; P=.99). However, women in the premenopausal group more often reported substantial discomfort than women in the postmenopausal group (35.6% vs 20.9%; P=.04). After adjusting for confounders, premenopausal risk-reducing salpingo-oophorectomy was associated with substantially more discomfort during sexual intercourse than postmenopausal risk-reducing salpingo-oophorectomy (odds ratio, 3.1; 95% confidence interval, 1.04–9.4). Moreover, after premenopausal risk-reducing salpingo-oophorectomy, more severe complaints of vaginal dryness were observed (odds ratio, 2.6; 95% confidence interval, 1.4–4.7). Women with a risk-reducing salpingo-oophorectomy before the age of 41 years reported similar pleasure and discomfort scores as women with a risk-reducing salpingo-oophorectomy between ages 41 and 45 years.	
<b>(Tucker et al., 2021).</b>	cross-sectional	172 BC women : 76 women in the BSO group and 96 women with at least one ovary remaining			sexual function and quality of life (QoL)	There was no difference in FSD between the two groups: 63/76 (82.9%) women who had undergone BSO had FSD compared to 75/96 (78.1%) controls (p = 0.458). No difference in HSDD was observed (p = 0.084) between the BSO group 70/76 (96.0%) and the controls 96/96 (100%). Women who had undergone BSO had lower general health scores compared to the control group (p = 0.034). Both groups had similar energy levels, emotional well-being, pain scores, physical functioning levels and social functioning levels.	In this study, women with prior treatment for breast cancer had high levels of FSD and HSDD, irrespective of whether they had undergone BSO. Both groups reported similar sexual function scores and QoL.
<b>(Dedden et al., 2023)</b>	Review	Hysterectomy  8 RCTS, 20 prospective studies, 2 retrospective studies, 1 cross-sectional study, and 1 secondary analysis, comprising			Sexual function	Hysterectomy was not associated with significant change in overall sexual function irrespective of surgical route, with patients tending to report potentially remaining sexual dysfunction posthysterectomy. Cervix removal was not significantly associated with differences in magnitude of change. Hysterectomy without BSO was associated with significantly stronger improvement in lubrication and orgasm than hysterectomy with BSO, which was not the case for desire, arousal or overall sexual function. However, these significant differences were not replicated within studies that directly compared cases with and without BSO.	



		g a total of 4054 patients.					
<b>(Morgan et al., 2023)</b>	Review	Prophylactic mastectomies and bilateral salpingo-oophorectomies among patients who are BRCA positive  11 studies			postsurgical sexual function	Sexual function was measured via validated and investigator-generated surveys. All studies, no matter the survey metric, found significant reduction in sexual function with bilateral salpingo-oophorectomy; no studies revealed sexual function changes associated with mastectomy postsurgery. Few studies indicated that menopause hormone therapy resulted in significant improvement in sexual function, and all studies reported that postoperative sexual function could not reach baseline levels with therapy. No studies were high quality by GRADE metrics.	
<b>(Su et al., 2020)</b>	Study	415 women (215 HSCT women and 200 naturally menopausal women as control group)			Menopausal symptoms and quality of life were evaluated using the modified Kupperman index (KI), menopause rating scale (MRS), and menopause quality of life questionnaire.	The total KI and MRS scores were $12.53 \pm 8.27$ and $7.69 \pm 6.50$ in the HSCT group and $21.57 \pm 9.23$ and $12.05 \pm 6.70$ in the control group, respectively ( $P < 0.05$ ). The scores related to sexual problems and vaginal dryness were $1.20 \pm 1.24$ and $1.07 \pm 1.24$ in the HSCT group and $1.15 \pm 1.01$ and $1.01 \pm 1.01$ in the control group, respectively ( $P > 0.05$ ). Age was a risk factor for menopausal symptoms (odds ratio 1.70, 95% confidence interval 1.01-1.12). The main reasons for consultations in the HSCT group were amenorrhea and infertility (76.74%).	
<b>(Benetti-Pinto et al., 2015b).</b>	Cross-sectional study	80 women with POI, matched by age to 80 women with normal gonadal function.			SF through the "Female Sexual Function Index" (FSFI),	The FSFI score was significantly worse for women with POF, with a decrease in arousal, lubrication, orgasm, satisfaction, and dyspareunia. Exploratory factor analysis of SF showed that the domain with greater influence in the SF was arousal, followed by desire, together accounting for 41% of the FSFI. The domains with less influence were dyspareunia and lubrication, which together accounted for 25% of the FSFI.	Women with POF have impaired SF, determined mainly by changes in arousal and desire. Aspects related to lubrication and dyspareunia complaints have lower determination coefficient in SF.



<p><b>(Podfigurna-Stopa et al., 2016).</b></p>	<p>Review</p>	<p>POI</p>			<p>characterize the long-term consequences</p>	<p>Lack of ovarian steroids synthesis has serious consequences for women's health. The short-term effects are similar to spontaneous menopause and refer mainly to the climacteric syndrome. In a longer perspective, POI affects a variety of aspects. It obviously and drastically reduces the chances for spontaneous pregnancies. Oestrogen loss leads also to urogenital atrophy. The most common urogenital symptoms include vaginal dryness, vaginal irritation and itching. The urogenital atrophy and hypoestrogenism interferes also with sexual functioning. Patients with POI are threatened by a decrease in bone mineral density (BMD). POI women also experience psychological distress and some studies have shown an increased risk of neurodegenerating diseases. Overall, POI women have a shortened life expectancy, mainly due to cardiovascular disease. Some studies have reported a reduced risk of breast cancer in this group of patients.</p>	<p>there are several well-characterized health risks in POI women. With every patient, an individualized approach is required to properly recognize and prevent these risks.</p>	
<p><b>(Javadpour et al., 2021).</b></p>	<p>case-control study</p>	<p>132 (66 women with POI and 66 women of reproductive age with normal ovarian function) matched in terms of the age</p>			<p>WHOQOL-BREF questionnaire and the Female Sexual Function Index (FSFI) questionnaire</p>	<p>The mean score of sexual function in premature menopausal women was <math>21.35 \pm 4.82</math> and in non-menopausal women was <math>25.4 \pm 6.61</math> (OR = 0.11, 95% CI = 0.04-0.28). All areas of sexual function; desires disorder (OR = 0.21 95% CI = 0.07-0.56), Arousal disorder (OR = 0.28, 95% CI = 0.08-0.93), orgasm disorder (OR = 0.36 95% CI = 0.16-0.80), lubrication disorder (OR = 0.21 95% CI = 0.05-0.78), satisfaction disorder (OR = 0.11, 95% CI = 0.04-0.28) and quality of life domains: physical health (OR = 0.4 95%CI = 0.06-0.3), mental health (OR = 0.28 95% CI = 0.06-0.1), environmental health (OR</p>	<p>The results demonstrated that premature menopausal women are found to be weaker than the control group in all areas of sexual function and quality of life. Among the areas of sexual function, such as libido, arousal, satisfaction, and pain have the</p>	



						= 0.22 95%CI = 0.04-0.6) and social health (OR = 0.28 95%CI = 0.01-0.2) saw a decrease in the premature menopausal women group compared to the control group.	most impact on quality of life. Therefore, based on the results from improving sexual function, this issue can improve the quality of life.	
<b>(Gosset et al., 2023).</b>	cross-sectional observational	88 POI			DIVA questionnaire and the FSFI.	66 (75%) answered the questionnaires. Mean $\pm$ SD age at POI diagnosis was $32.6 \pm 6.9$ years and mean age at questionnaire time was $41.6 \pm 6.9$ years. The highest mean scores on the DIVA questionnaire were found in the self-perception and body image domain ( $2.05 \pm 1.36$ ), followed by the sexual functioning domain ( $1.52 \pm 1.28$ ). The mean FSFI score was 23.08 (95% CI, 21.43-24.73), with 32 women (78% of sexually active women) having a score $<26.55$ , which defines sexual dysfunction. There was no difference in the FSFI score and for all DIVA domains whether or not women were taking hormone replacement therapy or local hormone therapy.	POI can have a negative impact on sexual quality of life, which raises the needs for specific advice and care.	
<b>(Cardona Attard et al., 2020).</b>	Cross-sectional observational study	302 women with TS and 53 women with karyotypically normal POI (median age 33.0 [15.0-78.4] and 26.3 [17.8-52.3], respectively).			relationship and sexual experiences  self-reporting questionnaire	Women with TS were older than women with POI ( $P = .002$ ). Compared to women with POI, a smaller proportion of women with TS had ever had vaginal sexual intercourse (VSI) (40 [78.4%] vs 169 [58.1%], respectively, $P = .006$ ) and women with TS exhibited a delay in the median age at first relationship and VSI (POI $19.3 \pm 0.4$ vs TS $22.2 \pm 1.1$ , $P = <.001$ ). Start of oestrogen replacement therapy at $\leq 14$ years of age compared with $> 14$ years did not result in earlier relationship and sexual debut. After adjusting for	Turner syndrome and induction of puberty are associated with a reduced likelihood and a delay in relationship and sexual experiences. Women needing puberty induction and women with TS more than POI have a	



						age and diagnosis, induction of puberty, as opposed to spontaneous puberty, was associated with a delay in the median age at first relationship and VSI and a reduced probability of having VSI (HR 0.44 [95% CI: 0.32-0.60], P=<.001).	delayed mean age at first VSI compared to the general population.	
<b>(Engberg et al., 2022)</b>	cross sectional study	20 women with CAIS, 8 women with 46,XY GD, 8 women with 46,XX GD, 21 women with POI, and 62 population-derived controls.	gynecological examination for anatomical measurements and evaluation of tactile sensitivity. They responded to the validated Sexual Activity Log (SAL), Profile of Female Sexual Function (PFSF), and the Personal Distress Scale (PDS).		sexual function	The women with CAIS, XY GD, XX GD and POI showed overall satisfying sexual function in comparison to controls with a median of 1 to 2 satisfying sexual episodes per week among both the patients and the controls depending on available partner. Women with CAIS had shorter vagina and smaller clitoris and women with XY GD had a significantly shallower vagina in comparison to controls. Clitoral width was also significantly smaller among women with XX GD compared to controls. However, results showed overall good genital touch sensitivity with no significant differences between groups.	Women with differences of sex development or early loss of gonadal function show overall good sexual well-being, however clinicians have to make efforts to optimize caretaking and treatment to ensure good sexual quality of life for all patients.	

### Evidence to recommendations

QUESTION RECOMMENDATION	<b>What are the consequences of POI for sexuality? HCPs should advise women that a diagnosis of POI can have a significant impact on sexual wellbeing and function.</b>
Desirable effects	A diagnosis of POI can have a significant impact on sexual wellbeing and function
Undesirable effects	Limited undesirable effects for information provision, a sensitive approach is recommended as a GPP
Certainty of evidence	Observational data only
Values	
Balance of effects	Strong recommendation for providing information
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	NA

QUESTION GOOD PRACTICE POINT	<b>What are the consequences of POI for sexuality? The guideline group recommends that HCPs routinely and sensitively ask permission of women with POI to discuss sexual wellbeing and function.</b>
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Justification

Limited undesirable effects for information provision, a sensitive approach and requesting permission to address the topic is recommended as a GPP



## PICO QUESTION: WHAT ARE THE MANAGEMENT OPTIONS FOR THE EFFECTS OF POI ON SEXUALITY?

<b>Population</b>	POI
<b>Interventions</b>	Androgen replacement Indications (fatigue, loss of libido, despite Estrogen) Sex therapy, psychotherapy, cognitive behavioural therapy,
<b>Control</b>	
<b>Outcomes</b>	Relief of symptoms / Quality of life / Bone density / Side effects/adverse events / Patient preferences / Psychosexual outcomes

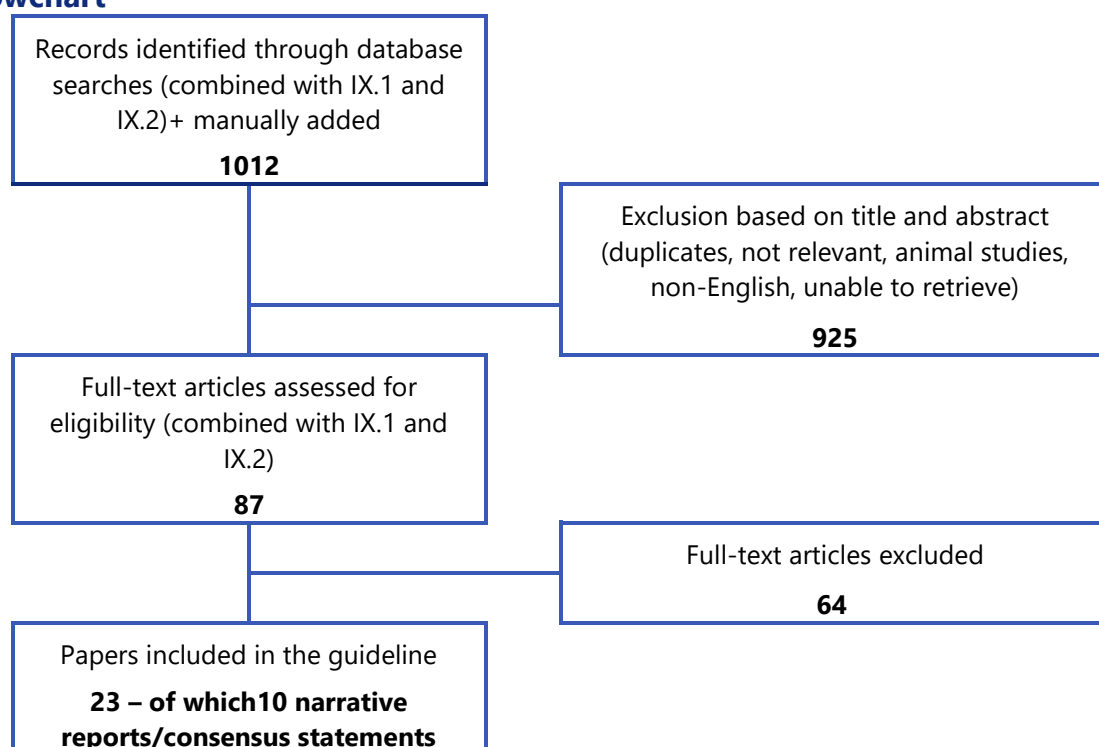
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (((Androgen OR "androgenic hormone" OR testosterone OR DHEA OR "dihydroepiandrosterone" OR Dehydroepiandrosterone) AND ("Quality of life" OR "Quality of Life"[Mesh] OR "Side effects" OR "adverse events" OR "adverse effects" [Subheading] OR "Patient preferences" OR "Patient Preference"[Mesh] OR sexuality OR "Sexuality"[Mesh] OR "Psychosexual function" OR "Satisfaction with sexual life" OR "sexual fantasies" OR masturbation OR arousal OR lubrication OR "genital pain" OR desire OR "frequency of sexual contact" OR orgasm OR "sexual debut" OR "sexual identity" OR libido OR "hypoactive sexual desire disorder")) OR ("Sex therapy" OR psychotherapy OR "cognitive behavioural therapy" OR "Cognitive Therapy"[Mesh] OR "Psychotherapy"[Mesh] OR "Behavior Therapy"[Mesh]))

Literature search was limited to the period between 01/01/2014 and 19/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Systemic Estrogens</b>								
(Nappi <i>et al.</i> , 2021).								Narrative review
(Zilio Rech <i>et al.</i> , 2019).	Cohort	Recently postmenopausal women and 45 controls (C)	81 treated with transdermal E2, 36 with bilateral oophorectomy (O),	45 controls (C)	hormonal profile, Female Sexual Function Index, Mini Mental, and Beck Depression	T levels, as expected, were lower in O than in C ( $p = 0.001$ ); nonetheless, O presented a lower risk of sexual dysfunction (55.6% vs. 85.7%, $p = 0.037$ ), due to less pain ( $p = 0.005$ ), increased lubrication ( $p = 0.012$ ), and satisfaction ( $p = 0.042$ ). O, however, required 50% higher E2 gel doses to control vasomotor	Despite lower T levels, O women receiving E2 therapy had better global sexual function. Earlier onset and longer E2 treatment could have prevented vulvovaginal atrophy in O. Oophorectomized patients may require	



					on Inventor	<p>symptoms (VMS) than did C. In O, all T measurements were positively, although weakly, correlated with desire (<math>r = 0.374-0.381</math>, <math>p = 0.016-0.024</math>). E2 levels were positively correlated with arousal in all women (<math>r = 0.338</math>, <math>p = 0.038</math>) and in O (<math>r = 0.521</math>, <math>p = 0.032</math>). Depression and cognition scores did not differ between the groups.</p>	<p>higher doses of E2 replacement. E2 levels, achieved by appropriate hormone therapy for VMS control, and very low T levels correlated with distinct sexual domains and may act in complementary areas of sexuality in postmenopausal women.</p>
<b>(Vermeulen et al., 2017).</b>	Review		RRSO		<p>quality of life, endocrine symptoms, sexual function, osteoporosis, cardiovascular health, metabolic syndrome, cognitive impairment and safety of hormone replacement therapy</p>	<p>Surgical menopause leads to more menopausal complaints and sexual dysfunction than natural menopause. Overall quality of life is not affected by surgery. In the limited literature, there is no evidence that RRSO leads to more osteopenia in comparison with natural menopause at a young age. Cohort studies show a slight impaired cardiovascular health. Cognitive function decreases later in life in premenopausal oophorectomized women. Short-term hormone replacement therapy seems to decline postmenopausal complaints and does not seem to increase the risk for breast carcinoma in mutation carriers without a personal history of breast carcinoma.</p>	<p>Conclusions are limited by the absence of RCTs. There is growing evidence from observational studies that RRSO may impact negatively on all-cause non-survival endpoints.</p>
<b>(Islam et al., 2021).</b>	Prospective observational	<p>73 premenopausal women at elevated risk of ovarian cancer planning RRBSO and 68 premenopausal controls at population risk of ovarian cancer</p>	Estrogen		<p>Female Sexual Function Index and the Female Sexual Distress Scale-Revised</p> <p>Change from baseline following RRBSO was compare</p>	<p>Baseline sexual function domains did not differ between controls and those who underwent RRBSO and subsequently initiated (56.2%) or did not initiate (43.8%) estrogen therapy. At 12 months, sexual desire and satisfaction were unchanged in the RRBSO group compared with controls. After RRBSO, nonestrogen therapy users demonstrated significant impairment in sexual arousal (<math>\beta</math>-coefficient (95% confidence interval) -2.53 (-4.86 to -0.19), <math>P &lt; 0.03</math>),</p>	<p>The findings suggest premenopausal RRBSO adversely affects several aspects of sexual function which may be mitigated by the use of estrogen therapy. Further research is needed to understand the effects of RRBSO on sexual function and sexually related personal distress, and the potential for estrogen therapy to mitigate against any adverse effects.</p>



					d with controls at 12 months according to estrogen therapy use.	lubrication (-3.40 (-5.84 to -0.96), $P < 0.006$ ), orgasm (-1.64 (-3.23 to -0.06), $P < 0.04$ ), and pain (-2.70 (-4.59 to 0.82), $P < 0.005$ ) compared with controls. Although sexually related personal distress may have been more likely after RRBSO, irrespective of estrogen therapy use, there was insufficient data to formally test this effect.		
<b>(Moss et al., 2022).</b>	Cohort	pre-menopausal comparisons who retained their ovaries (n = 99), RRBSO HT users (n = 57) and RRBSO non-HT users (n = 38).	hormone therapy (HT)		Symptoms	Three symptom profiles were identified: Most Symptoms (81-87% non-HT; 36-41% HT; 7-9% comparisons), Few Symptoms (7-13% non-HT; 36-42% HT; 77-80% comparisons), and Sexual Symptoms (0-10% non-HT; 17-27% HT; 14-15% comparisons). Most of the non-HT group reported Most Symptoms at 3 months with only a 2% chance of improvement by 12 months. The HT group were split between profiles at 3 months with a 5-13% chance of improvement by 6 months (14% chance of worsening), and a 12-32% chance of improvement by 12 months (4-25% chance of worsening).	Symptoms cluster into distinct profiles after premenopausal RRBSO. Most non-HT users are highly symptomatic with little chance of improvement by 12 months. In contrast, two-thirds of HT users have fewer symptoms and a much higher chance of improvement. These findings can inform patient decision-making and expectations.	Participants were premenopausal women from a longitudinal controlled study (What Happens After Menopause? (WHAM)).
<b>(Benetti-Pinto et al., 2015b).</b>	Cross-sectional study	80 women with POI, matched by age to 80 women with normal gonadal function.			SF through the "Female Sexual Function Index" (FSFI),	The FSFI score was significantly worse for women with POF, with a decrease in arousal, lubrication, orgasm, satisfaction, and dyspareunia. Exploratory factor analysis of SF showed that the domain with greater influence in the SF was arousal,	Women with POF have impaired SF, determined mainly by changes in arousal and desire.	



						followed by desire, together accounting for 41% of the FSFI. The domains with less influence were dyspareunia and lubrication, which together accounted for 25% of the FSFI.	Aspects related to lubrication and dyspareunia complaints have lower determination coefficient in SF.	
<b>(Meziou et al., 2023)</b>	Review + meta-analysis.	perimenopausal and postmenopausal women  47 RCTs (35,912 participants) in the SR  34 RCTs (15,079 participants) in the meta-analysis.	HRT		sexual function	The meta-analysis revealed that, in comparison to control, estrogen therapy (standardized mean difference [SMD], 0.16; 95% confidence interval [CI], 0.02 to 0.29; I2 = 59%; 2,925 participants, 16 studies), estrogen plus progestogen therapy (SMD, 0.11; 95% CI, -0.07 to 0.29; I2 = 65%; 2,432 participants, 7 studies), tibolone (SMD, 0.15; 95% CI, 0.02 to 0.28; I2 = 0%; 916 participants, 2 studies), and selective estrogen receptor modulators (SMD, 0.18; 95% CI, 0.06 to 0.30; I2 = 0%; 1,058 participants, 4 studies) may result in no effect to small benefit on sexual function composite score.	Hormone therapy may slightly improve sexual functioning. This potential small benefit should be considered when discussing treatment options for other menopausal symptoms.	
<b>(Nappi et al., 2022b).</b>								Narrative review
<b>(Taylor et al., 2017).</b>	RCT	670 healthy, recently menopausal women. Women were 42 to 58 years old, within 36 months from last menstrual period.	0.45 mg/d oral conjugated equine estrogens (o-CEE), 50 µg/d transdermal 17β-estradiol (t-E2),  Also 200 mg oral micronized progesterone (if randomized to o-CEE or t-E2) or placebo (if	placebo	Sexual Function	The t-E2 treatment was associated with a significant yet moderate improvement in the FSFI overall score across all time points compared with placebo (average efficacy, 2.6; 95% CI, 1.11-4.10; adjusted P = .002). With o-CEE treatment, there was no significant difference in FSFI overall score compared with placebo (mean efficacy, 1.4; 95% CI, -0.1 to 2.8; adjusted P = .13). There was no difference in FSFI overall score between the t-E2 and o-CEE groups on average across 48 months (adjusted P = .22). In the individual domains of sexual function, t-E2 treatment was associated with a significant increase in mean lubrication (0.61; 95% CI, 0.25-0.97; P = .001) and decreased pain (0.67; 95% CI, 0.25-1.09; P = .002) compared with placebo. Overall, the proportion of women with LSF was significantly lower after t-E2 treatment compared with		



			randomized to placebo estrogens) for 12 days each month.			placebo (67%; 95% CI, 55%-77% vs 76%; 95% CI, 67%-83%; P = .04). For o-CEE there was no significant reduction in the odds of LSF.	
<b>(Both et al., 2019).</b>	Hormonal Contraception and Female Sexuality: Position Statements from the European Society of Sexual Medicine (ESSM)						
<b>(Nappi et al., 2019).</b>							Narrative review
<b>Systemic Testosterone and other androgenic compounds</b>							
<b>(Davis et al., 2019).</b>	Global Consensus Position Statement						
<b>(Parish et al., 2021)</b>	International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women						
<b>(Davis, 2021).</b>							Narrative review
<b>(Baber et al., 2016).</b>	2016 IMS Recommendations on women's midlife health and menopause hormone therapy						
<b>(Lara et al., 2023).</b>	Cochrane review	perimenopausal and postmenopausal women  36 studies (23,299 women)	Hormone therapy		sexual function	Estrogen alone versus control probably slightly improves the sexual function composite score in symptomatic or early postmenopausal women (SMD 0.50, 95% confidence interval (CI) (0.04 to 0.96; I <sup>2</sup> = 88%; 3 studies, 699 women; moderate-quality evidence), and probably makes little or no difference to the sexual function composite score in unselected postmenopausal women (SMD 0.64, 95% CI -0.12 to 1.41; I <sup>2</sup> = 94%; 6 studies, 608 women; moderate-quality evidence). The pooled result suggests that estrogen alone versus placebo or no intervention probably slightly improves sexual function composite score (SMD 0.60, 95% CI 0.16 to 1.04; I <sup>2</sup> = 92%; 9 studies, 1307 women, moderate-quality evidence). We are uncertain of the effect of estrogen combined with progestogens versus placebo or no intervention on the sexual function composite score in unselected postmenopausal women (MD 0.08 95% CI -1.52 to 1.68; 1 study, 104 women; very low-quality evidence). We are uncertain of the effect of synthetic steroids versus control on the sexual function composite score in symptomatic or early postmenopausal women (SMD 1.32, 95% CI 1.18 to 1.47; 1 study, 883 women; very low-quality evidence) and of their effect in unselected postmenopausal women (SMD 0.46, 95% CI 0.07 to 0.85; 1 study, 105 women; very low-quality evidence). We are uncertain of the effect of SERMs versus control on the sexual function composite score in symptomatic or early postmenopausal women (MD -1.00, 95% CI -2.00 to -0.00; 1 study, 215 women; very low-quality evidence) and of their effect in unselected postmenopausal women (MD 2.24, 95% 1.37 to 3.11	



						2 studies, 1525 women, $I^2 = 1\%$ , low-quality evidence). We are uncertain of the effect of SERMs combined with estrogen versus control on the sexual function composite score in symptomatic or early postmenopausal women (SMD 0.22, 95% CI 0.00 to 0.43; 1 study, 542 women; very low-quality evidence) and of their effect in unselected postmenopausal women (SMD 2.79, 95% CI 2.41 to 3.18; 1 study, 272 women; very low-quality evidence). The observed heterogeneity in many analyses may be caused by variations in the interventions and doses used, and by different tools used for assessment.	
<b>Psychosexual management</b>							
<b>(Simon et al., 2018b).</b>	The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review						
<b>(Santos Silva et al., 2022).</b>	Review	Postmenopausal Sexual Dysfunction  8 studies - 619 women, aged between 39 and 75 years old, all in menopause for less than 5 years.	sexual education programs, with 4-10 sessions, 45-60 minutes each, including themes like sexual anatomy, physiological sexual response, menopause, methods of stimulation, and common sexual myths. Five studies also included cognitive-behavior therapy and 3 studies assessed mindfulness techniques.		Six studies evaluated the effectiveness of sexual educational programs using FSFI.	The results showed that sexual counselling educational programs had statistically significant effects on enhancing the total FSFI score (mean difference = +7.14, 95% confidence interval = 3.70-10.6, $P < .0001$ ) in comparison to routine care. Results were also significant in all evaluated sex domains: pain, arousal, lubrication, desire, orgasm and satisfaction ( $P < .05$ ).	
<b>(Kingsberg et al., 2017)</b>	Female Sexual Dysfunction-Medical and Psychological Treatments, Committee 14						
<b>(van Driel et al., 2019a).</b>	RCT	66 women carriers of the BRCA1/2 mutation who developed at least two moderate-	8-week mindfulness-based stress reduction (MBSR) training programme or to care as usual (CAU).		Change in the Menopause-Specific Quality of Life Questionnaire (MENQOL	At 3 and 12 months, there were statistically significant improvements in the MENQOL for the MBSR group compared with the CAU group (both $P = 0.04$ ). At 3 months, the mean MENQOL scores were 3.5 (95% confidence interval, 95% CI 3.0-3.9) and 3.8	Mindfulness-based stress reduction was effective at improving quality of life in the short- and



		to-severe menopausal symptoms after RRSO			L), the Female Sexual Function Index, and the Female Sexual Distress Scale, administered from baseline at 3, 6, and 12 months.	(95% CI 3.3-4.2) for the MBSR and CAU groups, respectively; at 12 months, the corresponding values were 3.6 (95% CI 3.1-4.0) and 3.9 (95% CI 3.5-4.4). No significant differences were found between the MBSR and CAU groups in the other scores.	long-term for patients with menopausal symptoms after RRSO; however, it was not associated with an improvement in sexual functioning or distress.
<b>(Thomass et al., 2023).</b>	randomized controlled pilot study	61 Women aged ≥45 years with low libido	31 - mindfulness instruction and practice, group discussion	30 – educated on sexuality and aging	sexual function (Female Sexual Function Index) and sexual distress (Female Sexual Distress Scale-Revised) at 6 weeks postconclusion.	Eighteen women in the intervention group and 23 in the control group attended at least 1 session. Time conflict was the main reason for nonattendance. Of the 41 women who started attending groups, 37 (90%) attended at least 5 sessions. In the mindfulness group, 73% of women were very or extremely satisfied. Women in the mindfulness group were more likely to recommend it to another person with low libido as compared with those in the education group (P = .031); 67% said that they would probably or definitely recommend it. There were no significant changes in sexual function in either group (mean Female Sexual Function Index score, 22.6 to 18.6 [P = .101] with mindfulness and 21.2 to 19.7 [P = .537] with education). Women in the mindfulness group had significant improvements in sexual distress (mean Female Sexual Distress Scale-Revised score, 27.1 to 19.7; P = .021) while women in the education group did not (19.0 to 15.8; P = .062).	
<b>(Bober et al., 2015).</b>	Single arm trial	37 women with BRCA1/2 mutations who previously underwent RRSO	one-time, half-day educational session comprised of targeted sexual health education, body awareness and relaxation training, and mindfulness-based cognitive therapy strategies,		baseline and postintervention assessments	Overall sexual functioning (P = 0.018), as well as desire (P = 0.003), arousal (P = 0.003), satisfaction (P = 0.028), and pain (P = 0.018), improved significantly. There were significant reductions in somatization (P = 0.029) and anxiety scores (P < 0.001), and, overall, for the Global Severity Index (P < 0.001) of the Brief Symptom Inventory. Sexual self-efficacy and sexual knowledge also improved significantly from baseline to postintervention (both	This intervention integrates elements of cognitive behavioural therapy with sexual health education to address a much-neglected problem after RRSO.



			followed by two sessions of tailored telephone counseling			P < 0.001). Women were highly satisfied with the intervention content and reported utilizing new skills to manage sexual dysfunction.	Results from this promising single-arm study provide preliminary data to move toward conducting a randomized, controlled trial.	
(Alexandre et al., 2017).								Narrative review

### Evidence to recommendations

QUESTION GOOD PRACTICE POINT	What are the management options for the effects of POI on sexuality? <b>The guideline group recommends personalized management using the biopsychosocial model for the impact of POI on sexuality.</b>
Justification	There is a lack of agreement on the best strategy to improve sexual function in women with POI and therapeutic management should be on an individual basis. The diverse presentations of sexual dysfunction are unique for each woman suggesting the need for combined therapy and a mix of pharmacological and non-pharmacological strategies.

QUESTION RECOMMENDATION	What are the management options for the effects of POI on sexuality? <b>Where available, transdermal testosterone therapy, in doses that approximate physiological premenopausal testosterone concentrations, can be considered as it may improve hypoactive sexual desire disorder and sexual function.</b>
Desirable effects	Partnered (especially Caucasian) women who are medically and psychologically uncomplicated, who prior to POI had a satisfying sexual life and are currently distressed about low sexual desire despite adequate estrogen replacement, may benefit from at least a 6-month short-term trial of transdermal testosterone with dosing to maintain testosterone levels in premenopausal physiological range. The international consensus on the use of testosterone therapy in women (Davis et al., 2019) should guide clinical practice, with the clear understanding that long-term risks are unknown.
Undesirable effects	
Certainty of evidence	Low quality data only
Values	
Balance of effects	Benefit versus availability and acceptability
Resource use, equity, acceptability and feasibility	Not available in some countries



Subgroup considerations (if applicable)	Recommendation only for women with hypoactive sexual desire disorder and sexual function problems
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QUESTION	What are the management options for the effects of POI on sexuality?
RECOMMENDATION	<b>HCPs should be aware that HT prescribed to women with POI for other indications may improve sexual function, although the effect is generally small.</b>
Desirable effects	Adequate estrogen replacement, with additional local treatment if necessary for dyspareunia, is essential in women with POI and sexual dysfunction.
Undesirable effects	
Certainty of evidence	Very limited data
Values	To limited data to support a recommendation
Balance of effects	Recommendation for awareness, not for prescribing HT with the sole aim of improving sexual function
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	NA



## PICO QUESTION: WHAT TREATMENTS ARE AVAILABLE FOR GENITAL-URINARY SYMPTOMS IN POI?

<b>Population</b>	POI and <ul style="list-style-type: none"> <li>• genito-urinary symptoms</li> <li>• Incontinence</li> <li>• Urinary incontinence</li> <li>• Vaginal atrophy</li> <li>• Dyspareunia</li> <li>• prolapse</li> </ul>
<b>Interventions</b>	Vaginal lubricants/ moisturiser/sylk/replens Estrogen, hormone replacement therapy/HRT/COCP/combined oral contraceptive pill Vaginal oestrogen
<b>Control</b>	
<b>Outcomes</b>	Relief of symptoms Symptom score Sexual function

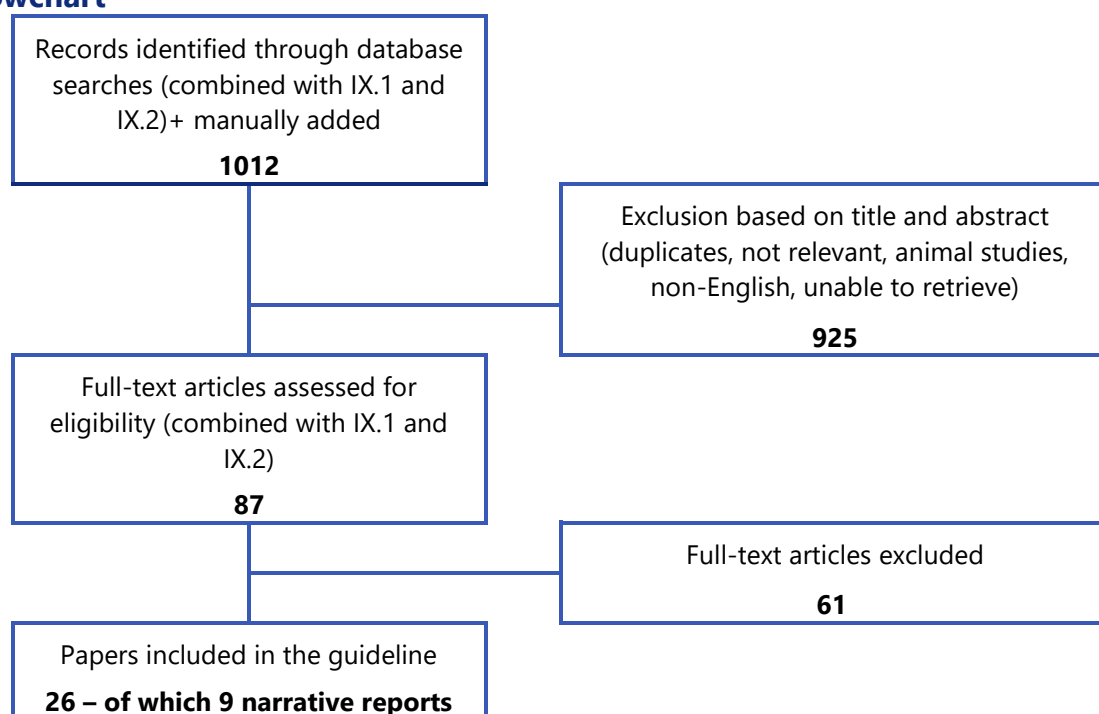
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause" OR menopause OR "estrogen deficiency" OR "low estrogen" OR hypoestrogenic) AND ("genitourinary symptoms" OR "urinary symptoms" OR Incontinence OR "Vaginal atrophy" OR Dyspareunia OR prolapse OR "vaginal dryness" OR "urogenital symptoms") AND ("Vaginal lubricant" OR moisturiser OR Moisturizer OR sylk OR replens OR lubricant OR Estrogen OR oestrogen OR "hormone replacement therapy" OR HRT OR COCP OR "oral contraceptive pill" OR "Hormone Replacement Therapy"[Mesh] OR "Estrogens"[Mesh] OR "Contraceptive Agents, Female"[Mesh])

Literature search was limited to the period between 01/01/2014 and 19/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Systemic therapy</b>								
<b>(Christmas et al., 2023)</b>	systematic review (based on 10 RCTs),		systemic HT.		urinary incontinence or worsen existing urinary symptoms		There is insufficient evidence to confirm that menopause is associated with urinary symptoms. The effect of HT on urinary symptoms depends on type. Systemic HT may cause urinary incontinence or worsen existing urinary symptoms. Vaginal estrogen improves dysuria, frequency, urge and stress incontinence, and recurrent UTI in menopausal women.	
<b>(Staller et al., 2017).</b>	prospective cohort	55,828 postmenopausal women (mean age, 73 years) who	current and past use of HT		faecal incontinence		Compared with women who never used MHT, the multivariate hazard ratio for FI was 1.26 (95% CI, 1.18-1.34) for past users of MHT and 1.32 (95% CI, 1.20-1.45) for current users. The risk of FI increased with	FI as a report of at least 1 liquid or solid FI episode



		participated in the Nurses' Health Study				longer duration of MHT use (P trend $\leq$ .0001) and decreased with time since discontinuation. There was an increased risk of FI among women receiving MHT that contained a combination of estrogen and progestin (hazard ratio, 1.37; 95% CI, 1.10-1.70) compared with estrogen monotherapy.	per month during 4 years of follow-up from self-administered
<b>(Tan et al., 2018).</b>	study	149 patients with POI and 303 control women with similar age, BMI, and parity			Prevalence of Stress Urinary Incontinence (SUI)	prevalence of SUI in the POI group tended to be higher than that in the control group (20.9%, 30/149 vs. 16.2%, 49/303), although not significantly ( $p = 0.297$ ). About 41.6% (62/149) of patients with POI received HT. Patients with POI and SUI were older ( $p = 0.018$ ) and had higher BMI ( $p = 0.007$ ) than women with POI without SUI ( $p = 0.007$ ). Compared to nulliparas, primiparas were more likely to have SUI ( $p = 0.046$ ). However, SUI developed irrespective of time since onset of oligomenorrhea/amenorrhea or HT use. Furthermore, regression analysis showed that the prevalence of SUI was higher in women 30-39 years of age (odds ratio [OR] = 3.27, $p = 0.002$ ) and older than 40 years (OR = 7.78, $p = 0.001$ ). Primiparas (OR = 2.89, $p = 0.001$ ) and vaginal delivery (OR = 2.58, $p = 0.023$ ) were associated with SUI.	
<b>(Fante et al., 2020).</b>	secondary analysis of a cross-sectional study	Women with POI	HT		pelvic floor muscle assessment and symptoms		
<b>Local therapies</b>							
<b>(Palacios et al., 2023).</b>	RCT	174 women aged 18 to 65 years with mild-to-moderate vaginal dryness and dyspareuni	water-based personal lubricants  Participants were randomized to 1 of 5 lubricants (A-E) from 3 brands (Durex, KY, Queen V).		change from baseline in total FSFI score after 4 weeks of product use.	The primary end point—a prespecified increase in FSFI $\geq$ 4 points from baseline after 4 weeks of use—was met by all 5 lubricants tested. A statistically significant improvement was observed across all 6 domains of the FSFI from baseline to 4 weeks of use with all 5 lubricants ( $P < .0001$ for lubrication and pain reduction and $P < .05$ for all other domains). No serious adverse events occurred in the study, and the tolerance of all 5 lubricants was good/very good.	



<b>(Cox and Panay, 2023).</b>								Narrative review
<b>(Nappi et al., 2022a)</b>								Narrative review
<b>Farahat et al., 2023</b>	Review	Seven studies with 631 postmenopausal women with vaginal atrophy	oxytocin gel	placebo gel			Regarding the maturation index, there was a statistically insignificant increase in the oxytocin arm (MD = 12.34, 95% CI (-12.52-37.19), P = 0.33). Clinically assessed vaginal atrophy showed a statistically significant reduction in the oxytocin group (RR = 0.32, 95% CI (0.23 - 0.10), P < 0.00001). For dyspareunia, vaginal pH, and histological evaluation of vaginal atrophy, there was a statistically insignificant difference between the two groups (RR = 1.02, 95% CI (0.82-1.27), P = 0.84), (MD = -0.74, 95% CI (-1.58-0.10), P = 0.08), and (MD = -0.38, 95% CI (-0.82-0.06), P = 0.09), respectively. There was no significant difference in the safety profile between the two groups as measured by endometrial thickness (MD = 0.00, 95% CI (-0.23-0.23), P = 0.99).	
<b>Radnia et al., 2023</b>	RCT	64 postmenopausal women suffering from genitourinary syndrome	combined vaginal cream of vitamins D and E	conjugated estrogen vaginal creams for 12 weeks.	libido, orgasm, and frequency of sexual intercourse, vaginal symptoms		At four visits, libido, orgasm, and frequency of sexual intercourse, as well as vaginal symptoms such as burning, itching, dryness, and dyspareunia were improved in both groups (P < .05). However, there was no difference between the two groups in terms of the frequency of severity of these symptoms during the four visits (P > .05). Investigating the female sexual function index showed that using vitamin D and E vaginal creams, like the use of conjugated estrogens vaginal creams, improves sexual function in women (P < .01).	
<b>(Lethaby et al., 2016)</b>	Review	30 RCTs (6235 women)	intra-vaginal oestrogenic preparations	Compared with each other and with placebo			1. Oestrogen ring versus other regimens There was no evidence of a difference in improvement in symptoms (participant assessment) either between oestrogen ring and oestrogen cream (odds ratio (OR) 1.33, 95% CI 0.80 to 2.19, two RCTs, n = 341, I(2) = 0%, low-quality evidence) or between oestrogen ring and oestrogen tablets (OR 0.78, 95% CI 0.53 to 1.15, three RCTs, n = 567, I(2) = 0%, low-quality evidence).	



					<p>However, a higher proportion of women reported improvement in symptoms following treatment with oestrogen ring compared with placebo (OR 12.67, 95% CI 3.23 to 49.66, one RCT, n = 67). With respect to endometrial thickness, a higher proportion of women who received oestrogen cream showed evidence of increase in endometrial thickness compared to those who were treated with oestrogen ring (OR 0.36, 95% CI 0.14 to 0.94, two RCTs, n = 273; I(2) = 0%, low-quality evidence). This may have been due to the higher doses of cream used.</p> <p>2. Oestrogen tablets versus other regimens There was no evidence of a difference in the proportions of women who reported improvement in symptoms between oestrogen tablets and oestrogen cream (OR 1.06, 95% CI 0.55 to 2.01, two RCTs, n = 208, I(2) = 0% low-quality evidence). A higher proportion of women who were treated with oestrogen tablets reported improvement in symptoms compared to those who received placebo using a fixed-effect model (OR 12.47, 95% CI 9.81 to 15.84, two RCTs, n = 1638, I(2) = 83%, low-quality evidence); however, using a random-effect model did not demonstrate any evidence of a difference in the proportions of women who reported improvement between the two treatment groups (OR 5.80, 95% CI 0.88 to 38.29). There was no evidence of a difference in the proportions of women with increase in endometrial thickness between oestrogen tablets and oestrogen cream (OR 0.31, 95% CI 0.06 to 1.60, two RCTs, n = 151, I(2) = 0%, low-quality evidence).</p> <p>3. Oestrogen cream versus other regimens There was no evidence of a difference in the proportions of women with improvement in symptoms between oestrogen cream and isoflavone gel (OR 2.08, 95% CI 0.08 to 53.76, one RCT, n = 50, low-quality evidence). However, there was evidence of a difference in the proportions of women with improvement in symptoms between oestrogen cream and placebo with more women who received oestrogen cream reporting improvement in symptoms compared to those who were treated with placebo (OR 4.10, 95% CI 1.88 to 8.93, two RCTs, n = 198, I(2) = 50%, low-quality evidence). None of the included studies in this comparison reported data on endometrial thickness.</p>
<b>(Comini et al., 2023).</b>	Review	Breast Cancer Survivors presenting with VVA symptoms	topical vaginal estradiol and estriol preparations, vaginally applied testosterone,	safety and serum estrogen levels of hormonal therapy	among patients treated with the estriol and estradiol preparations, there was an average increase of 7.67 pg/mL (SMD 7.67 pg/mL; 95% CI -1.00, 16.35; p < .001). Analysis of the testosterone group found



		17 studies	DHEA, and ospemifene.			temporary peaks of serum estradiol levels, but 1 study showed persistent elevation above normal postmenopausal levels. One study with prasterone revealed no elevation of serum estradiol concentration. One study with ospemifene demonstrated no increase in the risk of BC recurrence.	
<b>(Wasserman and Rubin, 2023).</b>							Narrative review
<b>(Klasa et al., 2020).</b>	study	38 females after allo-HCT in whom gynecological examination with cervical smear and USG were performed, followed by colposcopy				chronic graft-versus-host disease incidence: 71% anogenital zone (cGVHDgyn) : 29%, including 5 patients with score 3 at the time of diagnosis. The other manifestations (frequently noted) included the skin, mucosa, eyes, and liver. Menopause was diagnosed in 93% females, and in 81% of them, POI criteria were fulfilled. Ovarian function resumed in 2 cases. The rate of abnormal cytology was 26%: 4 ASCUS, 1 AGUS, 1 LSIL, 3 HSIL/ASC-H, and one cytological suspicion of cervical cancer. GVHDgyn was documented in 10 patients, and 6 of them had abnormal cervical cytology. Early topical estrogen therapy led to a significant reduction in vaginal dryness ( $p < 0.05$ ), dyspareunia ( $p < 0.05$ ), and less frequent cGVHDgyn ( $p < 0.05$ ).	
<b>(Crean-Tate et al., 2020)</b>							Narrative review
<b>(Kearley-Shiers et al., 2022)</b>	Review	moderate to severe vulvovaginal atrophy in postmenopausal women	Intravaginal dehydroepiandrosterone (DHEA)			A literature search revealed four original trials suitable for appraisal, three evaluating change in dyspareunia or dryness as a primary outcome, one evaluated safety as a primary outcome. In two trials of 255 and 558 women without cancer, the benefit of placebo (nightly vaginal suppositories with a lipophilic base) was a 0.9 and 1 point reduction in dyspareunia as measured on a 3 point scale, an unvalidated outcome measure. With nightly DHEA, dyspareunia was reduced by an additional 0.4 points compared to placebo. When 464 women with gynaecological cancer were randomised, those using nightly plain moisturiser gel reported a reduction of 'most bothersome symptom' (either dyspareunia	



						or dryness) of 1.5 points on a 3 point scale. Those using nightly DHEA reported an additional symptom reduction of 0.3 points. This is also an unvalidated outcome measure. Data evaluating the efficacy of DHEA over placebo is unconvincing and based on unvalidated primary outcome measures that also do not reflect the complex psycho-sexual and socio-cultural components of genitourinary menopausal symptoms.	
<b>(Davis et al., 2018).</b>	RCT	37 Postmenopausal women taking an AI with VVA symptoms.	Intravaginal Testosterone		Sexual Satisfaction and Vaginal Symptoms	At 26 weeks, the mean between-group difference in the baseline-adjusted change in FSFI satisfaction scores was significantly greater for the IVT group than the placebo group (mean difference 0.73 units; 95% CI, 0.02 to 1.43; P = 0.043). IVT cream resulted in significant improvements, compared with placebo, in FSDS-R scores (P = 0.02), sexual concerns (P < 0.001), sexual responsiveness (P < 0.001), vaginal dryness (P = 0.009), and dyspareunia (P = 0.014). Serum sex steroid levels did not change. Few women had UI symptoms, with no treatment effect.	
<b>Physical therapy</b>							
<b>(Mercier et al., 2023).</b>							Narrative review
<b>Lasers and other thermal energies</b>							
<b>(Cucinella et al., 2023).</b>							Narrative review
<b>(Li et al., 2021a).</b>	RCT	Women With Postmenopausal Vaginal Symptoms	Fractional Carbon Dioxide Laser Three treatments using a fractional microablative carbon dioxide laser system performed 4 to 8 weeks apart n=43	Sham N=42	Symptom Severity (VAS) + Vulvovaginal Symptom Questionnaire	78 (91.7%) completed the 12-month follow-up. From baseline to 12 months, there was no significant difference between the carbon dioxide laser group and the sham group in change in symptom severity (VAS score for overall vaginal symptoms: -17.2 vs -26.6; difference, 9.4 [95% CI, -28.6 to 47.5]; VAS score for the most severe symptom: -24.5 vs -20.4; difference -4.1 [95% CI, -32.5 to 24.3]; VSQ score: -3.1 vs -1.6; difference, -1.5 [95% CI, -5.9 to 3.0]). There were no significant differences between the laser and sham group in the mean quality of life score (6.3 vs 1.4; difference, 4.8 [95% CI, -3.9 to 13.5]) and Vaginal Health Index Score (0.9 vs 1.3; difference, -0.4 [95% CI, -	



						4.3 to 3.6]) or in histological comparisons between laser and sham treatment groups. There were 16 adverse events in the laser group and 17 in the sham group, including vaginal pain/discomfort (44% vs 68%), spotting, discharge, and lower urinary tract symptoms. No severe adverse events were reported in either group.	
<b>(Mensio <i>et al.</i>, 2023).</b>	RCT	Breast Cancer Receiving Aromatase Inhibitors for Genitourinary Syndrome of Menopause	Fractional Carbon Dioxide Laser (35 participants)	Sham (37 participants)	sexual function, (FSFI) Other measures of efficacy included a VAS of dyspareunia, vaginal pH, a Vaginal Health Index, quality of life (assessed via Short-Form 12), and body image  vaginal maturation index, vaginal epithelial elasticity and vaginal epithelial thickness	At 6 months, both groups showed improvement in FSFI (mean [SD] score at baseline vs 6 months: CLT, 14.8 [8.8] points vs 20.0 [9.5] points; SLT, 15.6 [7.0] points vs 23.5 [6.5] points), but there was no significant difference between CLT and SLT groups in the improvement of sexual function evaluated through the FSFI test overall (mean [SD] difference, 5.2 [1.5] points vs 7.9 [1.2] points; P = .15) or after excluding women who were not sexually active (mean [SD] difference, 2.9 [1.4] points vs 5.5 [1.1] points; P = .15). There were also no differences between improvement of the 2 groups at 6 months of follow-up in the other assessed subjective outcomes, including dyspareunia (mean [SD] difference, -4.3 [3.4] vs -4.5 [2.3]; P = .73), Vaginal Health Index (mean [SD] difference, 3.3 [4.1] vs 5.0 [4.5]; P = .17), body image (mean [SD] difference, -3.7 [4.5] vs -2.7 [4.8]; P = .35), and quality of life (mean [SD] difference, -0.3 [3.6] vs -0.7 [3.2]; P = .39). Similarly, there were no differences in improvements in objective outcomes, including vaginal pH (mean [SD] difference, -0.6 [0.9] vs -0.8 [1.2]; P = .29), vaginal maturation index (mean [SD] difference, 10.2 [17.4] vs 14.4 [17.1]; P = .15), vaginal epithelial thickness (mean [SD] difference, 0.021 [0.014] mm vs 0.013 [0.012] mm; P = .30), vaginal epithelial elasticity (mean [SD] difference, -1373 [3197] Pascals vs -2103 [3771] Pascals; P = .64). There were significant improvements in the overall analysis regardless of group in many outcomes. The 2 interventions were well tolerated, but tolerance was significantly lower in the CLT group than the SLT group (mean [SD] Likert scale score, 3.3 [1.3] vs 4.1 [1.0]; P = .007). No differences were observed in complications or serum estradiol levels.	
<b>(Hickey <i>et al.</i>, 2023).</b>	pilot sham-controlled study	postmenopausal women with self-reported vaginal dryness	ultrasound treatment (n = 21)	sham (n = 21) for 12 weeks.	change from baseline to week 12 in Vaginal Assessment Scale symptoms (dryness, soreness, irritation,	women showed reduction in Vaginal Assessment Scale with ultrasound treatment versus sham (n = 15, -0.5 ± 0.2 vs n = 15, -0.4 ± 0.3; P = 0.9) and improved Vaginal Health Index (n = 9, 2.7 ± 0.9 vs n = 9, 0.6 ± 1.4; P = 0.3). In the per-protocol analysis population, ultrasound treatment (n = 9) versus sham (n = 8) significantly reduced	



					dyspareunia). Secondary: scoring of clinician-reported Vaginal Health Index  treatment-emergent adverse events	symptoms score ( $-0.6 \pm 0.3$ vs $-0.0 \pm 0.4$ ; $P = 0.05$ ) and significantly improved Vaginal Health Index ( $2.7 \pm 0.9$ vs $-0.4 \pm 1.2$ ; $P = 0.03$ ). Improvement in effectiveness endpoints were seen at 1 year compared with baseline. There were no differences in treatment-emergent adverse events between ultrasound treatment versus sham and no serious adverse events.	
<b>(Jang et al., 2022).</b>	systematic review and meta-analysis of RCTs	270 women from 6 RCTs	Carbon Dioxide Laser	Vaginal Estrogen Therapy	Severity of Genitourinary Syndrome of Menopause Symptoms	vaginal laser treatment is associated with similar improvement in genitourinary symptoms as LET	
<b>(Gold et al., 2023).</b>	RCT	43 women (aged 49-58 years, mean age 54 years) with urogenital atrophy and a history of BC	Vaginal laser therapy (n=22)	hyaluronic acid suppositories (n=21)	Vaginal Health Index after 3 months. Secondary endpoints were subjective bother on a numeric rating scale for all urogenital atrophy domains, quality of life, sexual health and pelvic organ prolapse symptoms using validated questionnaires.	At 3 months score on the Vaginal Health Index had improved significantly in both groups ( $p = 0.001$ ), without a significant difference between treatment groups ( $p = 0.232$ ). Significant improvement was also seen in both groups for subjective bother of urogenital atrophy, quality of life and sexual health, without significant differences between laser or hyaluronic acid therapy.	
<b>OTHER LOCAL APPROACHES</b>							
<b>(Francés - Herrero et al., 2022).</b>	RCT				Owing to inconsistencies in the study measurements and designs, the findings were assessed qualitatively rather than by meta-analysis. Hydrogels and scaffolds were commonly applied in various bioengineering-related studies of the female reproductive tract. Emerging technologies, such as organoids and bioprinting, offered personalized diagnoses and alternative treatment options, respectively. Promising microfluidic systems combining various	Narrative description of results	



					bioengineering approaches have also shown translational value.	
(Berreni et al., 2021).						Narrative review
(Isaza, 2019).						Narrative review

*Evidence to recommendations*

QUESTION RECOMMENDATION	What treatments are available for genital-urinary symptoms in POI? <b>HCPs should offer vaginal estrogen therapy to improve genitourinary and sexual symptoms. Women with POI may be offered vaginal estrogen therapy if genitourinary symptoms are not fully relieved by using systemic HT.</b>
Desirable effects	approved LET are all similarly effective in relieving vaginal dryness and dyspareunia, thus the choice should consider patient’s preference LET improves dysuria, frequency, urge incontinence, stress incontinence, and recurrent urinary tract infections in menopausal women
Undesirable effects	Limited negative effects, some concern about urinary incontinence or faecal incontinence
Certainty of evidence	Low/very low quality of evidence
Values	
Balance of effects	Limited negative effects
Resource use, equity, acceptability and feasibility	Already applied, even without prescription
Subgroup considerations (if applicable)	Only for symptomatic patients

QUESTION RECOMMENDATION	What treatments are available for genital-urinary symptoms in POI? <b>Vaginal lubricants and moisturizers can be used for treatment of vaginal discomfort and dyspareunia in women with POI and can be combined with other treatments.</b>
Desirable effects	Symptom relief Vaginal lubricants, moisturisers, and menopause hormone therapy (both systemic and local) can be used to treat genitourinary symptoms.
Undesirable effects	
Certainty of evidence	Low/very low quality of evidence
Values	
Balance of effects	
Resource use, equity, acceptability and feasibility	Vaginal lubricants and moisturisers are available over the counter, but their chemical composition can vary significantly. They should be body similar to avoid irritation and minimise the risk of epithelial damage.



Subgroup considerations (if applicable)	These strategies may be used when there is a need for local treatment where (i) systemic HT is contraindicated, as in iatrogenic POI, secondary to treatment for estrogen sensitive cancer (ii) in women who are averse to HT or (iii) still experience genitourinary symptoms despite an appropriate HT dose
QUESTION GOOD PRACTICE POINT	What treatments are available for genital-urinary symptoms in POI? <b>The guideline group currently does not recommend laser or thermal energy as standard care for genitourinary symptoms due to inconclusive evidence of benefit from RCTs.</b>
Justification	Lack of evidence



## X. POI and neurological function

### PICO QUESTION: WHAT ARE THE CONSEQUENCES OF POI ON COGNITION/NEUROLOGICAL FUNCTION?

<b>Population</b>	POI - Turner - Non-Turner / surgical menopause
<b>Interventions</b>	
<b>Control</b>	
<b>Outcomes</b>	Neurological function Cognitive function Dementia Parkinson's disease Self-reported memory loss Memory concentration

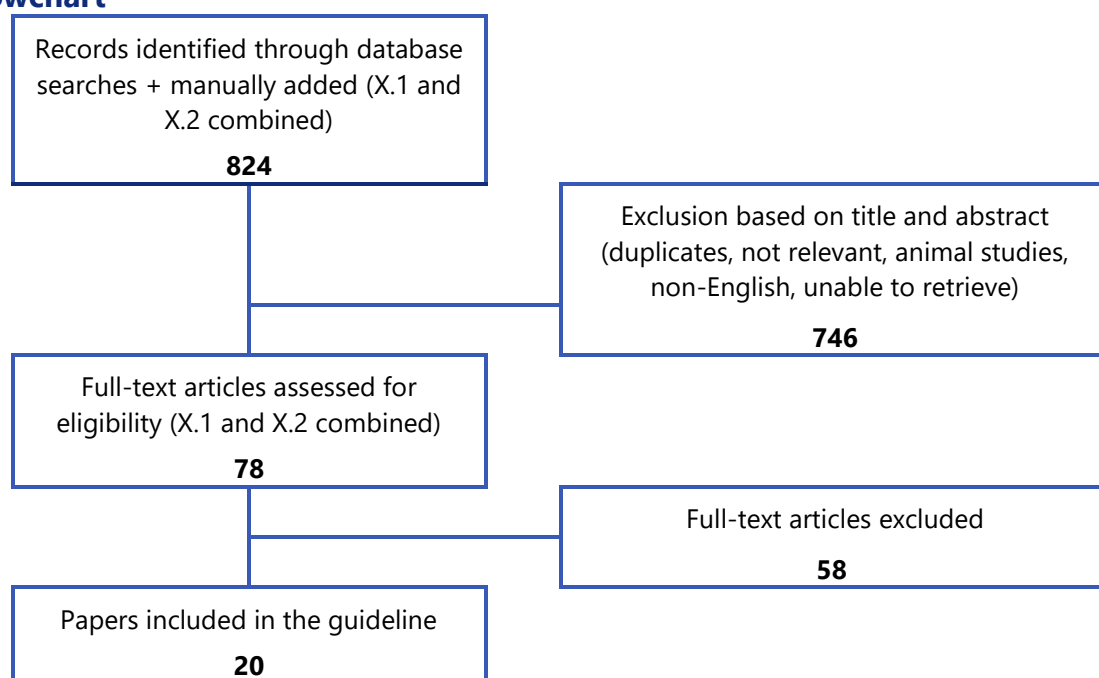
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause" OR "Turner syndrome") AND ("Neurological function" OR "Cognitive function" OR Dementia OR "Dementia"[Mesh] OR "Parkinson's disease" OR "Parkinson Disease" OR "Parkinson Disease"[Mesh] OR "memory loss" OR "Memory Disorders"[Mesh] OR Memory OR "Memory"[Mesh] OR "Amnesia"[Mesh] OR concentration OR "Attention"[Mesh])

Literature search was limited to the period between 01/01/2014 and 19/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Cognitive impairment and dementia after non-iatrogenic POI</b>								
(Georgakis et al., 2016)	Review	13 studies			association of age at menopause/reproductive period (i) dementia and (ii) cognitive function	Age at menopause (13 studies; 19,449 participants) and reproductive period (4 studies; 9916 participants) in the highest categories were not associated with odds of dementia (effect size [ES]: 0.97 [0.78-1.21]) and Alzheimer's disease (ES: 1.06 [0.71-1.58]). Significant heterogeneity was however noted in both analyses ( $I^2$ : 63.3%, $p=0.003$ and $I^2$ : 72.6%, $p=0.01$ , respectively).  In 9/13 studies assessing cognitive function, advanced age at menopause/longer reproductive period was significantly associated with better cognitive performance/lower decline.		



<b>(Fu et al., 2022).</b>	Review	22 studies (475 9764 women)		association between any exposure (age of menarche, age at menopause, reproductive period, estradiol level) and any endpoint variable [all-cause dementia, Alzheimer's disease (AD), vascular dementia (VD), cognitive impairment (CI)].	Later menopause ( $\geq 45$ vs $< 45$ years) was consistently associated with a lower risk of all-cause dementia (pooled RR: 0.87, 95%CI: 0.78-0.97, I <sup>2</sup> =56.0%), AD (0.67, 0.44-0.99, I <sup>2</sup> =78.3%), VD (0.87, 0.80-0.94) and CI (0.82, 0.71-0.94, I <sup>2</sup> =19.3%)	
<b>(Karamitrou et al., 2023)</b>	Review	Eleven studies (nine assessed as of good and two as of fair quality) (n = 4,716,862).		association between EM or POI and the risk of dementia of any type	Women with EM demonstrated a greater risk of dementia of any type than women of normal age at menopause (OR 1.37, 95 % CI 1.22-1.54; I <sup>2</sup> 93%). However, after excluding a large retrospective cohort study, the results were altered (OR 1.07, 95 % CI 0.78-1.48; I <sup>2</sup> 94%).  Increased risk of dementia in women with POI (OR 1.18, 95 % CI 1.15-1.21; I <sup>2</sup> 0%). Subgroup analysis showed that this risk was mostly evident in cohort studies, and those which included women with natural menopause.	
<b>(Gong et al., 2022).</b>	population-based cohort study	1,866 dementia cases were recorded in women		risk of incident all-cause dementia + associated with reproductive factors	HR 1.32 (1.15, 1.51) (p = 0.008) for natural menopause at $< 47$ compared to 50 years; 1.12 (1.01, 1.25) (p = 0.039) for hysterectomy; 2.35 (1.06, 5.23) (p = 0.037) for hysterectomy with previous oophorectomy; and 0.80 (0.72, 0.88) (p < 0.001) for oral contraceptive pills use.	UK biobank
<b>(Hao et al., 2023).</b>	population-based cohort study	160 080 women who participated in the UK Biobank study		risk of all-cause dementia+ link with menopause	Compared to women with age at menopause of 46-50 years, women with earlier natural menopause younger than 40 years (1.36, 1.01-1.83) and 41-45 years (1.19, 1.03-1.39) had a higher risk of all-cause dementia, while late natural menopause $> 55$ years was linked to lower risk of dementia (0.83, 0.71-0.98). Compared to natural menopause, surgical menopause was associated with 10% higher risk of dementia (1.10, 0.98-1.24).	UK biobank
<b>(Coughlan et</b>	cross-section	292 cognitively unimpaired		regional tau at a given level	There were 98 female HT users (52.2%) (past/current). Female sex	



<p><b>al., 2023).</b></p>	<p>nal study</p>	<p>individuals, - 193 females</p>		<p>of Aβ, both measured with positron emission tomography (PET).  Association with sex, age at menopause, and HT</p>	<p>(standardized β = -0.41; 95% CI, -0.97 to -0.32; P &lt; .001), earlier age at menopause (standardized β = -0.38; 95% CI, -0.14 to -0.09; P &lt; .001), and HT use (standardized β = 0.31; 95% CI, 0.40-1.20; P = .008) were associated with higher regional tau PET in individuals with elevated</p>	
<p><b>Cognitive impairment and dementia after iatrogenic POI</b></p>						
<p><b>(Georgakis et al., 2019)</b></p>	<p>Systematic review</p>	<p>women having undergone surgical menopause  11 eligible studies (N = 18,867). "i) cohort and cross-sectional studies comparing risk of dementia and Alzheimers disease, cognitive performance (single cognitive assessment in a cross-sectional setting), rate of cognitive decline (time-series assessments in a longitudinal setting), and the extent of neuropathological indices of Alzheimers disease, between postmenopausal women having undergone a surgical menopause and postmenopausal women having experienced a natural menopause  ii) cohort or cross-sectional studies of only women having undergone surgical menopause exploring the association of the age at surgery with the same outcomes (risk of dementia and Alzheimer's</p>	<p>Surgical menopause</p>	<p>risk of dementia  cognitive performance  cognitive decline  Alzheimers disease neuropathological indices</p>	<p>risk of dementia no association for surgical menopause at any age RR: 1.16, 95%CI: 0.94-1.43; 4studies, 12,731 women; 891 dementia events)  Higher risk with early surgical menopause (≤45 years of age) (2 studies; RR: 1.70, 95%CI: 1.07-2.69; 6256 women; 331 dementia events).  cognitive performance / cognitive decline  Surgical menopause at any age was associated with faster decline in verbal memory, semantic memory, and processing speed, whereas early surgical menopause was further associated with faster global cognitive decline.  (TABLE 2 FOR DETAILS)  In cross-sectional analyses examining cognitive performance at a single time point, we found no significant associations between surgical menopause and cognitive performance in any of the examined domains  Among women undergoing surgical menopause, a younger age at surgery was associated with faster decline in global cognition, semantic and episodic memory, worse performance in verbal fluency and executive function, and accumulation of Alzheimers neuropathology (3 Studies, TABLE 3)" current evidence supports that surgical menopause induced by bilateral oophorectomy at a young age may be associated with higher risk of dementia and cognitive decline later in life. Yet, our review further identified literature gaps and thus calls for additional research encompassing data from large cohorts that</p>	<p>Only systematic review of oophorectomy and cognitive decline or dementia</p>



		disease, cognitive performance, rate of cognitive decline, Alzheimers neuropathology indices)"				should shed light in this clinically relevant field.	
<b>(Bove et al., 2014).</b>	2 longitudinal studies	(total n = 1,884).			primary analysis : association between age at surgical menopause and decline in a global cognition score.  Secondary analyses examined additional outcomes: 1) decline in 5 cognitive subdomains and 2) a global measure of the burden of AD pathology.	surgical menopause: earlier age at menopause was associated with <ul style="list-style-type: none"> <li>- faster decline in global cognition (p = 0.0007), specifically episodic memory (p = 0.0003) and semantic memory (p = 0.002).</li> <li>- increased AD neuropathology (p = 0.038), in particular neuritic plaques (p = 0.013).</li> </ul> HRT use for at least 10 years, when administered within a 5-year perimenopausal window, was associated with decreased decline in global cognition.  No associations were seen in women who had natural menopause.	
<b>(Rocca et al., 2021a).</b>	case-control study and cross-sectional study	283 women with MCI (10.4%) and 2449 women without cognitive impairment (89.6%).  cross-sectional study: 625 women with a history of BSO (median [IQR] age, 75 [70-82] years) and 2107 women without a history of BSO (median [IQR] age, 73 [65-80] years).			mild cognitive impairment (MCI)  global or domain-specific cognitive performance.	BSO before menopause and before age 46 years was associated with clinically diagnosed MCI (adjusted OR, 2.21; 95% CI, 1.41-3.45; P < .001)  The presence of an association with MCI varied by surgical indication, with an association among 259 women with BSO before menopause and before age 50 years for the indication of benign ovarian condition (aOR, 2.43; 95% CI, 1.36-4.33; P = .003) but not for cancer or no ovarian condition. The presence of an association did not vary by estrogen therapy after BSO  Premenopausal BSO was associated with decreased global cognition z score ( $\beta$ , -0.17; 95% CI, -0.32 to -0.03; P = .02), attention and executive domain z score ( $\beta$ , -0.21; 95% CI, -0.36 to -0.05; P = .009), and Short Test of Mental Status score ( $\beta$ , -0.51; 95%CI, -0.95 to -0.08; P =.02)	combining data from the Mayo Clinic Study of Aging (MCSA ) and the Rochester Epidemiology Project (REP) medical record – linkage system .
<b>(Uldbjerg et al., 2022).</b>	prospective cohort study	24,851 female nurses from the Danish Nurse			Dementia & BSO association	1,238 (5.0%) nurses developed dementia and 1,969 (7.9%)/1,016 (4.1%) contributed person-time	



		Cohort. Nurses were followed from age 60 years or entry into the cohort, whichever came last, until date of dementia, death, emigration or end of follow-up (December 31, 2018), whichever came first.				after bilateral-/unilateral oophorectomy.  In adjusted analyses, an 18% higher rate of dementia was observed following BSO (aRR 1.18: 95% CI, 0.89-1.56) and 13% lower rate (aRR 0.87: 95% CI, 0.59-1.23) following unilateral oophorectomy compared to nurses who retained their ovaries.		
<b>(Blümel et al., 2022).</b>	Case control study	healthy postmenopausal women aged 60 years and over from six Latin American countries 941 women;	30.2% had undergone bilateral oophorectomy and 40.3% had used MHT. A total of 232 women (24.7%) had MCI.		mild cognitive impairment (MCI)	<p>MCI: women with intact ovaries, higher prevalence in non-MHT users as compared to MHT users (29.3% vs. 11.7%; OR 0.32; 95% CI 0.20-0.51)</p> <p>oophorectomized women, higher prevalence in non-MHT users compared to MHT users (45.2% vs. 12.8% ; OR 0.18; 95% CI 0.10-0.32)</p> <p>Logistic regression analysis: Variables associated with MCI</p> <ul style="list-style-type: none"> <li>- age &gt; 65 years (OR 1.69; 95% CI 1.20-2.38)</li> <li>- parity (having &gt; 2 children; OR 1.69; 95% CI 1.21-2.37)</li> <li>- bilateral oophorectomy (OR 1.56; 95% CI 1.09-2.24)</li> <li>- hypertension (OR 1.41; 95% CI 1.01-1.96)</li> <li>- being sexually active (OR 0.56; 95% CI 0.40-0.79)</li> <li>- education &gt; 12 years (OR 0.46; 95% CI 0.32-0.65)</li> </ul>	Age, parity, bilateral oophorectomy and hypertension are independent factors associated with MCI; contrary to this, higher educational level, maintaining sexual activity and using MHT are protective factors.	Original data on bilateral oophorectomy. Six Latin American countries.



						- MHT use (OR 0.31; 95% CI 0.21â€"0.46)		
<b>(Hao et al., 2023)</b>								See above
<b>(Fernández-Pena et al., 2024).</b>		201 women, of whom 67 underwent premenopausal BSO and hysterectomy surgery (39 were mothers)  Age matched controls	Clinical status MRI		cortical brain differences associated with surgical menopause + mitigating factors	significant atrophy in the frontal and temporal regions in women who experienced surgical menopause. Nulliparous women with surgical menopause showed significant lower cortical volume in the left temporal gyrus extending to the medial temporal lobe cortex, as well as in the precuneus bilaterally compared to parous women with surgical menopause; whereas our results revealed no significant differences between parous women with surgical menopause and both parous and nulliparous women who reached a non-surgical menopause. Furthermore, in the surgical menopause group, we found a negative correlation between cortical volume and age at first pregnancy in the temporal lobe.		UK Biobank
<b>(Hassan et al., 2024).</b>	review	Hx + BSO vs women who had a hysterectomy with ovarian conservation or no surgery.			Hx+ BSO = < different associations	<p>Hx + BSO:</p> <p>decreased risk of breast cancer (HR, 0.78; 95% CI, 0.73e0.84)</p> <p>increased risk of colorectal cancer (hazard ratio, 1.27; 95% confidence interval, 1.10e1.47).</p> <p>increased risk of total cardiovascular diseases, coronary heart disease, and stroke with hazard ratios of 1.18 (95% confidence interval, 1.11e1.25), 1.17 (95% confidence interval, 1.10e1.25), and 1.20 (95% confidence interval, 1.10e1.31), respectively</p> <p>Hx+BSO before the age of 50 years</p> <p>increased risk of hyperlipidemia (hazard ratio, 1.44; 95% confidence interval, 1.25e1.65),</p> <p>diabetes mellitus (hazard ratio, 1.16; 95% confidence interval, 1.09e1.24),</p> <p>hypertension (hazard ratio, 1.13; 95% confidence interval, 1.06e1.20),</p> <p>dementia (hazard ratio, 1.70; 95% confidence interval, 1.07e2.69),</p> <p>depression (hazard ratio, 1.39; 95% confidence interval, 1.22e1.60).</p>		



						The evidence on the association with all-cause mortality in young women showed substantial heterogeneity between the studies (I <sup>2</sup> =85%, P<0.01)	
<b>(Rocca et al., 2017).</b>	report	premenopausal women who BSO for a noncancerous condition before age 50 years Matched controls born in the same year (±1 year) who had not undergone BSO			accelerated aging	women who underwent oophorectomy before age 46 years experienced an accelerated rate of accumulation of the 18 chronic conditions considered together (HR 1.24; 95% CI: 1.12, 1.37; p < .001). The single-year incidence rate of new conditions was most different in the first 6 years after oophorectomy but the difference attenuated thereafter.  Dementia: 1.4% in patients – 1.0% in controls;	Roche ster Epide miology Project record s-linkage system
<b>Parkinsonism and Parkinson's disease after iatrogenic POI</b>							
<b>(Rocca et al., 2022).</b>	cohort study	2750 women BSO for a benign indication before spontaneous menopause + 2749 age-matched women			Incidence and risk of parkinsonism or PD, with diagnoses confirmed by in-person examination or medical record review.	Bilateral oophorectomy was associated with an increased risk of parkinsonism overall (HR 1.59; 95% CI, 1.02-2.46) and in women younger than 43 years at oophorectomy (HR, 7.67; 95% CI, 1.77-33.27). There was a pattern of increasing risk with younger age at the time of oophorectomy using 4 age strata (≥50 years: HR, 1.43 [95% CI, 0.50-4.15]; 46-49 years: HR, 1.55 [95% CI, 0.79-3.07]; 40-45 years: HR, 1.36 [95% CI, 0.64-2.89]; <40 years: HR, 8.82 [95% CI, 1.08-72.00]; P = .02 for trend). The number needed to harm was 53 women overall and 27 women younger than 43 years at the time of oophorectomy. Bilateral oophorectomy was also associated with an increased risk of PD in women younger than 43 years at oophorectomy (HR, 5.00; 95% CI, 1.10-22.70), with a number needed to harm of 48 women.	Roche ster Epide miology Project record s-linkage system
<b>(Lv et al., 2017).</b>	Review - 6 case-control and 5 cohort studies		oophorectomy  Age at menopause - type of menopause (natural/surgical) -		risk of Parkinson's disease	The pooled relative risks (RRs) of PD risk:  use of OCs (ever versus never): 1.00 (95% CI: 0.79-1.28) age at menopause: 0.98 (95% CI: 0.75-1.29) type of menopause (surgical versus natural) : 0.93 (95% CI: 0.68-1.29)  In the subgroup analysis stratified by study design, age, caffeine intake and smoking, an inverse association was found between surgical menopause and risk of PD	



			OCP use			<p>for those adjusting for caffeine intake (RR: 0.67, 95% CI: 0.45–0.99) and smoking (RR: 0.77, 95% CI: 0.63–0.94); while a positive association was found between surgical menopause and PD risk for those not adjusting for smoking (RR: 1.91, 95% CI: 1.29–2.83).</p> <p>Findings from this meta-analysis of observational studies overall revealed no significant associations between ever use of OCs, age at menarche, age at menopause, fertile lifespan, parity, and the risk of PD in women.</p>	
<b>(Ibrahim et al., 2022).</b>	Retrospective	76 women with PD + 80 controls			Association with Hx before menopause	<p>OR and RR of PD was significantly higher after surgical menopause in the study group (30 [39.5%]) compared to controls (17 [21.25%]), (OR 2.4 [95% CI: 1.19–4.8]; p = 0.01, RR 1.9 [95% CI: 1.12–3.1]; p = 0.016). In addition, the OR and RR of PD was significantly higher after BSO in the study group (19 [25%]) compared to controls (8 [10%]), (OR 3.0 [95% CI: 1.22–7.4]; p = 0.016, RR 2.5 [95% CI: 1.16–5.4]; p = 0.01).</p>	
<b>(Pesce et al., 2023).</b>	Population based study	1165 incident Parkinson disease cases during a mean follow-up of 22.0 years			Association with menopause/POI	<p>Women with artificial (surgical, iatrogenic) menopause were at greater risk than women with natural menopause (HR=1.28, 95% CI=1.09–1.47), especially when artificial menopause occurred at an early age (≤45.0 years). Postmenopausal hormone therapy tended to mitigate greater risk associated with artificial or early menopause (≤45.0 years)</p>	E3N study
<b>Other neurological diseases after iatrogenic POI</b>							
<b>(Huo et al., 2021).</b>	Cohort study	<p>Premenopausal Bilateral Oophorectomy</p> <p>1653 women</p> <p>1653 age-matched women (control)</p>			Restless Legs Syndrome	<p>restless legs syndrome before the index date (32 women [1.9%] vs 14 women [0.8%]; P = .008). Women who underwent bilateral oophorectomy prior to natural menopause had a higher risk of restless legs syndrome after the index date compared with women in the reference group (120 diagnoses vs 74 diagnoses), with an adjusted hazard ratio (HR) of 1.44 (95% CI, 1.08-1.92; P = .01). After stratification by indication for the bilateral oophorectomy, there was an increased risk of restless legs syndrome among women without a benign ovarian condition (HR, 1.52; 95% CI, 1.03-2.25; P = .04) but not among women with a benign condition (HR, 1.25; 95%</p>	Mayo Clinic Cohort Study



						CI, 0.80-1.96; P = .34). Treatment with estrogen therapy through the age of 46 years in women who underwent bilateral oophorectomy at younger ages was not associated with a difference in risk.	
(Hassan <i>et al.</i> , 2024).							See above

*Evidence to recommendations*

QUESTION	WHAT ARE THE CONSEQUENCES OF POI ON COGNITION/NEUROLOGICAL FUNCTION?
RECOMMENDATION	<b>HCPs and women should be aware that POI is associated with an increased risk of cognitive impairment and dementia. The possible detrimental effect on cognition and increased risk of dementia, parkinsonism, and other neurologic diseases should be discussed when planning bilateral oophorectomy under the age of 45 years, especially for women at an average risk of ovarian cancer.</b>
Desirable effects	Although the cut-off age used to separate early menopause from late menopause varied across studies, there is adequate evidence that younger age at menopause (either spontaneous or iatrogenic) is associated with increased risk of dementia, parkinsonism, and possibly other neurological diseases. These findings should apply also to POI.
Undesirable effects	
Certainty of evidence	Low – observational data only
Values	Awareness and prevention
Balance of effects	Strong recommendation for awareness in women with POI and clinicians, and strong recommendation to consider the effects upon deciding for BSO
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations	NA



## PICO QUESTION: WHAT ARE THE MANAGEMENT OPTIONS FOR THE EFFECT OF POI ON COGNITION/NEUROLOGICAL FUNCTION?

<b>Population</b>	POI - Turner - Non-Turner / surgical menopause
<b>Interventions</b>	sex steroid replacement therapy
<b>Control</b>	
<b>Outcomes</b>	Neurological function Cognitive function Dementia Parkinson's disease Self-reported memory loss Memory concentration

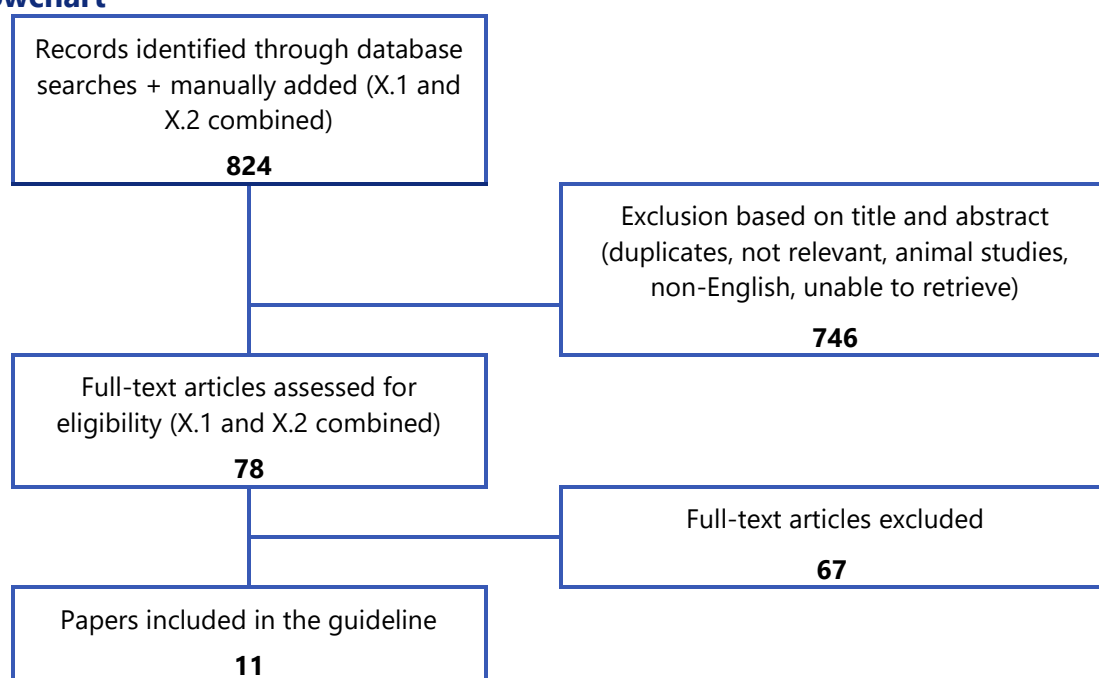
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (estrogen OR estradiol OR "contraceptive ring" OR progesterone OR progestagen OR progestogen OR progestogens OR "Cyclic medroxyprogesterone acetate" OR "Norethisterone" OR "dydrogesterone" OR "oral contraceptives" OR "oral contraceptive pill" OR OCP OR COCP OR "Levonorgestrel intrauterine device" OR Androgen OR "androgenic hormone" OR testosterone OR "dihydroepiandrosterone" OR DHEA OR Dehydroepiandrosterone OR HRT OR "hormone replacement therapy") AND ("Neurological function" OR "Cognitive function" OR Dementia OR "Dementia"[Mesh] OR "Parkinson's disease" OR "Parkinson Disease" OR "Parkinson Disease"[Mesh] OR "memory loss" OR "Memory Disorders"[Mesh] OR Memory OR "Memory"[Mesh] OR "Amnesia"[Mesh] OR concentration OR "Attention"[Mesh])

Literature search was limited to the period between 01/01/2014 and 19/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



(Bove *et al.*, 2014)

## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Long-term estrogen replacement therapy for cognitive impairment and dementia after POI</b>								
<b>(Ryan <i>et al.</i>, 2014)</b>	Population-based cohort study.	4868 women ≥65 yo  371 POI	107 POI + HT	2264 POI and no HT	<small>Table 4. The relationship between cognitive function and hormone use in women with a history of POI. The data are presented as mean (SD) for continuous variables and n (%) for categorical variables. The results are presented for the total population and for the POI group. The results are presented for the total population and for the POI group. The results are presented for the total population and for the POI group.</small>		HT at the time of premature menopause appeared beneficial for later-life visual memory but increased the risk of poor verbal fluency.	French Three-City Study
<b>(Hao <i>et al.</i>, 2023)</b>	population-based cohort study	POI / menopause	MHT use (ever use)	No MHT	HR for all-cause dementia, Alzheimer's disease (AD) and	Women with early natural menopause without taking MHT at baseline had		UK Biobank



					vascular dementia (VD)	an increased risk of AD (1.36, 1.03–1.81), while no such relationship was observed in those taking MHT at baseline (1.03, 0.78–1.37)		
<b>(Rocca et al., 2021a)</b>	case-control study and cross-sectional study	283 women with MCI (10.4%) and 2449 women without cognitive impairment (89.6%).  cross-sectional study: 625 women with a history of BSO (median [IQR] age, 75 [70-82] years) and 2107 women without a history of BSO (median [IQR] age, 73 [65-80] years).			mild cognitive impairment (MCI)  global or domain-specific cognitive performance.	BSO before menopause and before age 46 years was associated with clinically diagnosed MCI (adjusted OR, 2.21; 95% CI, 1.41-3.45; P < .001)  The presence of an association with MCI varied by surgical indication, with an association among 259 women with BSO before menopause and before age 50 years for the indication of benign ovarian condition (aOR, 2.43; 95% CI, 1.36-4.33; P = .003) but not for cancer or no ovarian condition. The presence of an association did not vary by estrogen therapy after BSO  Premenopausal BSO was associated with decreased global cognition z score ( $\beta$ ,	combining data from the Mayo Clinic Study of Aging (MCSA) and the Rochester Epidemiology Project (REP) medical record-linkage system.	case-control study and cross-sectional study



						<p>-0.17; 95% CI, -0.32 to -0.03; P = .02), attention and executive domain z score (<math>\beta</math>, -0.21; 95% CI, -0.36 to -0.05; P = .009), and Short Test of Mental Status score (<math>\beta</math>, -0.51; 95%CI, -0.95 to -0.08; P =.02)</p>		
<p><b>(Blümel et al., 2022)</b></p>	<p>Case control study</p>	<p>healthy postmenopausal women aged 60 years and over from six Latin American countries</p> <p>941 women; 30.2% had undergone bilateral oophorectomy and 40.3% had used MHT. A total of 232 women (24.7%) had MCI.</p>				<p>"MCI: women with intact ovaries, higher prevalence in non-MHT users as compared to MHT users (29.3% vs. 11.7%; OR 0.32; 95% CI 0.20-0.51)</p> <p>oophorectomized women, higher prevalence in non-MHT users compared to MHT users (45.2% vs. 12.8% ; OR 0.18; 95% CI 0.10-0.32)</p> <p>Logistic regression analysis:</p> <p>Variables associated with MCI</p> <ul style="list-style-type: none"> <li>- age &gt; 65 years (OR 1.69; 95% CI 1.20-2.38)</li> <li>- parity (having &gt; 2 children; OR 1.69; 95% CI 1.21-2.37)</li> <li>- bilateral oophorectomy</li> </ul>	<p>Age, parity, bilateral oophorectomy and hypertension are independent factors associated with MCI; contrary to this, higher educational level, maintaining sexual activity and using MHT are protective factors.</p>	



						(OR 1.56; 95% CI 1.09â€"2.24) - hypertension (OR 1.41; 95% CI 1.01â€"1.96) - being sexually active (OR 0.56; 95% CI 0.40â€"0.79) - education > 12 years (OR 0.46; 95% CI 0.32â€"0.65) - MHT use (OR 0.31; 95% CI 0.21â€"0.46)"	
<b>(Gleason et al., 2015)</b>	RCT	727 women enrolled  52.6 y old, and 1.4 y past their last menstrual period	Group 1 (n=220) : 4 y of 0.45 mg/d oral conjugated equine estrogens (o-CEE) plus 200 mg/d micronized progesterone (m-P) for the first 12 d of each month, Group 1 (n=211) 50 µg/d transdermal estradiol (t-E2) plus 200 mg/d m-P for the first 12 d of each month, -	Control (n=262) placebo pills and patches	Modified Mini-Mental State examination; four cognitive factors: verbal learning/memory, auditory attention/working memory, visual attention/executive function, and speeded language/mental flexibility; and a mood measure, the Profile of Mood States (POMS)	No treatment-related benefits were found on cognitive outcomes. For mood, model estimates indicated that women treated with o-CEE showed improvements in depression and anxiety symptoms over the 48 mo of treatment, compared to women on placebo. The model estimate for the depression subscale was $-5.36 \times 10^{-2}$ (95% CI, $-8.27 \times 10^{-2}$ to $-2.44 \times 10^{-2}$ ; ES = 0.49, $p < 0.001$ ) and for the anxiety subscale was $-3.01 \times 10^{-2}$ (95% CI, $-5.09 \times 10^{-2}$ to $-9.34 \times 10^{-3}$ ; ES = 0.26, $p < 0.001$ ). Mood outcomes for women randomized to t-E2 were similar to those for women on placebo.	Missing data ( $n = 662$ in cognitive analyses, and $n = 661$ in mood analyses)  Treatment for 4 years
<b>(Henderson et al., 2016)</b>	RCT	567 women healthy women within 6 years of menopause or 10+ years after menopause	oral 17β-estradiol 1 mg/d  Women with a uterus received cyclic micronized progesterone vaginal gel or placebo.	Placebo	The primary outcome: change in a standardized composite of neuropsychological test scores assessing	For verbal memory, the mean estradiol minus placebo standardized difference in composite scores ( $-0.06$ , 95% CI $-0.22$ to $0.09$ ) was not significant (2-tailed $p = 0.33$ ). Differences were similar in early and late postmenopause groups (2-tailed interaction $p = 0.88$ ). Interactions between postmenopause groups and differences between treatment	treatment duration of 57 months.



					verbal episodic memory.  (assessed at 2.5 and 5 years)  Secondary outcome: executive functions and global cognition.	groups were not significant for executive functions or global cognition.	
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<b>(Rocca et al., 2014)</b>	invited review				Impact on cognition	<p><b>Ovarian conservation *</b></p> <ul style="list-style-type: none"> <li>Rocca et al., 2007: HR = 0.61 (0.40 – 0.87)</li> <li>Phung et al., 2010: RR = 0.43 (0.27 – 0.69)</li> </ul> <p><b>Estrogen treatment in early post-menopause</b></p> <ul style="list-style-type: none"> <li>Yaffe et al., 1998: OR = 0.71 (0.53 – 0.96)</li> <li>Hogervorst et al., 2000: OR = 0.56 (0.46 – 0.68)</li> <li>LeBlanc et al., 2001: OR = 0.66 (0.53 – 0.82)</li> <li>MIRAGE, Henderson et al., 2005: OR = 0.35 (0.19 – 0.66)</li> <li>Kaiser, Whitmer et al., 2011: HR = 0.74 (0.58 – 0.94)</li> <li>Cache County, Shao et al., 2012: HR = 0.70 (0.49 – 0.99)</li> </ul> <p><b>Estrogen treatment in late post-menopause</b></p> <ul style="list-style-type: none"> <li>WHIMS CEE + MPA, Shumaker et al., 2003: HR = 2.05 (1.21 – 3.48)</li> <li>WHIMS CEE only, Shumaker et al., 2004: HR = 1.49 (0.83 – 2.66)</li> <li>MIRAGE, Henderson et al., 2005: OR = 0.88 (0.50 – 1.50)</li> <li>Kaiser, Whitmer et al., 2011: HR = 1.48 (1.10 – 1.98)</li> <li>Cache County, Shao et al., 2012: HR = 1.03 (0.68 – 1.55)</li> </ul> <p>0.15 0.25 0.5 1.0 2.0 4.0 Reduced risk ← → Increased risk</p>	<p>the effects of estrogen on the brain are probably beneficial when initiated early after menopause, but when vascular or degenerative lesions have occurred estrogen cannot reverse the lesions or halt progression</p> <p>A combination of current scientific evidence from animal studies and from observational studies suggests that estrogen is neuroprotective against cognitive decline and dementia; however, the neuroprotective effects are dependent on age at the time of initiation, type of menopause, and stage in menopause. The apparent contradiction of results between observational studies and clinical trials may be explained by the timing hypothesis</p>
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<b>(Rocca et al., 2021b )</b>	invited review				scientific evidence about the optimal dose, route of administration, or length of treatment for ERT is not available. With some major simplification, a common recommendation is to treat women after bilateral oophorectomy with transdermal 17β estradiol at 100 µg/day (or higher), or with a therapeutic equivalent, starting immediately after surgery and continuing up to age 50–51 years (see Figure 1). The objective of dosing ERT is to achieve a blood level of estradiol approximating the physiologic level of the early follicular phase. However, the optimal dose may vary across women (individualized optimal dose).
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**Long-term estrogen replacement therapy for other neurologic diseases after POI**

<b>(Rocca et al., 2022)</b>	cohort stud	2750 women after BSO for a benign	Estrogen therapy	No Estrogen therapy	Incidence and risk of parkinsonism or PD	<b>Parkinsonism</b> With ERT HR 1.72 (0.54-5.53)	Bilateral oophorectomy was also associated with an	Mayo Clinic Cohort Study
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		indication before spontaneous menopause between January 1, 1950, and December 31, 2007 (oophorectomy cohort), and 2749 age-matched women who did not undergo BSO			Age group < 45 YO	<p>No ERT HR; 2.05 (0.80-5.23)</p> <p><b><u>Parkinson disease</u></b></p> <p>With ERT HR 1.53 (0.29-8.23)</p> <p>No ERT HR; 2.75 (0.84-9.04)</p>	<p>increased risk of PD in women younger than 43 years at oophorectomy (HR, 5.00; 95% CI, 1.10-22.70), with a number needed to harm of 48 women. Among women who underwent oophorectomy at 45 years and younger, the risk was lower in women who received estrogen after the procedure and through age 50 years compared with women who did not.</p>	
<b>(Pesce et al., 2023)</b>	cohort study	98068 women aged 40–65 years in 1990 followed until 2018.	MHT	No MHT	Incidence and risk of parkinsonism or PD	Women with artificial (surgical, iatrogenic) menopause were at greater risk than women with natural menopause (HR=1.28, 95% CI=1.09–1.47), especially when artificial menopause occurred at an early age (≤45.0 years). Postmenopausal hormone therapy tended to mitigate greater risk associated with artificial or early menopause (≤45.0 years).	E3N cohort study	
<b>(Huo et al., 2021)</b>	cohort study	1653 women who underwent premenopausal BSO before the age of 50 years for a benign indication  1653 age-matched women	estrogen therapy	No MHT	Diagnosis of restless legs syndrome	<p>Women who underwent BSO had higher risk of restless legs syndrome <i>before</i> the index date (32 women [1.9%] vs 14 women [0.8%]; P = .008).</p> <p>+ a higher risk of restless legs syndrome <i>after</i> the index date (120 diagnoses vs 74 diagnoses)</p> <p>Treatment with estrogen therapy through the age of 46 years was not associated with a difference in risk.</p>	Mayo Clinic Cohort Study	



*Evidence to recommendations*

QUESTION	What are the management options for the effect of POI on cognition/neurological function?
RECOMMENDATION	<p><b>HT is recommended in women with POI until the usual age of menopause to reduce the possible risk of cognitive impairment and dementia.</b></p> <p><b>HT may be recommended in women with POI to protect neurological function even in the absence of menopausal symptoms.</b></p>
Desirable effects	Several long-term cohort studies or case-control studies suggest that women with POI caused by oophorectomy who did not receive ERT had accelerated cognitive decline and an increased risk for dementia and possibly other neurologic diseases compared to women who received ERT.
Undesirable effects	
Certainty of evidence	
Values	
Balance of effects	Some of the inconsistent findings may be explained by differences in study design, quality of the data, lack of stratification by age at oophorectomy, inadequate length of follow-up to detect dementia or other diseases, or lack of data on hormone treatment. Two studies confirmed a protective effect of ERT also after non-iatrogenic POI.
Resource use, equity, acceptability and feasibility	NA

QUESTION	What are the management options for the effect of POI on cognition/neurological function?
GOOD PRACTICE POINT	<p><b>The guideline group recommends that women with POI should be encouraged to adopt a healthy lifestyle (including physical activity, healthy diet, avoiding smoking, and maintaining normal body weight) to reduce the risk of cognitive impairment and dementia.</b></p>
	<p>Hormone treatment should probably be part of a lifestyle change to reduce risk for vascular disorders associated with age-related cognitive impairment and dementia, such as lowering abdominal fat, hypertension, hyperlipidaemia, and insulin resistance risk in midlife by cessation of smoking, exercising, and eating a healthy diet (Clifford, 2009, Lazar et al., 2021).</p> <p>Lifestyle interventions may reduce the risk of cognitive impairment and dementia, but also mediate other sequelae related to POI. Advice regarding modifiable risk factors should be provided.</p>



## XI. HRT

### Hormone therapy (HT) in POI: Principles and indications

RECOMMENDATION/ GOOD PRACTICE POINT	<p>HT is recommended for women with POI until the usual age of menopause for primary prevention to reduce the risk of morbidity and mortality, whether there are estrogen deficiency symptoms or not.</p> <p>Women with POI should be advised that HT is recommended for the treatment of symptoms due to low estrogen concentrations.</p> <p>The guideline group recommends that when women with POI reach the age at which usual menopause occurs, HCPs consider the need for continued HT based on a personalized risk–benefit assessment and current evidence.</p> <p>The guideline group recommends that HCPs advise women with POI that hormone replacement therapy (HRT) does not provide contraception, in order to assist them with their family planning</p> <p>In women with POI with evidence of intermittent ovarian function and desiring natural pregnancy, recommendations for HRT remain unchanged and do not impact chances of natural conception. A sequential HRT regimen is recommended.</p>
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## XI.1. HRT Risks

### PICO QUESTION: WHAT ARE THE RISKS OF HORMONE THERAPY?

<b>Population</b>	POI patients (not postmenopausal women)
<b>Interventions</b>	<b>Estrogen replacement/sex steroid replacement - Different options as discussed under XI;3 HT treatment options</b>
<b>Control</b>	(No estrogen replacement)
<b>Outcomes</b>	Risk, side effect; adverse event, Safety, Mortality Cancer, breast cancer, Endometrial cancer endometrial hyperplasia, colorectal cancer Cardiovascular events, pulmonary embolism, thrombosis, blood clot, venous thromboembolism, VTE, deep vein thrombosis, DVT, Thromboembolism, thrombosis, Coronary heart disease, ischaemic heart disease, myocardial infarction, cardiac death, Stroke hip fracture dementia liver function Irregular vaginal bleeding

### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic

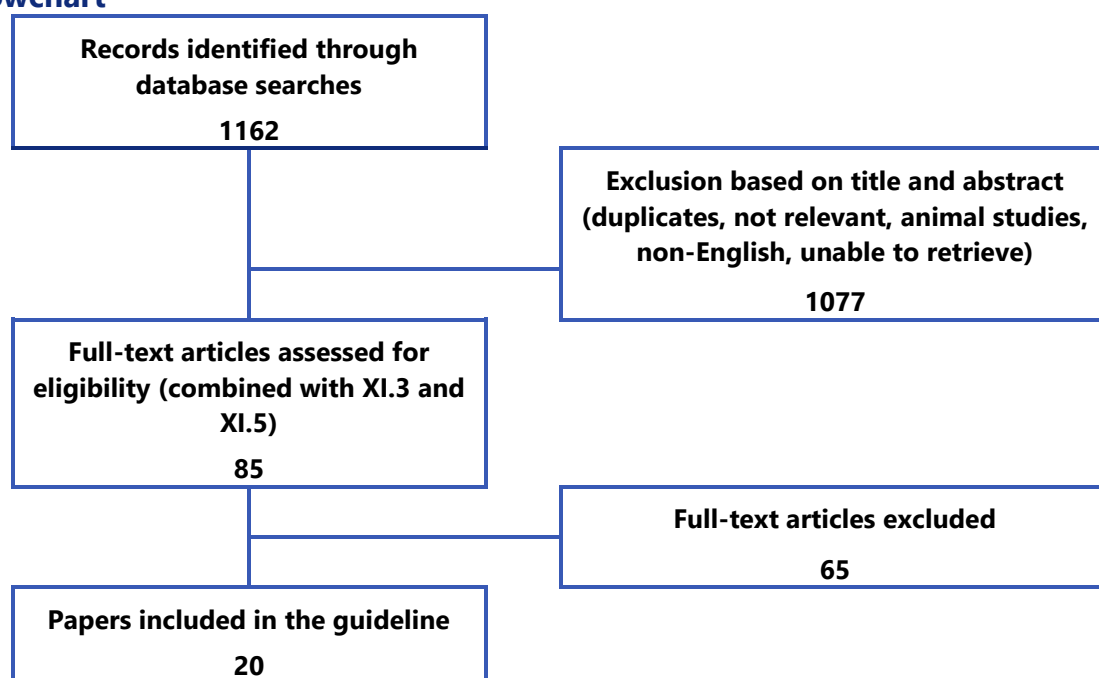


amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (estrogen OR estradiol OR "contraceptive ring" OR progesterone OR progestagen OR progestogen OR "Cyclic medroxyprogesterone acetate" OR "Oral micronized progesterone" OR "Norethisterone" OR "dydrogesterone" OR "natural progestogens" OR "vaginal progestogens" OR "synthetic progestogens" OR "oral contraceptives" OR "oral contraceptive pill" OR OCP OR COCP OR "Levonogestrel intrauterine device" OR Androgen OR "androgenic hormone" OR testosterone OR "Testosterone"[Mesh] OR DHEA OR "dihydroepiandrosterone" OR Dehydroepiandrosterone OR HRT OR "hormone replacement therapy" OR "hormone replacement" OR "Menopausal hormone therapy") AND (Risk OR "side effect" OR "adverse event" OR "adverse effects" [Subheading] OR safety OR cancer OR "endometrial hyperplasia" OR "Cardiovascular event" OR Thromboembolism OR thrombosis OR Mortality OR "Coronary heart disease" OR "ischaemic heart disease" OR "myocardial infarction" OR "cardiac death" OR Stroke OR "pulmonary embolism" OR "blood clot" OR "hip fracture" OR "dementia" OR "liver function" OR "Irregular vaginal bleeding")

Literature search was limited to the period between 01/01/2014 and 24/10/2022, and updated 19/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table - Risk of breast cancer

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size Authors conclusion	Comments
<b>Risk of breast cancer</b>							
<b>(Allen-Brady et al., 2024)</b>	Case-control population-based study	Women with POI (n = 613)  Relatives were linked using the Utah Population Database records from 1995 to 2022 - Utah			relative risk of cancer in women with POI and relatives  Whole genome sequencing was performed on a subset of women.	Breast cancer was increased in women with POI (OR, 2.20; 95% CI, 1.30-3.47; P = .0023) and there was a nominally significant increase in ovarian cancer.  Second-degree relatives : increased risk of breast (OR, 1.28; 95% CI, 1.08-1.52; P = .0078) and colon cancer (OR, 1.50; 95% CI, 1.14-1.94; P = .0036).  Prostate cancer was increased in first- (OR, 1.64; 95% CI, 1.18-2.23; P = .0026), second- (OR, 1.54; 95% CI, 1.32-1.79; P < .001), and third-degree	Causal and candidate genes were identified.



						<p>relatives (OR, 1.33; 95% CI, 1.20-1.48; P &lt; .001).</p> <p>Data suggest common genetic risk for POI and reproductive cancers</p>	
<b>(Bosze et al., 2006).</b>	Letter	62 women with Turner syndrome	prolonged (> 25 years) use of combined HT commencing at the age of 11-19 years		breast density (Mammography from the age of 35-40 years)	<p>none of these women had an increase in breast density</p> <p>none of these women were diagnosed with breast cancer or a benign breast disorder</p>	Report, not formal study
<b>(Benetti-Pinto et al., 2014)</b>	cohort study	56 women with POI  mean (SD) age at diagnosis was 32.35 (5.95) years.	taking HRT	not taking HRT	breast density (Mammography from the age of 35-40 years) at 2 timepoints  Mean (SD) interval between mammograms was 5.25 (3) years	<p>Mean (SD) percentage of mammographic density PMD decreased from 27.78% (21.04%) to 17.53% (15.71%) (P = 0.007). Comparing PMD between women taking HRT and those not taking HRT, we observed no significant differences.</p> <p>no significant difference in mammographic density between the groups</p>	5-year period
<b>(van Barele et al., 2021)</b>	RCT	women (N = 114) with a high risk of breast cancer (familial risk +/- BRCA1/2 mutation)  Controls; women aged 30-50 years who had undergone RRBSO	tibolone	conjugated estrogens with medroxyprogesterone acetate (CEE-MPA);	Breast density	<p>Breast density decreased by 46% in untreated women, 39% in tibolone treated women and 17% in CEE-MPA treated women; the difference in the latter group versus the untreated group was significant (p=0.017)</p> <p>A decline in breast density is seen after premenopausal RRBSO despite the use of both CEE + MPA or tibolone, although lower breast density is seen after tibolone use.</p>	
<b>(Collaborative Group on Hormonal Factors in Breast Cancer., 2012)</b>	Meta-analyses of Individual data from 117 epidemiological studies,	118 964 women with invasive breast cancer and 306 091 without the disease, none of whom had used menopausal	/	/	Relative risk of breast cancer by age at menopause	<p>Age group (mean, years) &lt;40(35,3)</p> <p>Cases/controls: 2397/7741</p> <p>RR 0.67; 95% CI 0.62 to 0.73</p>	



		hormone therapy					
<b>(Wu et al., 2014)</b>	population-based cohort study	10030 women with POI due to diverse causes compared with 36402 women with usual age menopause (China)	/	/	risk of total and cancer-specific mortality  incidence of breast cancer	HR (95%CI): 1.29 (1.08-1.54) and 1.38 (1.05-1.81), respectively).  decreased (OR 0.59; 95% CI 0.38 to 0.91) after adjustment for confounding factors	Similar results were observed when hormone replacement therapy users were excluded from the analysis
<b>(Ewertz et al., 2005)</b>	study	cohort of 15,631 women  Control: 62,749 unexposed women.	any form of HRT (non-systemic HRT not included),	unexposed	breast cancer risk	breast cancer incidence was non-significantly lower among women exposed to HRT in the age groups 40-44 (RR 0.56; 95% CI 0.07 to 2.01) and 45-49 (RR 0.62; 95% CI 0.62 to 1.22).	mean follow-up of 10 years
<b>(Collaborative Group on Hormonal Factors in Breast Cancer., 2019).</b>	Observational study	women in early menopause (vs never users of HRT)			breast cancer	excess risk RR 2.22 (95% CI 1.96 to 2.52) in those on estrogen and progestogen HRT and of RR 1.33 (95% CI 1.19 to 1.48) in those on estrogen alone, for 5-14 years of current usage.	the comparator group were never users of HRT, rather than age matched women with normal ovarian function
<b>Risk of breast cancer in women with iatrogenic POI and a BRCA mutation</b>							
<b>(Xu et al., 2022).</b>	cohort study	178 379 women, recruited in 2006-2010.  Postmenopausal women who had reported age at menopause (natural or surgical) or hysterectomy, and information on MHT and cause-	HRT use		breast cancer	HRT use was associated with a lower risk of breast cancer mortality following surgical menopause before 45 years (HR 0.17; 95% CI 0.08 to 0.36), at 45-49 years (HR 0.15; 95% CI 0.07 to 0.35) or at ≥50 years (HR 0.28; 95% CI 0.13 to 0.63)  The association between HRT use and the risk of breast cancer mortality did not differ by HRT use duration (<6 or 6-20 years). HRT use was also associated with a lower risk of breast cancer mortality following spontaneous menopause before 45 years (HR 0.59; 95% CI 0.36 to 0.95) or hysterectomy before 45 years (HR 0.49; 95% CI 0.32 to 0.74).	Self-reported data



		specific mortality.					
<b>HT Regimens and breast cancer risk</b>							
<b>(Lambri noudaki , 2014)</b>	Review	postmenopausal women	continuous combined estrogen-progestogen regimens compared with the sequential or estrogen-only regimens		breast cancer	There is consistent evidence that the addition of a progestogen to estrogen in postmenopausal hormone therapy increases the risk of breast cancer. Direct comparisons of different progestogens in RCTs are not available, but large epidemiological studies indicate that natural progesterone and dydrogesterone may be associated with a more favorable risk profile with respect to breast cancer risk, compared to the other progestogens. Continuous estrogen-progestogen therapy appears to confer a higher risk of breast cancer compared to sequential therapy. Tibolone's effect on breast cancer risk is unclear since there is evidence for increase, no effect and decrease of breast cancer risk.	
<b>(Vinogradova et al., 2020).</b>	follow-up study with a nested case-control analysis	postmenopausal women	estradiol/dydrogesterone (E/D) users users of other HRT,	non-users of HRT	risk of developing breast, ovarian, endometrial/uterine or cervical cancer	The breast cancer incidence rates were 2.41 (95% CI 1.81-3.15), 3.28 (95% CI 3.01-3.55) and 3.16 (95% CI 2.92-3.42) per 1000 person-years for E/D users, users of other HRT or non-users, respectively. In a direct comparison, the breast cancer risk for E/D users was lower than for users of other HRT (odds ratio 0.76, 95% CI 0.56-1.05). The incidence rates of other gynecological cancers were similar or also slightly lower for E/D users than for users of other HRT.  the risk of developing gynecological cancers with E/D use of several months to a few years is similar to the risks of developing gynecological cancer without HRT or use of other HRT.	different progestogens
<b>(Schneider et al., 2009)</b>	Two nested case-control studies	98 611 women aged 50-79 with a primary diagnosis of breast cancer between	different progestogens		Breast cancer diagnosis	Compared with never use, in recent users (<5 years) with long term use (≥5 years), oestrogen only therapy and combined oestrogen and progestogen therapy were both associated with increased risks of breast cancer (adjusted odds ratio 1.15 (95% CI 1.09 to	Odds ratios for HRT types, adjusted for personal characteristics, smoking



		1998 and 2018, matched by age, general practice, and index date to 457 498 female controls.				1.21) and 1.79 (1.73 to 1.85), respectively). For combined progestogens, the increased risk was highest for norethisterone (1.88, 1.79 to 1.99) and lowest for dydrogesterone (1.24, 1.03 to 1.48). Past long term use of oestrogen only therapy and past short term (<5 years) use of oestrogen-progestogen were not associated with increased risk. The risk associated with past long term oestrogen-progestogen use, however, remained increased (1.16, 1.11 to 1.21)	status, alcohol consumption, comorbidities, family history, and other prescribed drugs.
<b>(Fitzpatrick et al., 2023).</b>	meta-analyses	normal ovarian function	combined oral contraceptive pill		Breast cancer ORs	Breast cancer ORs were similarly and significantly raised if the last hormonal contraceptive prescription was for oral combined, oral progestagen-only, injected progestagen, or progestagen-releasing intrauterine devices (IUDs): ORs = 1.23 (95% CI [1.14 to 1.32]; p < 0.001), 1.26 (95% CI [1.16 to 1.37]; p < 0.001), 1.25 (95% CI [1.07 to 1.45]; p = 0.004), and 1.32 (95% CI [1.17 to 1.49]; p < 0.001), respectively. Our meta-analyses yielded significantly raised relative risks (RRs) for current or recent use of progestagen-only contraceptives: oral = 1.29 (95% CI [1.21 to 1.37]; heterogeneity $\chi^2_{25} = 6.7$ ; p = 0.2), injected = 1.18 (95% CI [1.07 to 1.30]; heterogeneity $\chi^2_{28} = 22.5$ ; p = 0.004), implanted = 1.28 (95% CI [1.08 to 1.51]; heterogeneity $\chi^2_{23} = 7.3$ ; p = 0.06), and IUDs = 1.21 (95% CI [1.14 to 1.28]; heterogeneity $\chi^2_{24} = 7.9$ ; p = 0.1).	

### Evidence to recommendations

QUESTION	<b>What are the risks of HT?</b>
RECOMMENDATION	<b>Women with POI can be informed that there is no evidence that HT use increases their risk of breast cancer compared to women of the same age without POI. CONDITIONAL - ++00</b>
RECOMMENDATION	<b>Women with BRCA1/2 mutations without a personal history of breast cancer should be advised that HT is an option after risk-reducing bilateral salpingo-oophorectomy. • STRONG • ++00</b>



Desirable effects	See earlier evidence and recommendations on the benefits of HRT
Undesirable effects	no data to indicate an increased risk of breast cancer in women with POI using HT compared to age-matched premenopausal women.
Certainty of evidence	Absence of evidence is not evidence of absence, we should continue to collect prospective safety data from the POI/EM populations, particularly as many of these women will be on long term treatment.
Values	Given the recognised long-term risks of untreated POI, recommendations were formulated to reassure women with POI that the pros are likely to outweigh the cons to use HT in this context, despite the lack of good quality breast safety data.
Balance of effects	recognised long-term risks of untreated POI vs uncertainty on the risk of BC
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	This also applies to women with BRCA1/2 mutations without a personal history of breast cancer.

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QUESTION	<b>What are the risks of HT?</b>
RECOMMENDATION	<b>HT is generally not recommended in women with a history of breast cancer. • STRONG • +++0</b>
Desirable effects	HT is recommended in women with POI to compensate the impact of low estrogen levels.
Undesirable effects	recurrence of the primary disease:
Certainty of evidence	Mainly observational data
Values	NA
Balance of effects	The possible additional risks of HRT, mainly related to recurrence of the primary disease are weighed against the benefits of HRT.
Resource use, equity, acceptability and feasibility	NA

*Evidence table - Risk of endometrial cancer and endometrial hyperplasia*

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Risk of endometrial cancer and endometrial hyperplasia</b>								
(Furness <i>et al.</i> , 2012).	Review (1966 to January 2012)		oral HRT		endometrial hyperplasia	all doses of unopposed estrogen therapy led to a significant increase of approximately 50% for endometrial hyperplasia within three	Hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and	



						years. Regimens combining estrogens with continuous progestogens are not significantly different from placebo at two years	progestogen to reduce the risk of endometrial hyperplasia.	
<b>(Weiderpass et al., 1999)</b>	population-based, case-control study	postmenopausal women aged 50-74 years.  709 cases (EC) 3368 controls	/	/	Risk factors for endometrial cancer	Treatment with estrogens alone was associated with a marked duration- and dose-dependent increase in the relative risk of endometrial cancer. Five or more years of treatment had an OR of 6.2 for estradiol (95% confidence interval [CI] = 3.1-12.6) and of 6.6 for conjugated estrogens (95% CI = 3.6-12.0). Following combined estrogen-progestin use, the association was considerably weaker than that for estrogen alone; the OR was 1.6 (95% CI = 1.1-2.4) after 5 or more years of use. This increase in risk was confined to women with cyclic use of progestins, i.e., fewer than 16 days per cycle (most commonly 10 days per cycle [OR = 2.9; 95% CI = 1.8-4.6 for 5 or more years of use]), whereas continuous progestin use along with estrogens was associated with a reduced risk (OR = 0.2; 95% CI = 0.1-0.8 for 5 or more years of use).		
<b>(Michels et al., 2018).</b>	Population based study	women with normally functioning ovaries	OC use (never/<1 year (referent), 1-4, 5-9, ≥10 years)		development of incident cancers, incl risk of endometrial hyperplasia and endometrial cancer	Any OC use conferred a 3% reduction in the risk for any cancer (hazard ratio = 0.97, 95% confidence interval: 0.95, 0.99). Expected risk reductions that strengthened with duration of use were identified for ovarian and endometrial cancers and were suggested for kidney cancer (all P for trend < 0.05). Non-Hodgkin lymphoma risk (hazard ratio = 0.79, 95% confidence interval: 0.64, 0.97) was reduced with 10 or more years of OC use. There was a 37% reduced risk for bladder cancer and 46% increased risk for pancreatic cancer among long-term OC users who were 60 years of age or younger at baseline. OC use did not influence risks for most other cancers evaluated.		



### Evidence to recommendations

QUESTION	<b>What are the risks of HT?</b>
RECOMMENDATION	<b>A progestogen should be given in combination with estrogen therapy to all women with an intact uterus to prevent endometrial hyperplasia/cancer. • STRONG • ++00</b>
GPP	<b>The guideline group recommends that the dose of progestogen is increased when higher doses of estrogen therapy are used.</b>
Desirable effects	See earlier evidence and recommendations on the benefits of HRT
Undesirable effects	Hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestogen to reduce the risk of endometrial hyperplasia. The dose of progestogen required for adequate endometrial protection is related to the dose of estrogen used.
Certainty of evidence	Strong evidence but indirect
Values	
Balance of effects	Strong emphasis on safety
Resource use, equity, acceptability and feasibility	Not specifically considered
Subgroup considerations (if applicable)	It is important that adequate progestogen doses are used for endometrial protection (unless the woman has severe progestogen intolerance) (Hamoda, 2022)

QUESTION	<b>What are the risks of HT?</b>
GOOD PRACTICE POINT	<b>The guideline group recommends that in women with POI, as with any women using HT, unscheduled bleeding requires assessment.</b>
Desirable effects	No evidence supporting this GPP has been sought, but the clinicians considered it relevant to emphasize early referral in case of unscheduled bleeding in women with POI, as in other women.
Undesirable effects	
Certainty of evidence	
Values	
Balance of effects	
Resource use, equity, acceptability and feasibility	Not specifically considered

### Evidence table - Risk of Stroke / VTE

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Risk of Stroke</b>								
(Honigberg <i>et al.</i> , 2019).	Cohort	144,260 postmenopausal women  POI vs control			Cardiovascular effects – stroke		POI was independently associated with increased risk for a composite cardiovascular outcome, that included CAD, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke,	



						peripheral artery disease, and venous thromboembolism		
						Stroke; In natural POI HR 1.50 (1.01- 2.25) In natural POI – excluding women with past or current HRT use: 0.4 (0.1-1.2)		
<b>(Zhu et al., 2020)</b>	Pooled individual-level data from 10 studies	203 767 postmenopausal women	HRT		risk of stroke	non-iatrogenic POI + HRT: HR: 2.06; 95% CI 1.52 to 2.52; p<0.0001 Vs women who did not report the use of HRT HR: 1.45; 95% CI 1.11 to 1.89; (p=0.0067).	HRT for longer than 10 years had the lowest risk of cardiovascular disease compared with women with POI who did not use HRT or who used it for less than 10 years	InterLACE consortium
<b>(Rocca et al., 2012)</b>	review of observational studies	women who underwent BSO vs women who conserved their ovaries before age 50 years	HRT		risk of stroke	No meta-analysis The increased risk of stroke in women with (surgical) POI was found to be reduced by HRT	data are compatible with the theory that estrogen has protective effects before age 50 years and deleterious effects after age 50 years (particularly if used orally at 0.625 mg/day of conjugated estrogens)	evidence was limited by its retrospective observational design
<b>Risk of venous thromboembolic (VTE) disease</b>								
<b>(Canonic et al., 2014)</b>	Cohort (based on trial population)	women who had no history of VTE	HRT use (HRT (CEE+MPA, CEE alone)	placebo	VTE	During the follow-up, 426 women reported a first VTE, including 294 non-procedure-related events. No apparent interaction of reproductive life characteristics with HT assignment on VTE risk was detected	no significant link between occurrence of first VTE event in relation to HRT use compared with placebo	women with menopause < 39 years, had increased thrombotic risk as compared with women with age at menopause 40 -49 years (adjusted HR 1.8;



								95% CI 1.2 to 2.8)
<b>(Honigberg et al., 2019).</b>	Cohort	144,260 postmenopausal women  POI vs control			Cardiovascular effects – VTE	non-iatrogenic POI: independently associated with an increased VTE risk (HR 1.70; 95% CI 1.27 to 2.29)  surgical POI : (HR 2.73; 95% CI 1.46 to 5.14; p=0.002).		
<b>(Marjoribanks et al., 2017).</b>	Review	women with menopause at usual age  22 studies involving 43,637 women	oral HRT		risk of VTE	increased risk, which becomes most apparent in the first year of HRT use: increased risk from 2 per 1000 to between 4 and 11 per 1000 with combined continuous HRT in otherwise healthy users	combined continuous HT increased the risk of VTE (after 1 year's use: from 2 per 1000 to between 4 and 11 per 1000)  Oestrogen-only HT increased the risk of VTE (after 1 to 2 years' use: from 2 per 1000 to 2 to 10 per 1000; after 7 years' use: from 16 per 1000 to 16 to 28 per 1000),	
<b>Canonico et al., 2006</b>	multicenter case-control study	women with menopause at usual age	Estrogen use		risk of VTE – link with overweight	Oral estrogen : OR 4.5; 95% CI: 2.6-7.7 transdermal estrogen: OR 1.1; 95% CI: 0.7-1.7  Compared with non-users with normal weight, the combination of oral estrogen use and overweight or obesity further enhanced VTE risk (OR = 10.2; 95% CI: 3.5-30.2 and OR = 20.6; 95% CI: 4.8-88.1, respectively).  Transdermal users with increased BMI had similar risk as non-users with increased BMI (OR = 2.9; 95% CI: 1.5-5.8 and OR = 2.7; 95% CI: 1.7-4.5 respectively for overweight;	transdermal estrogen does not confer an additional risk of idiopathic VTE in women with increased BMI	



						OR = 5.4; 95% CI: 2.1-14.1 and OR = 4.0; 95% CI: 2.1-7.8 respectively for obesity).	
<b>Canonico et al., 2007</b>	multicenter case-control study	271 postmenopausal women 45 to 70 years with VTE - 610 controls	HRT use	nonusers	risk of VTE	current users of oral and transdermal estrogen OR 4.2 (95% CI, 1.5 to 11.6) nonusers: OR 0.9 (95% CI, 0.4 to 2.1). No significant association of VTE with micronized progesterone and pregnane derivatives (OR, 0.7; 95% CI, 0.3 to 1.9 and OR, 0.9; 95% CI, 0.4 to 2.3, respectively). Norpregnane derivatives were associated with a 4-fold-increased VTE risk (OR, 3.9; 95% CI, 1.5 to 10.0).	Oral but not transdermal estrogen is associated with an increased VTE risk.
<b>Canonico et al., 2008</b>	Systematic review and meta-analysis.	women with menopause at usual age  8 observational studies + 9 RCTs	hormone replacement therapy	Non-users	risk of VTE	oral oestrogen : OR 2.5 (95% CI 1.9 to 3.4) transdermal oestrogen: OR 1.2 (0.9 to 1.7). Past users had a similar risk to never users. higher in the first year of treatment (4.0, 2.9 to 5.7) compared with treatment for more than one year (2.1, 1.3 to 3.8; P<0.05)  unopposed oral oestrogen (2.2, 1.6 to 3.0) opposed oral oestrogen (2.6, 2.0 to 3.2).	
<b>Vinogradova et al., 2020</b>	Two nested case-control studies	98 611 women aged 50-79 with a primary diagnosis of breast cancer between 1998 and 2018, matched by age, general practice, and index date to 457 498 female controls.	different progestogens		Breast cancer diagnosis	Compared with never use, in recent users (<5 years) with long term use (≥5 years), oestrogen only therapy and combined oestrogen and progestogen therapy were both associated with increased risks of breast cancer (adjusted odds ratio 1.15 (95% CI 1.09 to 1.21) and 1.79 (1.73 to 1.85), respectively). For combined progestogens, the increased risk was highest for norethisterone (1.88, 1.79 to 1.99) and lowest for dydrogesterone (1.24, 1.03 to 1.48). Past long term use of oestrogen only therapy and past short term (<5 years) use of oestrogen-progestogen were not associated with increased risk. The risk associated with past long term oestrogen-progestogen use,	Odds ratios for HRT types, adjusted for personal characteristics, smoking status, alcohol consumption, comorbidities, family history, and other prescribed drugs.



						however, remained increased (1.16, 1.11 to 1.21)	
<b>(Panay et al, 2023)</b>	retrospective longitudinal study using real-world data	36,061 women menopause at usual age	conjugated equine estrogens/MPA	Oral estradiol /micronized progesterone	VTE risk	the incidence of venous thromboembolism was significantly lower for oral E2/P4 compared with oral CEE/MPA (37/10,000 women-years for oral E2/P4 vs 53/10,000 women-years for oral CEE/MPA; incidence rate ratio 0.70, 95 % CI: 0.53-0.92).	
<b>(Vinogradova et al, 2015)</b>	Two nested case-control studies	Women aged 15-49 years with a first VTE 5062 cases of VTE from CPRD and 5500 from QResearch	use of combined oral contraceptives in the previous year, adjusted for smoking status, alcohol consumption, ethnic group, body mass index, comorbidities, and other contraceptive drugs	no exposure	risk of VTE	current exposure to any COC was associated with an increased risk of VTE (adjusted OR 2.97, 95% CI 2.78 to 3.17) Types: (OR) desogestrel (4.28, 3.66 to 5.01) gestodene (3.64, 3.00 to 4.43), drospirenone (4.12, 3.43 to 4.96) cyproterone (4.27, 3.57 to 5.11) levonorgestrel (2.38, 2.18 to 2.59) norethisterone (2.56, 2.15 to 3.06) norgestimate (2.53, 2.17 to 2.96).	

*Evidence table - POI patients with potential higher risks of HT linked to comorbidities*

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Endometriosis</b>								
The question on how to treat vasomotor symptoms in women with endometriosis has also been discussed in the "ESHRE guideline: Endometriosis" (Becker <i>et al.</i> , 2022) and similar recommendations were formulated. The reader is referred to that guideline for details on the supporting evidence.								
<b>Migraine</b>								
<b>(Nappi et al., 2022c).</b>	Narrative review							
<b>(Ornello et al., 2020).</b>	Narrative review							

*Evidence to recommendations*

QUESTION	<b>What are the risks of HT?</b>
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GPP	<b>The guideline group recommends that women with POI and a history of endometriosis should be treated with combined estrogen–progestogen HT, even after hysterectomy, to avoid recurrence of endometriosis or malignant transformation.</b>
	The question on how to treat vasomotor symptoms in women with endometriosis has also been discussed in the “ESHRE guideline: Endometriosis” (Becker <i>et al.</i> , 2022) and similar recommendations were formulated. The reader is referred to that guideline for details on the supporting evidence.

QUESTION	<b>What are the risks of HT?</b>
RECOMMENDATION	<b>Migraine should not be considered a contraindication to HRT use by women with POI. • STRONG • ++00</b>
RECOMMENDATION	<b>HCPs should consider changing dose, route of administration, or regimen if migraine worsens during HRT. • STRONG• ++00</b>
RECOMMENDATION	<b>Women with POI and migraine with aura should be advised to use transdermal estrogen as this may be the lowest-risk route of administration. • STRONG • +000</b>
Desirable effects	HT is recommended in women with POI to compensate the impact of low estrogen levels.
Undesirable effects	potential risk of ischaemic stroke and whether HT might affect the occurrence of migraine. a good safety profile in women with menstrual migraine, especially if used with reduced or absent hormone free intervals (Nappi <i>et al.</i> , 2022c).
Certainty of evidence	Low, information drafted from narrative reviews
Values	
Balance of effects	In the absence of any data regarding the risks of HRT use for women with POI and migraine, it would seem reasonable to recommend it to protect against the consequences of estrogen deprivation, even in migraine sufferers.
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	Migraine with aura remains a contraindication for COC use in women, including those with POI, but HRT with transdermal estrogen is still an option in these patients.



## XI.2. HT – treatment options

### PICO QUESTION: WHAT ARE THE OPTIONS FOR HT?

<b>Population</b>	Women diagnosed with POI
<b>Interventions</b>	<p>ESTROGEN</p> <ul style="list-style-type: none"> <li>• Oral estrogen</li> <li>• Transdermal estrogen patch / transdermal estradiol</li> <li>• Implants/ subcutaneous</li> <li>• Vaginal estrogen/ contraceptive ring</li> <li>• Dose titration</li> <li>• natural estrogen</li> <li>• Continuous/sequential/cyclical</li> </ul> <p>PROGESTERONE</p> <ul style="list-style-type: none"> <li>• Cyclic medroxyprogesterone acetate</li> <li>• Oral micronized progesterone</li> <li>• Norethisterone / dydrogesterone</li> <li>• natural progestogens</li> </ul> <p>ORAL CONTRACEPTIVES</p> <ul style="list-style-type: none"> <li>• Levonogestrel intrauterine device</li> <li>• Vaginal estrogen and testosterone supplements</li> </ul>
<b>Control</b>	
<b>Outcomes</b>	Relief of symptoms, Hemostatic factors, vasomotor symptoms, onset and termination, mode of administration, doses, patient compliance, patient preferences, spontaneous pregnancy risk, bone protection, contraceptive effects

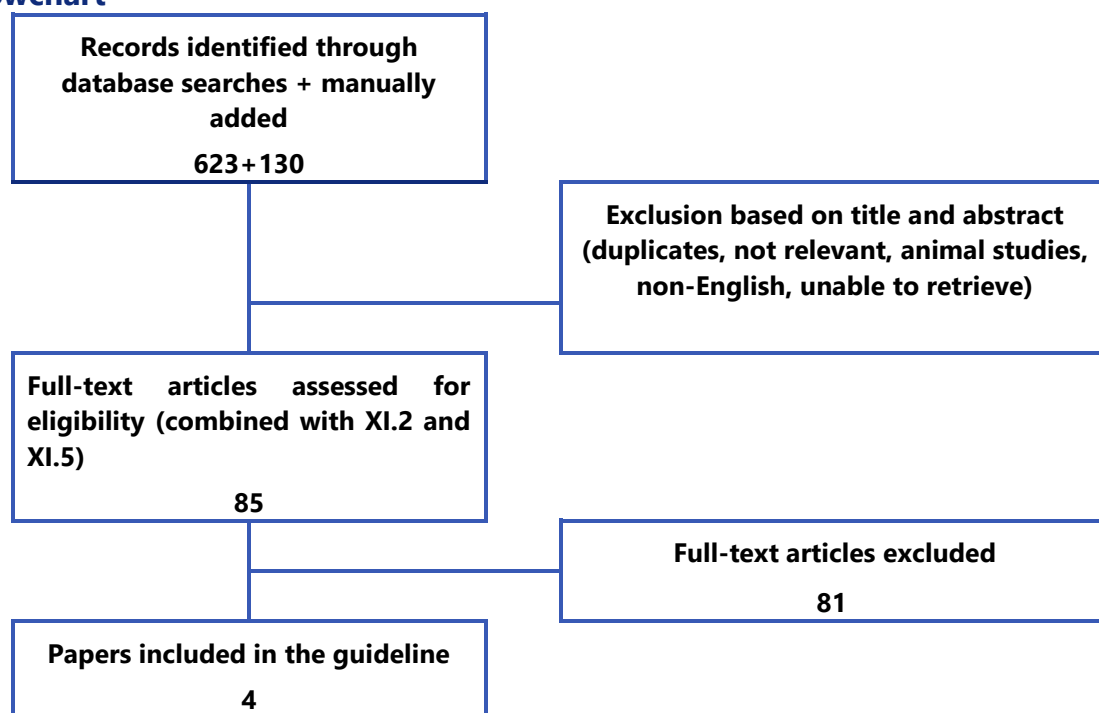
### Search strings

Database	Search String
<b>PUBMED</b>	<p>("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (estrogen OR estradiol OR "contraceptive ring" OR progesterone OR progestagen OR progestogen OR "Cyclic medroxyprogesterone acetate" OR "Oral micronized progesterone" OR "Norethisterone" OR "dydrogesterone" OR "natural progestogens" OR "vaginal progestogens" OR "synthetic progestogens" OR "oral contraceptives" OR "oral contraceptive pill" OR OCP OR COCP OR "Levonogestrel intrauterine device" OR DHEA OR "dihydroepiandrosterone" OR Dehydroepiandrosterone OR HRT OR "hormone replacement therapy" OR "hormone replacement" OR "Menopausal hormone therapy") AND ("Relief of symptoms" OR "symptom relief" OR "side effects" OR "Hemostatic factors" OR "vaginal dryness" OR "vasomotor symptoms" OR "hot flashes" OR "hot flashes" OR "night sweats" OR "patient compliance" OR "Induction of secretory endometrium" OR "uterine ultrasound" OR "pelvic ultrasound" OR "uterine size" OR "ovarian function" OR "quality of life" OR "menopause score" OR "sexual function" OR "blood pressure" OR "lipids" OR "cholesterol" OR "contraception" OR "pregnancy" OR "bone density" OR "bone turnover" OR "patient preferences")</p>



Literature search was limited to the period between 01/01/2014 and 24/10/2022, and updated 19/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.

## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table - Type of preparations: Estrogens and progestogens

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>COC versus HRT</b>								
<b>(Langrish et al., 2009)</b>	RCT Crossover trial  Starting groups comparable 3/4cancer 4/5 TS 8/9 idiopathic/surgical	34 (18 completed study)	'physiological' - Estraderm transdermal estradiol 100mcg daily for week 1 and 150mcg for weeks 2 to 4; and Cyclogest vaginal pessaries, progesterone 200 mg twice daily in weeks 3 to 4). Some	standard'- Loestrin COCP ethinylestradiol 30mcg and norethisterone 1.5 mg daily for weeks 1 to 3, followed by 7 "pill-free" days	Bp  24 hr bp  24 hr Heart rate  Arterial stiffness  Plasma angiotensin II, renin, aldosterone,	<b>Bp:</b> 'physiological' associated with a lower blood pressure (P0.0001 for both systolic and diastolic blood pressures and differed from the standard regimen at 3 (P0.05), 6 (P0.05), and 12 months (P0.01). At 12 months, there was an	lower mean blood pressure, reduced plasma angiotensin II and reduced serum-creatinine without altering plasma aldosterone	Low quality -  high drop out rate (53%)  Open label  Some used oral rather than vaginal progesterone



	(do not state how many of each)  Mean age 27		women used oral progesterone instead	2 month washout before starting and btw regimens	urea, creatinine, electrolytes, LH, FSH, 17Boestradiol, progesterone	overall 7.3 mm Hg (95% CI: 2.5 to 12.0 mm Hg) 24-hour mean systolic and 7.4 mm Hg (95% CI: 3.9 to 11.0 mm Hg) diastolic reduction  <b>Arterial stiffness/24 hour HR</b> – no differences  <b>Ang II</b> - lower with physiological (P 0.007)  <b>creatinine</b> lower with physiological (P 0.015)  <b>aldosterone</b> – no difference  <b>urea/N/electrolytes/BMI</b> – no difference	concentrations	Details of randomisation - ?given in another paper using same pts for bone assessment
<b>Progestogens</b>								
<b>(The Writing Group for the PEPI, 1996)</b>	3 year RCT	596 postmenopausal women aged 45 through 64 years	treatments in 28-day cycles: - placebo, - 0.625 mg/d of CEE - 0.625 mg/d of CEE plus 10 mg/d of MPA for the first 12 days, - 0.625 mg/d of CEE plus 2.5 mg/d of MPA, - 0.625 mg/d of CEE plus 200 mg/d of micronized progesterone (MP) for the first 12 days.	Histology of endometrium	Histology in placebo group (n = 119): normal n = 116, simple hyperplasia n = 1, complex hyperplasia n = 1, adenocarcinoma n = 1; in CEE-only group (n = 119): normal n = 45, simple hyperplasia n = 33, complex hyperplasia n = 27, atypia n = 14; in CEE + MPA (sequential) group (n = 118): normal n = 112, simple hyperplasia n = 4, complex hyperplasia n = 2; in CEE + MPA (continuous) group (n = 120): normal n = 119, simple hyperplasia n = 1; in CEE + MP (sequential) (n = 120): normal n = 114, simple hyperplasia n = 5, atypia n = 1; significant difference for CEE vs. placebo, p < 0.001)			
<b>(Stute et al., 2016)</b>	Review + recommendations	All (post/perimenopausal) women (natural or surgical menopause)	Progesterone (natural), exogenously administered on oral, transdermal or vaginal route;	Synthetic progestogens, placebo, no	Endometrium hyperplasia or endometrium carcinoma,	No meta-analysis, evidence tables available ;	Combining estrogens with sequential (12–14 days/month) oral MP at 200 mg/day for up to 5 years provides sufficient endometrial protection. If oral MP is to be applied	



		e) using systemic estrogen replacement therapy (estradiol or conjugated equine estrogen; estriol and estrogen were excluded) 40 studies	duration of study at least 3 months; in humans	comparison	endometrial biopsies investigating proliferative/antiproliferative effects, endometrial transformation or atrophy		continuously, the initial dosage should also be 200 mg/day.  the use of transdermal MP for endometrial protection cannot be recommended in postmenopausal women using estrogen therapy  oral MP at 200 mg daily for at least 12 days per month is the preferred route, dose and duration for postmenopausal women with an intact uterus when using estrogen therapy for up to 5 years
<b>(Mirkin et al., 2020)</b>	RCT	1,255 women with UAM	daily E2/P4 (mg/mg: 1/100, 0.5/100, 0.5/50, or 0.25/50), 12 months	placebo	Incidence of endometrial hyperplasia	≤0.36% with any dose of TX-001HR after 1 year of use (one-sided upper 95% CI ≤4%)  Few vaginal bleeding adverse events (1.0%-4.6% TX-001HR vs 0.7% placebo)	REPLENISH trial
<b>(Mittal et al., 2022).</b>	RCT - pilot randomised prospective open-label trial	66 Women under the age of 45-years diagnosed with EMPOI, with an intact uterus	cyclical MP (Utrogestan® 200mg) in conjunction with t-E <sub>2</sub> (Evorel® Patches 50mcg/day) for 12 months.	MPA (Provera® 10mg) in conjunction with t-E <sub>2</sub>	Carotid-femoral pulse wave velocity (cfPWV)  secondary endpoints: HR, SBP, diastolic blood pressure, PP, AI, cardiac output (CO), stroke volume (SV), TPR, total cholesterol, HDL, LDL, triglyceride (TG) levels and cholesterol ratio (total	PWV did not significantly change from baseline in either treatment arm. MP + t-E <sub>2</sub> demonstrated a positive effect on traditional CVD markers, with a significant improvement seen in cardiac output (CO) (0.71 ± 1.01 mL/min, 95% CI 0.20 to 1.21) and reduction in diastolic blood pressure (DBP) (-3.43 ± 6.31 mmHg, 95% CI -6.57 to -0.29) and total peripheral resistance (TPR) (-0.15 ± 0.19 mmHg·min·mL <sup>-1</sup> , 95% CI -0.24 to -0.05) after 12 months. MPA + t-E <sub>2</sub> , in contrast, did not demonstrate significant changes from baseline in traditional haemodynamic parameters.	



					cholesterol / HDL ratio).		
<b>(Roland et al., 2024)</b>	case control study	18 061 women who had intracranial surgery for meningioma + 90 305 matched controls Mean age 57.6 years (SD 12.8)	progesterone, hydroxyprogesterone, dydrogesterone, medrogestone, MPA, promegestone, dienogest, and intrauterine levonorgestrel		risk factors for intracranial meningioma	<p>use of medrogestone (42 exposed cases/18 061 cases (0.2%) v 79 exposed controls/90 305 controls (0.1%), OR 3.49 (95% CI 2.38 to 5.10)),</p> <p>use of MPA (injectable, 9/18 061 (0.05%) v 11/90 305 (0.01%), 5.55 (2.27 to 13.56))</p> <p>Use of promegestone (83/18 061 (0.5%) v 225/90 305 (0.2%), 2.39 (1.85 to 3.09)). This excess risk was driven by prolonged use (≥one year).</p> <p>No excess risk for progesterone, dydrogesterone, or levonorgestrel intrauterine systems.</p> <p>No conclusions for dienogest or hydroxyprogesterone</p>	

### Evidence to recommendations

QUESTION	<b>What are the options for HT?</b>
GOOD PRACTICE POINT	<b>The guideline group recommends shared decision making when prescribing each component of HT with consideration of patient preference, contraceptive needs, and presence of co-morbidities.</b>
RECOMMENDATION	<b>Different estrogens/progestogens have variable metabolic and other effects, which should be taken into consideration when personalizing care in POI.</b>
GOOD PRACTICE POINT	<b>The guideline group recommends that HCPs and women should be aware that compounded 'bio-identical' preparations of estrogen and progesterone are not recommended due to lack of data regarding efficacy and safety.</b>
RECOMMENDATION	<b>Women with POI should be advised that adherence to HT is important to minimize long-term health risks and therefore long-term follow-up is needed.</b>
Desirable effects	See earlier evidence and recommendations on the benefits of HRT few studies comparing different types and regimens
Undesirable effects	The little evidence there is suggests physiological sex steroid replacement regimens with HRT may be more beneficial than the combined oral contraceptive (COC) - the risks may be lower. However, risks of using the COC in the general female population, though small, are well documented and are not dependent on the presence of functioning ovaries. There may also be additional health benefits to using the COC although most of these are in women with normally functioning ovaries (Coelingh Bennink <i>et al.</i> , 2024).
Certainty of evidence	There have been very few studies comparing different types and regimens of estrogen and progestogen replacement for women with POI.



Values	personalisation, taking into account the individual benefit / risk balance + empowering women to make the choice that is right for them
Balance of effects	the key to optimal HT prescribing in women with POI is personalisation, taking into account the individual benefit / risk balance, considering all available evidence, and empowering women through the counselling process to make the choice that is right for them.
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	If contraception is required or adherence is improved with the use of the COC, then this is a reasonable alternative. However, continuous COC use is recommended to avoid estrogen deficiency occurring during the pill free (or inactive pill) days.

### XI.3. Monitoring HT

This chapter is a summary of evidence collected for other chapters.

GOOD PRACTICE POINT	The guideline group recommends that women with POI should have a regular clinical review, addressing individualised risk factors and adherence to therapy.
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### XI.4. Testosterone Therapy

#### PICO QUESTION: WHAT IS THE ROLE OF TESTOSTERONE THERAPY IN POI?

<b>Population</b>	Women diagnosed with POI
<b>Interventions</b>	ANDROGEN THERAPY androgenic hormone testosterone dihydrotestosterone and androstenedione
<b>Control</b>	
<b>Outcomes</b>	relief of symptoms Patient preferences

#### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND ("testosterone supplements" OR Androgen OR "androgenic hormone" OR testosterone OR "Testosterone"[Mesh]) AND

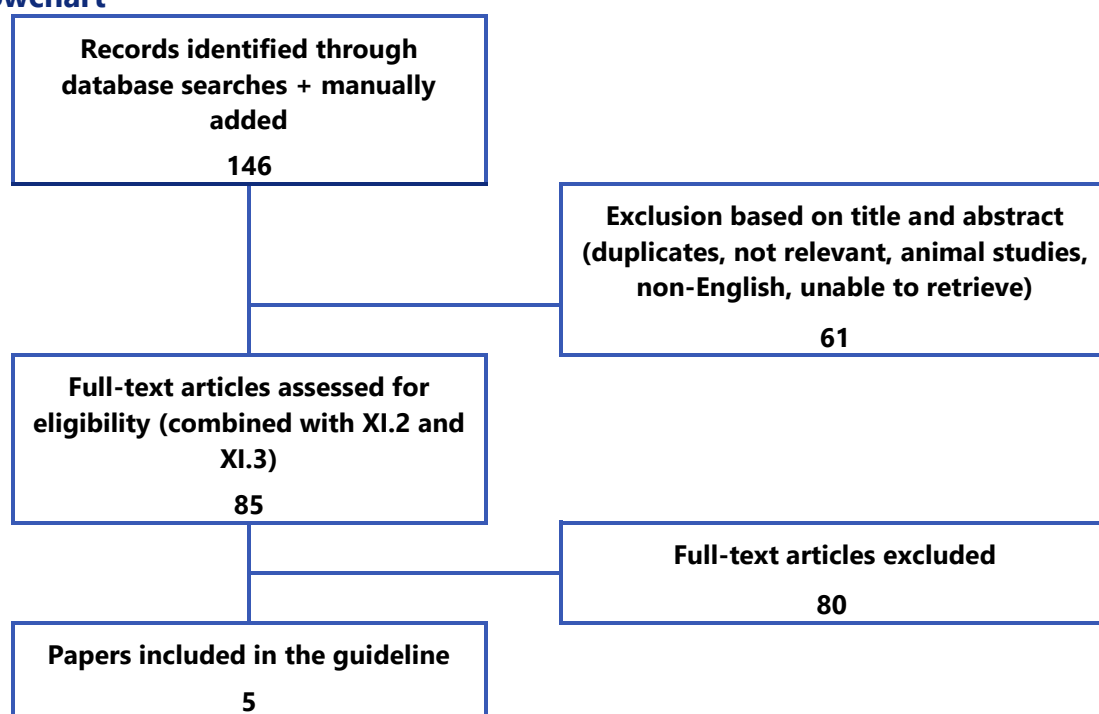


("Relief of symptoms" OR "symptom relief" OR "side effects" OR "Hemostatic factors" OR "vaginal dryness"  
OR "vasomotor symptoms" OR "hot flushes" OR "hot flashes" OR "night sweats" OR "patient compliance"  
OR "Induction of secretory endometrium" OR "uterine ultrasound" OR "pelvic ultrasound" OR "uterine size"  
OR "ovarian function" OR "quality of life" OR "menopause score" OR "sexual function" OR "blood pressure"  
OR "lipids" OR "cholesterol" OR "contraception" OR "pregnancy" OR "bone density" OR "bone turnover"  
OR "patient preferences")

Literature search was limited to the period between 01/01/2014 and 24/10/2022, and updated 19/01/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>TESTOSTERONE THERAPY + Sexual Function</b>								
<b>(Shifren et al., 2000)</b>	RCT	276 (mean age 53.9) – natural menopause Controls: 273 (54.0)	TDT: Dose 300 µg/d + Oral estrogen 24 weeks	placebo	PFSF scores - Sexual desire PDS score SAL score - No. of satisfying episodes % adverse events	PFSF scores: 5.79 [2.82-8.76] (p=0.0001) PDS score: -9.04 [-13.49 to -4.58] (p=0.0001) SAL score: 1.38 [0.72-2.03] (p<0.001) % AE: 79.0 (300)	Testosterone patch treatment increased the frequency of satisfying sexual activity and sexual desire, decreased personal distress, and was well tolerated in naturally menopausal women with hypoactive sexual desire disorder.	
<b>(Brauns et al.)</b>	RCT	328 (mean age 50.4, 49.6, 49.0) –	TDT: Dose 150, 300, 450 µg/d	placebo	PFSF scores - Sexual desire	PFSF scores: 5.3 [no CI] (p=0.05)	The 300-microg/d testosterone	



<b>al., 2005)</b>		surgical menopause Controls: 119 (48.5)	+ Oral estrogen 24 weeks		PDS score SAL score - No. of satisfying episodes % adverse events	PDS score:- (p=0.13) SAL score: 8.06 [no CI] (p<0.05) % AE: 77.0, 76.0, 75.0 (150,300, 450 resp)	patch increased sexual desire and frequency of satisfying sexual activity and was well tolerated in women who developed hypoactive sexual desire disorder after surgical menopause.	
<b>(Simon et al., 2005)</b>	RCT	283 (mean age 49.2) – surgical menopause Controls: 279 (48.9)	TDT: Dose 300 µg/d + Oral estrogen 24 weeks	placebo	PFSF scores - Sexual desire PDS score SAL score - No. of satisfying episodes % adverse events	PFSF scores: 5.12 [2.20-8.04] (p=0.0006) PDS score: -7.70 [-12.14 to - 3.26] (p=0.0006) SAL score: 1.11 [0.5-1.73] (p=0.0003) % AE: 77.7 (300)	In the Intimate SM 1 study, the testosterone patch improved sexual function and decreased distress in surgically menopausal women with HSDD and was well tolerated in this trial.	
<b>(Davis et al., 2006)</b>	RCT	537 (mean age 54.1, 54.3) – natural menopause Controls: 277 (54.4)	TDT: Dose 150, 300, µg/d (No oral estrogen) 52 weeks	placebo	PFSF scores - Sexual desire PDS score SAL score - No. of satisfying episodes % adverse events	PFSF scores: 7 [no CI] (p<0.001) PDS score: -11 (p<0.001) SAL score: 2.1 [no CI] (p<0.001) % AE: 84.3 – 87.6 (150,300 resp)	transdermal testosterone therapy via a skin patch improved sexual desire and other sexual function domains. It was well tolerated in these oophorectomized women with HSDD receiving concomitant transdermal estrogen.	
<b>(Panay et al., 2010)</b>	RCT	130 (mean age 56.2) – natural menopause Controls: 142 (57.0)	TDT: Dose 300, µg/d (No oral estrogen) 24 weeks	placebo	PFSF scores - Sexual desire PDS score SAL score - No. of satisfying episodes % adverse events	PFSF scores: 7.5 [no CI] (p<0.005) PDS score: -11.52 [-14.58 to -8.46] (p=0.0024) SAL score: 1.16 [0.82-1.5] (p=0.0089) % AE: 62.3 (300)	TTP was effective in treating HSDD and improving sexual function in this study of naturally menopausal women with and without concurrent hormone therapy.	
<b>(Davis et al., 2019)</b>	Consensus statement							
<b>TESTOSTERONE THERAPY + Neurological function</b>								
<b>(Sultana et al., 2023a)</b>	SR	postmenopausal women	testosterone		cognitive function		the findings were inconsistent	



		10 articles; 6 cross-sectional data, 7 longitudinal data + 1 case-control data					and inconclusive. Both positive and inverse associations were reported for each of global cognition and immediate and delayed verbal recall. The majority of studies reported no association between total or free testosterone and cognitive performance	
<b>(Sultana et al., 2023b)</b>	SR	postmenopausal women 4 studies : 3 placebo-controlled, crossover studies and 1 parallel-group clinical trial.	dehydroepiandrosterone therapy 50-mg oral daily dos	placebo	Cognitive performance	The only positive outcome was limited to a 4-wk cross-over study in which DHEA statistically significantly enhanced five of six tests of visual-spatial performance compared with placebo in 24 cognitively normal postmenopausal women. Improvement in cognitive performance with DHEA treatment over placebo group was not seen in any other study.	systematic review does not support a beneficial effect of DHEA therapy on cognitive performance in postmenopausal women.	
<b>TESTOSTERONE THERAPY + Bone health</b>								
<b>Studies summarized in bone chapter</b>								
<b>TESTOSTERONE THERAPY + Cardiovascular health</b>								
<b>(Popat et al., 2014)</b>	RCT	73 women with POI Control: 72 + control group of normal women (n = 70)	150mcg testosterone patch in addition to HRT (transdermal estradiol (100 µg/d) + oral MPA 10 mg/d (12 d/mo) 36 months	placebo	BMD (DXA) lipid profile	Normal control women lost femoral neck BMD over the study period, whereas patients on estradiol and progestin therapy gained BMD; and at the end of the study period, femoral neck BMD of patients on estradiol and progestin therapy did not differ from that of control women (0.80 g/cm <sup>2</sup> ) in both groups, P = .9). The addition of T showed no further benefit (percentage change in BMD 3.9 vs 2.4, respectively, P = .9). Nonetheless, using a repeated-measures model, the T group achieved a mean BMD in the femoral neck 0.015 g/cm <sup>2</sup> higher than the placebo group at 3 years (95% confidence interval -0.005 to 0.034, P = .13).	No significant differences in lipid profile	





					cognitive function	no effect of testosterone for any of the reported cognitive measures (3 RCTs, n=159)	
					musculoskeletal health.	no effect of testosterone on bone mineral density, body composition, or muscle strength (7 RCTs, n=500)	
					Secondary outcomes androgenic effects, cancer events, mood and wellbeing, and discontinuation rate.	<p>testosterone treatment did not modify depressive mood, irrespective of menopausal status (4 RCTs, n= 538+67)</p> <p>No benefits of testosterone for psychological general wellbeing index scores (8RCTs, n= 810+224)</p> <p>Mammographic breast density did not change with testosterone treatment</p> <p>No other adverse breast health effects of testosterone were identified</p> <p>No serious adverse event was more frequent with testosterone compared with placebo or a comparator (RR 0.97, 95% CI 0.65–1.44; p=0.884)</p> <p>testosterone was associated with a greater likelihood of acne (RR 1.46, 95% CI 1.11–1.92). (11 RCTs, n=3264)</p> <p>testosterone was associated with a greater likelihood of hair growth compared with placebo or a comparator (RR 1.69, 95% CI 1.33–2.14. (11 RCTs, n=4178)</p> <p>No other androgenic effects of testosterone (eg, alopecia, clitoromegaly, or voice change) were recorded</p>	

#### RISKS OF ANDROGEN THERAPY - Masculinising effects

<b>(Buster et al., 2005).</b>	RCT	533 women, 54 (10%) women with surgical POI	CEE plus testosterone patch 300 µg twice weekly; 24 weeks Patch	placebo	Primary outcome - Sexual function	<p>non-significant increase of</p> <ul style="list-style-type: none"> <li>- alopecia - 5.3 vs 2.6%</li> <li>- acne, 7.5 vs 4.1%</li> <li>- voice deepening - 3.0 vs 1.5%</li> </ul>	Data on POI mentioned, all data included in (Islam et al., 2019)
<b>(Simon et al., 2005)</b>	RCT	562 Surgical menopause with low sexual desire	Transdermal or oral oestrogen with transdermal testosterone patch 24 weeks,	placebo	Primary outcome: Sexual function side effect	unwanted (non-scalp) hair growth (9% in the treatment group vs. 5.3% in the placebo group)	Data on POI mentioned, all data included in (Islam et al., 2019)
<b>(Islam et al., 2019)</b>	SR						See above

#### RISKS OF ANDROGEN THERAPY - Endometrial effect

<b>(Davis et al., 2008).</b>	Multinational Multicentre clinical trial	814 Surgical menopause and natural menopause with low	Testosterone patch 150 µg or 300 µg daily; 52 weeks	placebo	Sexual function	<p>similar endometrial biopsy findings were identified between baseline and after 1-year use</p> <p>frequency of endometrial bleeding was increased in the group with higher dosage (300</p>	
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		sexual desire (age 20–70)				compared to 150µg), along with an increased occurrence of endometrial atrophy on biopsy no differences in breast density between transdermal testosterone and placebo use	
<b>RISKS OF ANDROGEN THERAPY – Breast cancer risks</b>							
<b>(Davis et al., 2008).</b>							See above
<b>(Davis et al., 2009).</b>	follow-up of six years	See above (Davis et al., 2008).	See above (Davis et al., 2008).	See above (Davis et al., 2008).	See above (Davis et al., 2008).	no increase in breast cancer incidence compared with that of the Australian reference population was identified during the follow-up	
<b>(Tamimi et al., 2006)</b>	prospective cohort study	women included in the Nurses' Health Study with a follow-up of 24 years - 4610 incident cases of invasive breast cancer were identified among postmenopausal women	menopausal status, PMH use, and breast cancer diagnosis was updated every 2 years through questionnaires			Among women with a natural menopause, the risk of breast cancer was nearly 2.5-fold greater among current users of estrogen plus testosterone therapies (multivariate relative risk, 2.48; 95% confidence interval, 1.53-4.04) than among never users of PMHs.  The risk of breast cancer associated with current use of E+T was significantly greater compared with E-only therapy (P for heterogeneity, .007) and marginally greater than E+P (P for heterogeneity, .11).  Women receiving PMHs with T had a 17.2% (95% CI, 6.7%-28.7%) increased risk of breast cancer per year of use.	this was not physiological replacement, and the estrogen could have had an effect
<b>(Islam et al., 2019)</b>	SR						See above – data limited for 24 months

### Evidence to recommendations

<b>QUESTION</b>	<b>What is the role of testosterone therapy in POI?</b>
<b>RECOMMENDATION</b>	<b>Testosterone treatment should be considered in women with iatrogenic POI to manage hypoactive sexual desire disorder when other biopsychosocial aetiologies are excluded. • STRONG ++00</b>



<b>RECOMMENDATION</b>	<b>Testosterone treatment could be considered in women with non-iatrogenic POI to manage hypoactive sexual desire disorder when other biopsychosocial aetiologies are excluded. •      CONDITIONAL ++00</b>
Desirable effects	Transdermal route of administration of testosterone at the dose that mimics premenopausal circulating levels is safe and should be monitored every 3-6 months to avoid supra-physiologic levels. No adverse cardiovascular or oncologic effects have been documented with transdermal testosterone but data in women with POI are lacking.
Undesirable effects	Long-term follow-up data of the effect of androgen therapy on the endometrium, breast cancer risk, and other safety parameters are not available.
Certainty of evidence	Low quality evidence, while based on on clinical trials, often with small sample sizes, short duration, and follow-up, conducted with a variety of products, and industry sponsored.
Values	
Balance of effects	The methodological limitations of the available studies indicate the need for a conservative approach to testosterone therapy. Adverse effects and the effect of the treatment should be evaluated and if no improvement of sexual function is seen after a maximum of 6 months, treatment should be discontinued.
Resource use, equity, acceptability and feasibility	Testosterone is likely widely available, but not always in the appropriate dose for use in women
Subgroup considerations (if applicable)	The only evidence-based indication for testosterone therapy for women is for the treatment of postmenopausal women with low sexual desire with associated personal distress (HSDD).

<b>QUESTION</b>	<b>What is the role of testosterone therapy in POI?</b>
<b>RECOMMENDATION</b>	<b>HCPs should be aware that although short-term treatment with transdermal testosterone at doses approximating physiological premenopausal levels is safe, longer term safety data are lacking. STRONG ++00</b>
<b>GOOD PRACTICE POINT</b>	<b>The guideline group recommends that women with POI are informed that there are limited data for androgen treatment for indications other than hypoactive sexual desire disorder, and that long-term health effects are unknown.</b>
Desirable effects	Transdermal route of administration of testosterone at the dose that mimics premenopausal circulating levels is safe and should be monitored every 3-6 months to avoid supra-physiologic levels. No adverse cardiovascular or oncologic effects have been documented with transdermal testosterone but data in women with POI are lacking.
Undesirable effects	Long term benefit and safety are unknown
Certainty of evidence	Low quality evidence, while based on on clinical trials, often with small sample sizes, short duration, and follow-up, conducted with a variety of products, and industry sponsored.
Values	Clear information on the limitations of the available evidence
Balance of effects	The methodological limitations of the available studies indicate the need for a conservative approach to testosterone therapy.
Resource use, equity, acceptability and feasibility	Testosterone is likely widely available, but not always in the appropriate dose for use in women
Subgroup considerations (if applicable)	NA

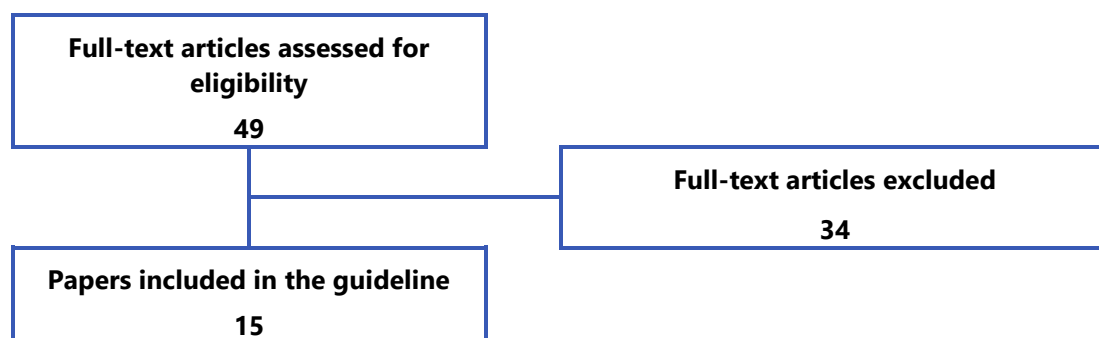


## XI.5. HRT in women with Iatrogenic POI

### PICO QUESTION: WHAT ARE THE SPECIFIC CONSIDERATIONS FOR HORMONE REPLACEMENT THERAPY IN IATROGENIC POI ?

Papers retrieved from the search on HRT (see XI.2 and XI.3) were split between general issues, and considerations for iatrogenic POI. The latter were considered here.

#### Flowchart



#### Evidence

##### Summary of Findings Table

Not applicable

##### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Women with breast cancer</b>								
<b>(Bundred et al., 2012)</b>	RCT	699 Women with surgically excised primary BC (T1-3, N0-2, M-0)	tibolone, 2.5 mg daily treatment for a maximum of 5 years	Placebo	the risk of breast cancer recurrence	Women with normal BMD had increased recurrence with tibolone, 22 (15.6%) of 141 compared with placebo, 11 (6.9%) of 159 (P = 0.016), whereas no increased BC recurrence was seen in women with low BMD; 15 (7.4%) of 204 taking tibolone versus 13 (6.7%) of 195 taking placebo.	Tibolone is contraindicated after BC treatment, as it increases BMD and BC recurrence	
<b>(Fahle n et al., 2013)</b>	RCT	Disease-free women with a history of breast cancer	HRT (n=188)	No HRT (n=190)	the risk of breast cancer recurrence - After 10.8 years of follow-up	no difference in new breast cancer events: 60 in the HRT group versus 48 among controls (HR=1.3; 95% CI 0.9-1.9). Among women on HRT, 11 had local recurrence and 12 distant metastases versus 15 and 12 for the controls. There were 14 contra-lateral breast	10.8 years of follow-up	



						cancers in the HRT group and four in the control group (HR=3.6; 95% CI=1.2-10.9; p=0.013).	
<b>(Kene mans et al., 2009)</b>	RCT	women surgically treated for a histologically confirmed breast cancer (T(1-3)N(0-2)M(0)) with vasomotor symptoms  3148 women randomised, 3098 were included in the ITT analysis (1556 tibolone 1542 placebo)	tibolone, 2.5 mg daily	Placebo	the risk of breast cancer recurrence	237 of 1556 (15.2%) women on tibolone had a cancer recurrence, compared with 165 of 1542 (10.7%) on placebo (HR 1.40 [95% CI 1.14-1.70]; p=0.001). Results in the per-protocol population were similar (209 of 1254 [16.7%] women in the tibolone group had a recurrence vs 138 of 1213 [11.4%] women in the placebo group; HR 1.44 [95% CI 1.16-1.79]; p=0.0009). Tibolone was not different from placebo with regard to other safety outcomes, such as mortality (72 patients vs 63 patients, respectively), cardiovascular events (14 vs 10, respectively), or gynaecological cancers (10 vs 10, respectively). Vasomotor symptoms and bone-mineral density improved significantly with tibolone, compared with placebo.	median follow-up of 3.1 years
<b>(Poggio et al., 2022)</b>	Review	breast cancer (BC) survivors  4 RCTS (n = 4050 patients)	HRT (estrogen/progestogen combination or tibolone) (n=2022)	placebo or no HRT (n=2023)	the risk of breast cancer recurrence + expression of hormone receptor (ER/PR)	HRT significantly increased the risk of BC recurrence compared to placebo (HR 1.46, 95% CI 1.12–1.91, p = 0.006). At the subgroup analysis, the risk of BC recurrence with the use of HRT was significantly increased in patients with hormone receptor-positive disease (HR 1.8, 95% CI 1.15–2.82, p = 0.010) but not in those with hormone receptor-negative tumors (HR 1.19, 95% CI 0.80–1.77, p = 0.390).	
<b>(Cui et al., 2014)</b>	Cohort	2,510 postmenopausal white women	ever-use of HRT		the risk of breast cancer recurrence	Women with natural menopause + BMI < 25 kg/m <sup>2</sup> , ever-use of HRT was associated with increased breast cancer risk (OR, 1.95; 95% CI, 1.32–2.88). Risk was elevated with duration of HRT use (P for trend ¼ 0.002).  Ever-HRT use in overweight women (BMI > 25 kg/m <sup>2</sup> ) showed no association with risk of breast cancer overall or by subtypes	




						Ever-HRT use was associated with decreased breast cancer risk (OR, 0.70; 95% CI, 0.38–1.31) among women with prior bilateral oophorectomy but elevated risk (OR, 1.45; 95% CI, 0.92–2.29) among those with hysterectomy without bilateral oophorectomy (P for interaction ¼ 0.057)		
<b>(Krul et al., 2017).</b>	nested case-control study	Radiation Therapy for Hodgkin Lymphoma  5-year HL survivors treated before age 41	radiation dose		breast cancer risk	linear radiation dose-response curve with an adjusted excess odds ratio (EOR) of 6.1%/Gy (95% CI: 2.1%-15.4%).  Women with menopause <30 years (caused by high-dose procarbazine or pelvic RT) had a lower BC risk (OR, 0.13; 95% CI, 0.03-0.51) than did women with menopause 50 years. BC risk increased by 6.4% per additional year of post-RT intact ovarian function (P<.001). Among women with early menopause (<45 years), HRT use for 2 years did not increase BC risk (OR, 0.86; 95% CI, 0.32-2.32), whereas this risk was non significantly increased among women without early menopause (OR, 3.69; 95% CI, 0.97-14.0; P for interaction: .06).		
<b>Women with Cervical cancer</b>								
<b>(Vargiu et al., 2021).</b>	Meta-analyses – 10 studies	Women with cervical adenocarcinoma	HRT	No HRT	risk of recurrence	(Standardised incidence ratio 1.83; 95% CI 1.24 to 2.59, 1 study, > 5 years of HRT)	Several studies reported a significantly reduced risk of developing cervical squamous cell carcinoma in postmenopausal women treated with HRT, while a weak increase in the incidence of adenocarcinoma has been shown. No evidence reports a harmful effect of HRT on CC oncological outcome, while several benefits, in terms of reduced metabolic risk and increased quality of life, have been described	
<b>Women with Endometrial cancer</b>								
<b>(Suriano et al., 2001).</b>	Case control study	249 endometrial cancer	130 received ERT after primary cancer treatments and 49% received	75 matched treatment-control	the risk of recurrence (number of recurrences and	There were two recurrences (1%) among the 75 estrogen users	not increase the risk of recurrence in patients with early-stage, low-	the two groups were matched by using decade of



			progesterone in addition	pairs (no HRT)	deaths from disease)	compared with 11 (14%) recurrences in the 75 nonhormone users. Hormone users had a statistically significant longer disease-free interval than nonestrogen users (P =.006).	risk endometrial cancer	age at diagnosis and stage of disease. Both groups were comparable in terms of parity, grade of tumor, depth of invasion, histology, surgical treatment, lymph node status, postoperative radiation, and concurrent diseases.
<b>(Barakat et al., 2006).</b>	RCT	stage I or II endometrial cancer  women, median age 57 years (<10% with POI)	HRT (n=251)	Placebo (n=681)	Recurrence	In HRT group: recurrence in 14 patients (2.3%). Incl 8 (1.3%) new malignancies. There were 26 deaths (4.2%), incl 5 (0.8%) from endometrial cancer.  In placebo group: 12 (1.9%) recurrence. 10 (1.6%) new malignancy. 9 deaths (3.1%) incl 4 (0.6%) from EC	absolute recurrence rate was low (2.3% in ERT patients versus 1.9% in placebo group) with stage I or II endometrial cancer with no significant increased risk of recurrence or death versus placebo	Median FU - 35.7 months
<b>(Shim et al., 2014).</b>	SR	1 RCT +5 observational studies (n=896 HRT users and 1079 nonusers)	HRT (896)	No HRT (1079)	risk of EC recurrence	19 / 896 HRT users vs 64/1079 controls  no significant increase in the risk of recurrence in EC survivors using HRT relative to the control group (OR: 0.53; 95%	no evidence of an increased risk of endometrial cancer recurrence with HRT use	



						CI: 0.30-0.96, I(2)=49.0). This pattern was also observed in the subgroup analysis for the stage and type of HRT.	
<b>Women with Ovarian cancer</b>							
<b>(Zhang et al., 2016)</b>	retrospective study	112 ovarian cancer - papillary serous ovarian cancer	HRT (n=31)	No HRT (n=81)	risk of recurrence - progression-free survival (PFS)	Median Kupperman score at the onset of HRT was 30.81 and 12.19 after the therapy (t = 3.302, P = 0.001).  HRT group and control group did not significantly differ in relapse rates (HR in HRT group:0.290; 95% CI: 0.31–2.47), Kaplan–Meier analysis showed the prognosis of HRT patients who received estrogen only was not significantly different from those who received combined estrogen-tibolone or tibolone only	HRT is not a prognostic factor for PFS in SOC patients
<b>(Saeabi et al., 2020).</b>	SR	surgery for epithelial ovarian cancer	HRT	No HRT	risk of recurrence - overall survival/PFS	HRT improved overall survival (HR 0.71; 95% CI 0.54 to 0.93) and had little or no effect on PFS (HR 0.76; 95% CI 0.57 to 1.07)   very low rates of breast cancer, transient ischemic attack, cerebrovascular accident, and myocardial infarction	
<b>(Achi mas-Cadariu et al., 2023).</b>	SR	11 studies (n=4191; low risk of bias in ten studies)  ovarian cancer	HRT	No HRT	risk of recurrence - overall survival/PFS	improved overall survival (HR 0.66; 95% CI 0.57 to 0.76) and PFS (HR 0.73; 95%CI 0.57 to 0.95)	
					POI outcomes	2 studies (n=227) assessed the effect of age: no difference was observed in PFS between women aged <40 and >40 years	subgroup analysis of type of ovarian cancer was not performed

### Evidence to recommendations

QUESTION	<b>What are the specific considerations for HT in iatrogenic POI?</b>
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GOOD PRACTICE POINT	<b>The guideline group recommends a personalized approach to risks and benefits of HT in women with iatrogenic POI after gynaecological/breast cancer.</b>
Desirable effects	HT is recommended in women with POI to compensate the impact of low estrogen levels.
Undesirable effects	In women with iatrogenic POI after gynaecological/breast cancer, there may be additional risks, mainly related to recurrence of the primary disease, which may need to be weighed against the benefits of HRT.
Certainty of evidence	NA
Values	Personalised approach
Balance of effects	To be considered individually, hence the recommendation for a personalised approach
Resource use, equity, acceptability and feasibility	NA

^

### *Evidence to recommendations – cervical cancer*

QUESTION	<b>What are the specific considerations for HT in iatrogenic POI?</b>
RECOMMENDATION	<b>HT does not increase the risk of recurrence of squamous cell carcinoma of the cervix and is recommended for women with iatrogenic POI due to the treatment of squamous cell carcinoma.</b> • <b>STRONG</b> • +++0
RECOMMENDATION	<b>HT may be associated with a slightly increased risk of recurrence of cervical adenocarcinoma and a personalized approach considering individualized HT risk and benefits is recommended.</b> • <b>STRONG</b> • ++00
Desirable effects	HT is recommended in women with POI to compensate the impact of low estrogen levels.
Undesirable effects	recurrence of the primary disease: HT does not increase the risk of recurrence of squamous cell carcinoma of the cervix HT may be associated with a slightly increased risk of recurrence of cervical adenocarcinoma
Certainty of evidence	Mainly observational data
Values	NA
Balance of effects	The possible additional risks of HRT, mainly related to recurrence of the primary disease are weighed against the benefits of HRT.
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	Differentiated recommendations, based on specific cervical cancer subgroups with different risk profiles

### *Evidence to recommendations – endometrial cancer*

QUESTION	<b>What are the specific considerations for HT in iatrogenic POI?</b>
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RECOMMENDATION	<b>HCPs could consider HT in women with iatrogenic POI due to early-stage low-risk endometrial adenocarcinoma, as there is no evidence that it increases the risk of cancer recurrence. • CONDITIONAL</b> • ++00
Desirable effects	HT is recommended in women with POI to compensate the impact of low estrogen levels.
Undesirable effects	recurrence of the primary disease: there is no evidence that it increases the risk of cancer recurrence
Certainty of evidence	Mainly observational data
Values	NA
Balance of effects	The possible additional risks of HRT, mainly related to recurrence of the primary disease are weighed against the benefits of HRT.
Resource use, equity, acceptability and feasibility	NA

#### *Evidence to recommendations – ovarian cancer*

QUESTION	<b>What are the specific considerations for HT in iatrogenic POI?</b>
RECOMMENDATION	<b>HCPs could consider HT in women with iatrogenic POI due to epithelial ovarian cancer. • CONDITIONAL +++0</b>
	<b>The effect of HT on the risk of recurrence of non-epithelial ovarian cancer is uncertain and it is suggested that HCPs use a personalized approach to prescribing HT, including consideration of tumour hormone receptor status. • CONDITIONAL• +000</b>
	<b>HT should be avoided in women with hormone-dependent ovarian or uterine tumours, including uterine sarcoma, endometrioid carcinoma, ovarian clear cell carcinoma, ovarian granulosa cell tumour, or sex cord-stromal tumours.</b>
Desirable effects	HT is recommended in women with POI to compensate the impact of low estrogen levels.
Undesirable effects	recurrence of the primary disease: <ul style="list-style-type: none"> <li>- epithelial ovarian cancer: low</li> <li>- non-epithelial ovarian cancer : uncertain</li> <li>- hormone-dependent ovarian tumours: high</li> </ul>
Certainty of evidence	Mainly observational data
Values	NA
Balance of effects	The possible additional risks of HRT, mainly related to recurrence of the primary disease are weighed against the benefits of HRT.
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	Differentiated recommendations, based on specific ovarian cancer subgroups with different risk profiles



Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<p><b>Women after Risk reducing bilateral oophorectomy</b></p> <p><b>HRT should be considered as early as possible after RRSO in women under 50 years old, especially under 46 years old, to reduce the incidence of estrogen deficiency related symptoms and co-morbidities (Manchanda <i>et al.</i>, 2022).</b></p>								
(Kotso poulos <i>et al.</i> , 2018)	prospective study	872 BRCA-1 mutation carriers undergoing RRSO before 45 years of age			HRT safety	HR 0.97 (95%CI 0.62-1.52; P= 0.89) for ever use of any type of HRT vs no use HR 0.73 (95%CI 0.41-1.32; p = 0.30) for ever use of E-HRT vs no use HR 1.31 (0.66-2.57; P= 0.44) for ever use of E+P HRT vs no use  estrogen-only therapy: reduced breast cancer risk (HR 0.24; 95% CI 0.06 to 0.98 for over 5 years of ERT use)  estrogen +progestin: increased risk of breast cancer (HR 1.78; 95% CI 1.17 to 9.73 for over 5 years of HRT)		
(Marchetti <i>et al.</i> , 2018).	meta-analysis	breast cancer in BRCA1/2 mutation carriers post RRSO (3 studies, n=1100)	HRT		BC risk	There was not a significantly higher BC risk in BRCA1 and BRCA2 mutation carriers receiving HRT after RRSO (HR = 0.98; 95% CI 0.63-1.52). There was a slightly but not significantly, benefit in BC risk reduction in favor of estrogen alone HRT versus estrogen plus progesterone HRT formulation (OR = 0.53; 95% CI 0.25-1.15).		
(Gaba and Manc)	Systematic	RRBSO			cardiovascular health,	RSO remains the gold standard for preventing OC in BRCA carriers with	HRT mitigates risks of	



<p><b>handa</b> , <b>2020).</b></p>	<p>review</p>				<p>neurological function and bone health. acceptability,</p> <p>HRT safety</p>	<p>uptake being higher in BRCA1 carriers, Caucasians, women who have completed childbearing and women with a personal history of BC. However, when performed in premenopausal BRCA carriers, it increases the risk of osteoporosis/ osteopenia, CHD and neurocognitive decline (though BRCA specific data on CHD and neurocognitive impact are limited). Use of HRT until natural menopause mitigates risks and there are data supporting safety of short term HRT use in BRCA carriers without a personal history of receptor positive BC.</p>	<p>premenopausal RRSO with evidence of safety for short term use in BRCA mutation carriers without breast cancer and recommends use after RRSO</p>																								
<p><b>(Huber et al., 2021).</b></p>	<p>Review</p> <p>OC: 1 case-control + 1 retrospective cohort</p> <p>EC: 1 case-control study</p> <p>BC: 5 studies + 1 MA</p>	<p>BRCA mutation carriers</p>	<p>HRT</p>		<p>risk of ovarian, endometrial cancer</p>	<p>OC:</p> <table border="1"> <thead> <tr> <th>Study</th> <th>Number</th> <th>Results</th> </tr> </thead> <tbody> <tr> <td>Huber et al. (2021)</td> <td>17 BRCA1, 17 BRCA2</td> <td>No increase in risk overall</td> </tr> <tr> <td>Case-control study</td> <td>17 BRCA1, 17 BRCA2</td> <td>BRCA1: OR 1.0 (95% CI 0.1-11.0), P=0.97 BRCA2: OR 0.9 (95% CI 0.2-4.0), P=0.87</td> </tr> <tr> <td>EC</td> <td>17 BRCA1, 17 BRCA2</td> <td>No increase in risk overall</td> </tr> <tr> <td>Case-control study</td> <td>17 BRCA1, 17 BRCA2</td> <td>BRCA1: OR 1.0 (95% CI 0.1-11.0), P=0.97 BRCA2: OR 0.9 (95% CI 0.2-4.0), P=0.87</td> </tr> </tbody> </table> <p>EC</p> <p>BC:</p> <table border="1"> <thead> <tr> <th>Study</th> <th>Number</th> <th>Results</th> </tr> </thead> <tbody> <tr> <td>Huber et al. (2021)</td> <td>5 studies + 1 MA</td> <td>No increase in risk overall</td> </tr> <tr> <td>Case-control study</td> <td>5 studies + 1 MA</td> <td>BRCA1: OR 1.0 (95% CI 0.1-11.0), P=0.97 BRCA2: OR 0.9 (95% CI 0.2-4.0), P=0.87</td> </tr> </tbody> </table>	Study	Number	Results	Huber et al. (2021)	17 BRCA1, 17 BRCA2	No increase in risk overall	Case-control study	17 BRCA1, 17 BRCA2	BRCA1: OR 1.0 (95% CI 0.1-11.0), P=0.97 BRCA2: OR 0.9 (95% CI 0.2-4.0), P=0.87	EC	17 BRCA1, 17 BRCA2	No increase in risk overall	Case-control study	17 BRCA1, 17 BRCA2	BRCA1: OR 1.0 (95% CI 0.1-11.0), P=0.97 BRCA2: OR 0.9 (95% CI 0.2-4.0), P=0.87	Study	Number	Results	Huber et al. (2021)	5 studies + 1 MA	No increase in risk overall	Case-control study	5 studies + 1 MA	BRCA1: OR 1.0 (95% CI 0.1-11.0), P=0.97 BRCA2: OR 0.9 (95% CI 0.2-4.0), P=0.87	<p>BC data not included here</p>
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Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Women after Hematopoietic stem cell transplantation (HSCT)</b>								
<b>(Ha et al., 2020),</b>	Prospective observational study	234 patients with POI after HSCT	HRT		Efficacy - relieve menopausal symptoms and correct bone loss			Bone data, details in Bone chapter
<b>(Yang et al., 2017)</b>	Prospective observational study	130 patients with POI after HSCT for malignant hematologic diseases	HRT		risk of recurrence of the primary disease	HRT was safe and no excessive recurrences or mortality were seen  103 (79.2%) patients had perimenopausal symptoms. The mean total Kupperman menopausal index score changed significantly from 13.50 ± 7.128 to 6.13 ± 5.97 after HT for 24 months. Among the 118 patients who received estrogen/progestin cyclic sequential therapy, 89 (75.4%) had withdrawal bleeding.		

Evidence to recommendations – ovarian cancer

QUESTION	<b>What are the specific considerations for HT in iatrogenic POI?</b>
RECOMMENDATION	<b>Women should be informed of the risks of iatrogenic POI and risks and benefits of HT before bilateral salpingo-oophorectomy to reduce cancer risk (RRSO). STRONG +000</b>
	<b>It is recommended that personalized HT or pubertal induction be commenced in girls/women with POI following haematopoietic stem cell transplantation or other gonadotoxic therapies. STRONG ++00</b>
Desirable effects	HT is recommended in women with POI to compensate the impact of low estrogen levels.
Undesirable effects	recurrence of the primary disease:
Certainty of evidence	Mainly observational data
Values	NA
Balance of effects	The possible additional risks of HRT, mainly related to recurrence of the primary disease are weighed against the benefits of HRT. Recommendation for providing information and a personalized approach
Resource use, equity, acceptability and feasibility	NA



## XII. Non-hormonal, complementary and lifestyle therapies

### XII.1. Non-hormonal therapies

#### PICO QUESTION: WHAT NON-HORMONAL THERAPIES ARE AVAILABLE FOR POI?

<b>Population</b>	People with POI of any cause including iatrogenic.
<b>Interventions</b>	Cognitive behavioural therapy Stellate ganglion block non hormonal therapies Selective serotonin and noradrenaline reuptake inhibitors / antidepressants Gabapentin and pregabalin Clonidine Oxybutynin / neurokinin receptor antagonists
<b>Control</b>	
<b>Outcomes</b>	Efficacy <ul style="list-style-type: none"> <li>• vasomotor symptoms</li> <li>• genito-urinary symptoms</li> <li>• Life expectancy</li> <li>• bone health</li> <li>• cardiovascular health</li> <li>• Quality of life</li> <li>• sexual function</li> <li>• neurological function</li> </ul>

#### Search strings

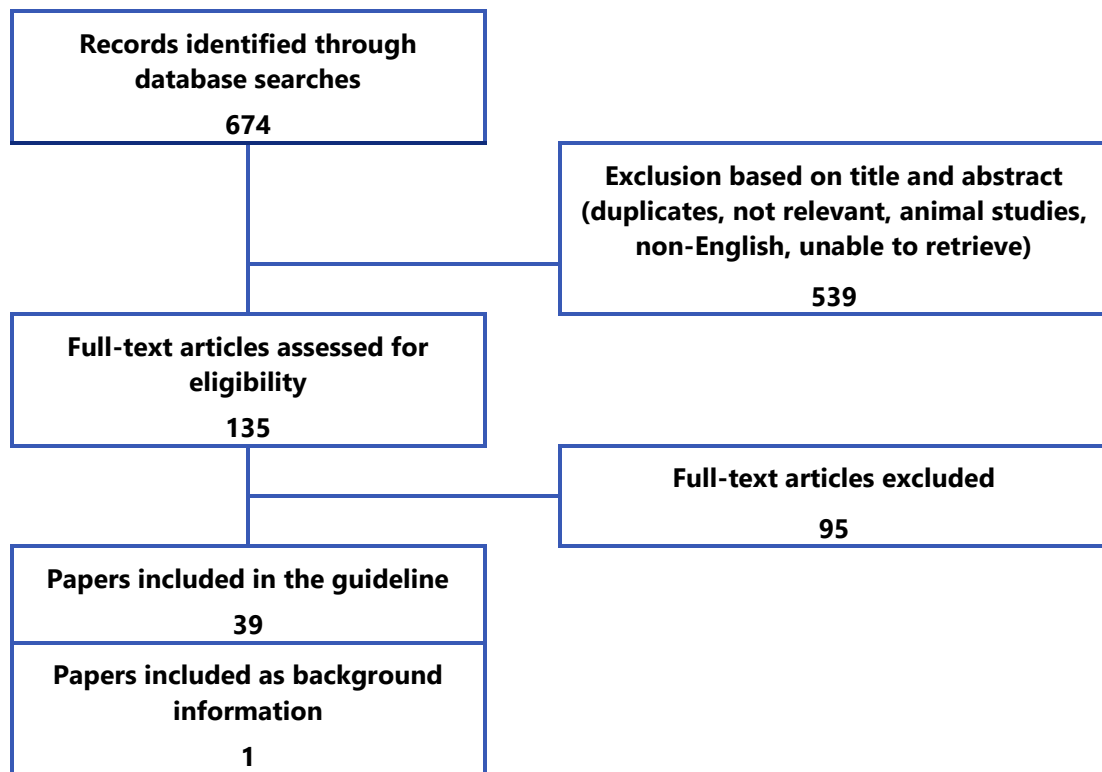
Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause" OR Menopause OR "Menopause"[Mesh]) AND (Alpha-2-agonist OR Clonidine OR alpha-agonist OR "α2 adrenergic agonist" OR "imidazoline receptor agonist" OR "Beta blocker" OR "Beta-blocker" OR "Selective serotonin and noradrenaline reuptake inhibitors" OR "Serotonin-norepinephrine reuptake inhibitor" OR SNRIs OR venlafaxine OR Duloxetine OR Milnacipran OR Sibutramine OR Bicyclanil OR Gabapentin OR "Nonhormonal therapies" OR "non hormonal therapies" OR "Nonhormonal therapy" OR "Stellate ganglion blockade" OR "Stellate ganglion block" OR "Selective serotonin reuptake inhibitors" OR "Serotonin Uptake Inhibitors"[Mesh] OR "Selective noradrenaline reuptake inhibitors" OR "selective serotonin-norepinephrine reuptake inhibitors" OR "Gabapentin"[Mesh] OR Pregabalin OR "Pregabalin"[Mesh] OR "Venlafaxine Hydrochloride"[Mesh] OR "Duloxetine Hydrochloride"[Mesh] OR paroxetine OR sertraline OR fluoxetine OR escitalopram OR "Antidepressive Agents"[Mesh] OR " antidepressants" OR Antidepressant OR "Cognitive behavioural therapy" OR "Cognitive Behavioral Therapy"[Mesh] OR "Cognitive Behavioral



Therapy" OR "Cognition Therapy" OR "Oxybutynin" OR "neurokinin receptor antagonists" OR "Neurokinin-1 Receptor Antagonists"[Mesh])

Literature search was limited to the period between 01/01/2014 and 18/12/2023. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.

### Flowchart



INCLUDED AS BACKGROUND INFORMATION: (Koysombat *et al.*, 2024).

### Evidence

#### Summary of Findings Table

Not applicable

#### Evidence table

Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Women with POI - Pharmacologic therapies for vasomotor symptoms</b>								
<b>Antidepressants</b>								



<b>(Azizi et al., 2022)</b>	Review	36 RCTs, 27 acceptable and 9 low quality	Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)		HF	<p>SSRIs : escitalopram, paroxetine, and fluoxetine have higher efficacy and safety in the treatment of menopausal HF than other drugs. Studies on the effectiveness of sertraline, citalopram, and fluvoxamine are limited in number or show inconsistent results.</p> <p>SNRIs: venlafaxine and desvenlafaxine showed significant efficacy in the treatment of menopausal HF. However, studies on the effectiveness of duloxetine are also limited, which requires further research.</p>	Most studies have indicated the efficacy and safety of some antidepressants, such as SSRIs and SNRIs, in decreasing the frequency and severity of HF. These drugs are therefore recommended for the treatment of menopausal HF.	
<b>(Guthrie et al., 2015)</b>	RCT	899 peri- and postmenopausal women with at least 14 bothersome vasomotor symptoms/week - Subgroups- randomisation; 104 to escitalopram and 101 to placebo (MsFLASH 01); 106 to exercise, 107 to yoga, and 142 to usual activity, and simultaneously , 177 to omega-3 and 178 to placebo (MsFLASH 02); 97 to estradiol, 96 to venlafaxine, and 146 to placebo (MsFLASH 03).	escitalopram 10-20 mg/day, non-aerobic yoga, aerobic exercise, 1.8 g/day omega-3 fatty acid supplementation, low-dose oral 17-beta-estradiol 0.5-mg/day, and low-dose venlafaxine XR 75-mg/day.	placebo	<p>changes from baseline in mean daily vasomotor symptoms frequency and bother during 8-12 weeks of treatment</p> <p>SAFETY</p>	<p>Reductions in vasomotor symptom frequency from baseline of similar size and statistical significance were observed in the escitalopram, estradiol, and venlafaxine groups, relative to control. Although most of the benefit was gained by week 4 for escitalopram and venlafaxine, participants in the estradiol group continued to improve over the intervention period, yielding comparable week 8 intervention effect estimates for these three medications (frequency escitalopram at -1.4/day (95% CI: -2.7 to -0.2), low-dose estradiol at -2.4 (95% CI: -3.4 to -1.3), and venlafaxine at -1.8 (95% CI: -2.8 to -0.8)). Decreases ranged from 1.4 to 2.4 fewer vasomotor symptoms per day, or 18% to 37% lower vasomotor symptom daily frequency, relative to control</p> <p>No effects on vasomotor symptoms frequency or bother were seen with aerobic exercise, yoga or omega-3 supplements.</p> <p>No serious adverse events (3 trials)</p> <p>stopped treatment due to adverse events: 7 (6.7%) escitalopram, 1 (0.6%) omega-3, 4 (4.1%) estradiol, 5 (5.2%) venlafaxine, and 4 (1.3% of n=318) placebo</p> <p>Notable adverse events included: 3 suicidal ideation while on study medication; 12 systolic blood pressure (SBP) &gt;165 mmHg or diastolic blood pressure (DBP) &gt;95 mmHg;</p> <p>among women with a uterus, 6/73 (8.2%) on estradiol, 2/124 (1.6%) on placebo, and none on venlafaxine developed abnormal vaginal bleeding. Three of 6 estradiol-treated participants with abnormal bleeding had an endometrial echo complex &gt;5 mm and underwent an</p>	These analyses suggest that escitalopram, low-dose estradiol, and venlafaxine provide comparable, modest reductions in vasomotor symptoms frequency and bother among women with moderate hot flushes	



						endometrial biopsy, all of which revealed no evidence of hyperplasia or malignancy.		
<b>(Caan et al., 2015)</b>	RCT	339 peri- and post-menopausal women with $\geq 2$ bothersome vasomotor symptoms per day (mean 8.1, SD 5.3/day)  40–62 years  $\geq 14$ VMS/week, at least some of which were considered bothersome or severe,	Low-dose oral 17-beta-estradiol 0.5-mg/day (n=97) OR low-dose venlafaxine XR 75-mg/day (n=96) (n=146) for 8 weeks.	placebo (n=146)	Primary outcome: mean daily frequency of vasomotor symptoms after 8 weeks of treatment.  Secondary outcome: vasomotor symptom severity, bother and interference.	Mean vasomotor symptom frequency (week 8) decreased by 53% with estradiol, 48% with venlafaxine, and 29% with placebo. Estradiol reduced the frequency of symptoms by 2.3 (95% CI 1.3–3.4) more per day than placebo ( $p < 0.001$ ), and venlafaxine by 1.8 (95% CI 0.8–2.7) more per day than placebo ( $p = 0.005$ ).  Results were consistent for symptom severity, bother and interference. Low-dose estradiol reduced symptom frequency by 0.6 more per day than venlafaxine (95% CI, 1.8 more per day to 0.6 fewer per day than venlafaxine; $p = 0.09$ ).  Treatment satisfaction was highest (69%) on estradiol ( $p < 0.001$ versus placebo), lowest (39%) on placebo, and intermediate (52%) for venlafaxine ( $p = 0.06$ versus placebo).  Both interventions were well tolerated. Only 11 (3.2%) subjects stopped treatment due to AEs (4 ET, 5 venlafaxine, 2 placebo). The most frequently reported AEs were insomnia on ET and fatigue on venlafaxine and placebo. 3 participants reported suicidal ideation (2.5% on ET; 0.7% placebo; 0 venlafaxine).	low-dose oral estradiol and venlafaxine are both effective treatments for vasomotor symptoms in midlife women. While the efficacy of low-dose estradiol may be slightly superior to that of venlafaxine, the difference is small in magnitude and of uncertain clinical relevance	
<b>(Riemma et al., 2019)</b>	Review up to July 2019	physiological or surgical postmenopausal women experiencing hot flushes and sleep disturbances  5 RCTs, including 1482 postmenopausal women - Significant heterogeneity ( $I^2 = 90\%$ )	Paroxetine	placebo	Efficacy - VMS frequency	4 trials including 1305 participants reported the frequency reduction at week 4.  Paroxetine significantly ( $P < 0.00001$ ) reduced the VMS frequency (MD 8.86 per week, 95% CI 5.69–12.04), with high variability ( $I^2 = 83\%$ ).  2 trials reported the frequency of VMS at week 6 : MD 6.05 per week, 95% CI 1.43 to 13.53, $P = 0.11$ , $I^2 = 93\%$ ).  3 trials reported the frequency of VMS at week 12: MD 7.36 per week, 95% CI 4.25–10.46, $P < 0.00001$ ( $I^2 = 62\%$ ).	There was moderate quality of evidence supporting the effectiveness of paroxetine for vasomotor symptoms; however, it causes nausea and dizziness	The quality of the evidence on the effect of paroxetine for VMS was moderate.



					Adverse events	Included studies reported nausea, dizziness, headache, fatigue/drowsiness/somnolence/lethargy, constipation, dyspepsia, insomnia, weight gain, mouth dryness, blurred vision, sleep disturbance and anxiety. The most consistently reported adverse events were nausea, dizziness, headache, fatigue and constipation. The risks of nausea and dizziness were respectively 2.45 times (95% CI 1.29–4.66, P = 0.006, I <sup>2</sup> = 0%) and 2.44 times (95% CI 1.02–5.85, P = 0.05, I <sup>2</sup> = 0%) higher than placebo.		
<b>(Wei et al., 2016)</b>	Review	5 RCTs, including 1482 postmenopausal women - Significant heterogeneity (I <sup>2</sup> = 90%)	paroxetine		Efficacy	<p>Paroxetine Hydrochloride</p> <p>2 pilot studies showed significant hot flash reduction. + a 4 week, double-blind, randomized, controlled, crossover study in 151 menopausal women, with the majority being breast cancer survivors. With 10 mg paroxetine HCl vs placebo, hot flash frequency was decreased by 40.6% vs 13.7% (P=0.0006). Furthermore, hot flash frequency was significantly decreased by 51.7% vs 26.6% (P=0.0002) with 20 mg paroxetine HCl vs placebo. Seventeen (11%) patients withdrew due to adverse effect</p> <p>Paroxetine Mesylate</p> <p>4 RCTs were conducted to assess paroxetine and VMS in women without breast cancer, including two Phase 3 RCTs looking at paroxetine mesylate. In these 4 trials, paroxetine was associated with a 33–65% reduction in hot flash frequency with 6–12 weeks of treatment compared to 17–38% reductions with placebo. Additionally, paroxetine was also associated with significant reductions in hot flash severity.</p>		
					Side Effects:	<p>most common with paroxetine mesylate were nausea (3.8% vs 1.4%), fatigue (3.4% vs 1.5%), and dizziness (2% vs 0.8%).</p> <p>Reasons that prompted discontinuation that occurred in at least 2% of patients and twice as often compared with placebo included muscle cramps, spasms, and/or twitching (3.4% vs 1.5%); restless leg feeling (2.6% vs 1.2%); and insomnia (2.6% vs 1.2%).<sup>22</sup></p> <p>Although uncommon, there is a black box warning for the potential of paroxetine HCl to increase the risk of suicidal thinking and behavior, however low dose paroxetine mesylate was not tested in women who have a history of depression, suicide attempts, or psychiatric conditions. Other adverse effects linked to SSRI use in general include syndrome of inappropriate antidiuretic hormone secretion, bone fractures, seizures, akathisia, acute angle closure glaucoma, and cognitive and/or motor impairment.</p>		
<b>(Rios-Espinosa et al., 2022)</b>	RCT	91 symptomatic postmenopausal Mexican women, average age 54 years	20mg fluoxetine	20mg citalopram	menopause rating scale scores	reduction in the menopause rating scale scores for both agents at 3 months and citalopram at 6 months follow-up; however, citalopram was associated with greater improvement compared with fluoxetine with benefits observed for vasomotor, psychological,		



						urogenital, libido and somatic subdomains		
<b>(Birkhauser et al., 2019)</b>	RCT	2 studies P012 and P013 with resp 942 and 946 participants	Esmirtazapine treatment (2.25, 4.5, 9.0, or 18.0 mg) - 12 week trial	placebo	<p>Daily frequency and severity of moderate to severe VMS, both at weeks 4 and 12) (based on participative LogPad daily diaries)</p> <p>Adverse events</p> <p>Visits occurred at the end of weeks 2, 4, 8, and 12. A telephone call was scheduled for 30 days (<math>\pm 7</math> days) after the last study medication</p> <p>Safety, The percentage of participants experiencing at least one AE during treatment was higher for esmirtazapine (Study P012, from 76.6% with 2.25 mg to 87.7% with 18.0 mg; Study P013, from 63.6% with 2.25 mg to 69.0% with 18.0 mg) than placebo (Study P012, 62.1%; Study P013, 51.6%). In both studies, the most frequently reported AEs with esmirtazapine were somnolence, fatigue, increased appetite, and weight gain, and with the exception of fatigue in Study P012 these AEs were more common with higher doses.</p> <p>A greater proportion of participants receiving esmirtazapine discontinued treatment due to AEs compared with placebo. Somnolence and fatigue were the most frequently reported AEs.</p> <p>SAEs were reported in 8 participants. Three SAEs were considered possibly/probably treatment-related: one participant with severe edema of the extremities in the esmirtazapine 9.0 mg group (participant recovered), and two placebo participants (one with nightmares and suicidal ideations [participant recovered with sequelae] and one with</p>	<p>The mean daily frequency and severity of moderate to severe VMS generally decreased over time with esmirtazapine and placebo, with differences between esmirtazapine and placebo observed as early as week 1. A decrease in moderate to severe VMS frequency was greater with all esmirtazapine doses compared with placebo in both studies. At weeks 4 (all doses) and 12 (4.5 mg) (co-primary endpoints), reductions in the frequency of moderate to severe VMS versus placebo were also observed in both studies (<math>p &lt; 0.01</math>). A reduction of 1.4–2.2 VMS was observed at weeks 4 and 12 (4.5 mg, both studies).</p> <p>A dose–response analysis of active doses on the four co-primary endpoints demonstrated that esmirtazapine 2.25 mg provided less improvement in moderate to severe VMS frequency versus other active doses at weeks 4 and 12 in both studies.</p> <p>Esmirtazapine (4.5 mg) significantly reduced the average daily frequency of moderate to severe VMS in postmenopausal women compared with placebo at weeks 4 and 12. Treatment effects were observed as early as week 1. Daily symptom severity was also reduced, with statistical significance observed at week 4. Esmirtazapine doses up to 18.0 mg were generally well tolerated, with a more favorable safety profile for lower doses. Since these studies were conducted,</p>	<p>Commercially sponsored; funding was provided by Organon, a subsidiary of Akzo Nobel at the time of study conduct, and subsequently of Merck Sharp &amp; Dohme Corp., a subsidiary of Merck &amp; Co., Inc., Kenilworth, NJ, USA. The sponsor discontinued further development of esmirtazapine</p>	



						vasovagal syncope [participant recovered]).		
<b>Gabapentanoids</b>								
(Shan <i>et al.</i> , 2020)	Review	Women experiencing menopausal vasomotor symptoms because of natural or medical reasons. Establishment of menopause did not have to be formal (amenorrhea for more than 12 months or amenorrhea more than 6 months with a serum FSH level greater than 40 mIU/mL and estrogen less than 20 pg/mL)	gabapentin and pregabalin	placebo, calcium, vitamins, and other treatment methods such as hormone therapy, herbal drugs, isoflavones, clonidine, and antidepressants	efficacy and safety for vasomotor symptoms reduction from baseline in frequency, severity, or duration of hot flashes. Severity was graded by scale or compound measurement method through multiplying severity score by frequency. Secondary outcomes included adverse events. Parameters related to quality of life, quality of sleep, change in depression and anxiety, and change in important blood test results were also included.	Gabapentin Reduction in hot flash frequency - compared to placebo/vit E: mean difference (MD), -1.62, 95% CI, -1.98 to -1.26 after 4 weeks (8 RCTs); MD, -2.77, 95% CI, -4.29 to -1.24 after 12 weeks (7 RCTs) Reduction in composite score - compared to placebo/vit E: standardized MD, -0.47, 95% CI -0.71 to -0.23 after 4 weeks (5 RCTs); standardized MD -0.77, 95% CI -1.15 to -0.40 after 12 weeks (2 RCTs) No difference in hot flash duration Subgroup; hot flash frequency after 4 weeks: MD, -1.62, 95% CI -2.56 to -0.68 in patients with breast cancer Gabapentin vs estrogen (2RCTs): estrogen was more effective in reducing hot flash frequency (MD, 1.11, 95% CI, 0.69-1.52) Both menopausal participants and patients with breast cancer benefited from treatment. Safety Higher risks of dizziness (risk ratio, 4.45, 95% CI, 2.50-7.94), somnolence (RR 3.29, 95% CI 1.97-5.48) and nausea (RR 2.24, 95% CI 1.18-4.24) in the gabapentin group than in the control group. Pregabalin - 2 trials Pregabalin superior to placebo for HF frequency + severity (1 RCT) Pregabalin inferior to Stellate ganglion block (1 RCT)	Favorable effects of gabapentin in relieving vasomotor symptoms were observed, compared with controls, but were less effective than those of estrogen. Evidence supporting the therapeutic effect of pregabalin is still lacking.	
(Yoon <i>et al.</i> , 2020)	Review  end date June 2018	postmenopausal women  7 RCTs	gabapentin	placebo	percentage reduction or mean difference in frequency, duration, or severity of hot flashes secondary outcomes: adverse events and dropout rate	Women who received gabapentin reported a significantly greater reduction in the frequency (SMD 2.99 [95% CI 2.01-3.98], P < 0.001), duration (0.89 [0.49-1.30], P < 0.001), and composite score (2.31 [1.50-3.11], P < 0.001) of hot flashes. Adverse events were significantly more frequent among those taking gabapentin than among those taking the placebo (OR 1.58 [0.98-2.18], P < 0.001; and 1.19 [0.43-1.95], P = 0.002 for dizziness and unsteadiness, respectively)	Gabapentin represents a potentially beneficial treatment for VMS in postmenopausal women who are contraindicated to HT or who prefer alternatives. Future studies should investigate the lowest effective dose of gabapentin to minimize adverse effects. Management of	



							menopausal symptoms should be individualized and address patients' aims and treatment preferences
<b>Oxybutynin</b>							
<b>(Simon et al., 2016)</b>	RCT	148 naturally postmenopausal women (40 to 65 years) experiencing at least seven moderate-to-severe vasomotor symptoms daily	oxybutynin 15 mg once daily (12 weeks)	placebo	<p>primary: change from baseline to week 12 in mean frequency and mean severity of moderate-to-severe vasomotor symptoms (diary)</p> <p>Secondary: change from baseline to week 4 in the frequency and severity of moderate-to-severe vasomotor symptoms; change from baseline to weeks 4 and 12 in the composite score of moderate-to-severe vasomotor symptoms; change in frequency, severity, and composite score of all vasomotor symptoms from baseline to weeks 4 and 12; the participant's global assessment of benefit (SGA); and the Pittsburgh Sleep Quality Index (PSQI).</p>	<p>at week 12 of therapy, women who received oxybutynin ER had significant decreases (<math>P &lt; 0.001</math>) in both the mean daily frequency and severity of moderate-to-severe vasomotor symptoms compared with those in the placebo group. Changes in the oxybutynin ER group were significantly greater than in the placebo group at both week 4 and week 12 (<math>P &lt; 0.001</math>) for all variables.</p> <p>A greater proportion of women in the oxybutynin ER group than in the placebo group reported no vasomotor symptoms at week 4 (6.9% vs 1.4%; <math>P = 0.116</math>) and week 12 (16.7% vs 5.5%; <math>P = 0.036</math>)</p> <p>Mean changes in frequency in the oxybutynin and placebo groups were 9.48 and 4.69 episodes/d, respectively, at week 12. Mean changes in severity (scale 0-3) in the oxybutynin and placebo groups were 1.27 and 0.30, respectively, at week 12. At the end of treatment, 73% of women in the oxybutynin group and 26.1% in the placebo group rated symptom improvement "much better" (<math>P &lt; 0.001</math>).</p> <p>Women treated with oxybutynin showed significant improvement in sleep quality, sleep disturbance, and the global sleep index on the Pittsburgh Sleep Quality Index (<math>P &lt; 0.023</math>).</p> <p>Dry mouth, dyspepsia, diarrhea, and urinary tract infections were more frequent in the oxybutynin ER group. Ten women in the oxybutynin ER group and three in the placebo group discontinued treatment due to adverse events. Five women (6.8%) were discontinued from oxybutynin ER because of dry mouth. No serious adverse events were reported</p>	Oxybutynin is an effective, nonhormonal therapy for moderate-to-severe vasomotor symptoms in postmenopausal women
<b>Neurokinin receptor antagonists</b>							



<b>(Morga et al., 2024)</b>	REVIEW	2 RCTs and 23 comparator studies	fezolinetant	placebo, paroxetine, desvenlafaxine or gabapentin	vasomotor symptoms	fezolinetant 45 mg reduced the frequency of moderate to severe vasomotor symptoms significantly more than placebo, paroxetine, desvenlafaxine or gabapentin with similar efficacy to low or usual dose HRT regimens at 12 weeks follow-up	Fezolinetant significantly reduced vasomotor symptom severity compared with placebo or 50mg desvenlafaxine but was less effective compared to tibolone or conjugated estrogen/bazedoxifene.	Bayesian network meta-analysis
<b>(Lederman et al., 2023)</b>	RCT	2205 Women aged 40-65 years with an average of seven or more moderate-to-severe hot flashes per day  173 in the fezolinetant 30 mg group and 174 in the fezolinetant 45 mg group  175 in the placebo group	fezolinetant 30 mg, or fezolinetant 45 mg	once-daily exact-matched placebo	safety and efficacy  Primary: mean change in frequency and severity of vasomotor symptoms from baseline to weeks 4 and 12.	23 participants in the placebo group, 31 in the fezolinetant 30 mg group, and 13 in the fezolinetant 45 mg group discontinued treatment before week 12, mostly due to adverse events or participant withdrawal.  Compared with placebo, fezolinetant 30 mg and fezolinetant 45 mg significantly reduced the frequency of vasomotor symptoms at week 4 (difference in change in least squares mean -1.87 [SE 0.42; p<0.001], -2.07 [SE 0.42; p<0.001]) and week 12 (-2.39 [SE 0.44; p<0.001], -2.55 [SE 0.43; p<0.001]). Compared with placebo, fezolinetant 30 mg and 45 mg significantly reduced the severity of vasomotor symptoms at week 4 (-0.15 [0.06; p=0.012], -0.19 [0.06; p=0.002]) and week 12 (-0.24 [0.08; p=0.002], -0.20 [0.08; p=0.007]). Improvements in frequency and severity of vasomotor symptoms were observed after 1 week and maintained over 52 weeks.  Treatment-emergent adverse events occurred in 37% of women in fezolinetant 30 mg, 43% in the fezolinetant 45 mg, and 45% in placebo	Data support the clinical use of fezolinetant as a non-hormonal treatment for vasomotor symptoms associated with menopause.	SKYLIGHT 1  FUNDING: Astellas Pharma.
<b>(Johnson et al., 2023)</b>	RCT	Follow-up SKYLIGHT 1  Completers were rerandomized to fezolinetant 30/45 mg for 40 additional weeks.	fezolinetant 30 mg, or fezolinetant 45 mg	once-daily exact-matched placebo	safety and efficacy  Primary: mean change in frequency and severity of vasomotor symptoms from baseline to weeks 4 and 12.	Both fezolinetant doses statistically significantly reduced VMS frequency/severity at W4 and W12 vs placebo. For VMS frequency, W4 least squares mean (SE) reduction vs placebo: fezolinetant 30 mg, -1.82 (0.46; P < .001); 45 mg, -2.55 (0.46; P < .001); W12: 30 mg, -1.86 (0.55; P < .001); 45 mg, -2.53 (0.55; P < .001). For VMS severity, W4: 30 mg, -0.15 (0.06; P < .05); 45 mg, -0.29 (0.06; P < .001); W12: 30 mg, -0.16 (0.08; P < .05); 45	Daily fezolinetant 30 and 45 mg were efficacious and well tolerated for treating moderate to severe VMS associated with menopause	SKYLIGHT 2



						mg, -0.29 (0.08; P < .001). Improvement in VMS frequency and severity was observed by W1 and maintained through W52.  Serious treatment-emergent adverse events were infrequent, reported by 2%, 1%, and 0% of those receiving fezolinetant 30 mg, fezolinetant 45 mg, and placebo, respectively.		
<b>Other</b>								
<b>(Vrselja et al., 2022)</b>	RCT	131 women were randomly assigned and received treatment (Q-122 n=65 and placebo n=66  Women, aged 18–70 years, taking a stable dose of tamoxifen or an aromatase inhibitor following breast cancer and experiencing at least 50 self-reported moderate to severe vasomotor symptoms per week)	oral Q-122 100 mg, twice daily for 28 days	placebo	Vasomotor Symptom Severity Score (msVMS-SS)  Secondary: mean percentage change from baseline in the tVMS-SS, the frequency of vasomotor symptoms  the effect on hot flash interference with daily activities (total HFRDIS score)  proportion of responders at week 4.	Q-122 resulted in a significantly greater mean percentage change in msVMS-SS from baseline over 28 days of treatment compared with placebo (least squares mean: Q-122 -39% [95% CI -46 to -31] vs placebo -26% [-33 to -18]; p=0.018). Treatment-emergent adverse events were generally mild to moderate and similar between the two groups (treatment-related treatment-emergent adverse events in 11 [17%] of 65 patients in the Q-122 group vs nine [14%] of 66 in the placebo group); zero patients in the Q-122 group and two (3%) patients in the placebo group had serious adverse events	Q-122 is an effective and well tolerated non-hormonal oral treatment for vasomotor symptoms in women taking oral adjuvant endocrine therapy after breast cancer. Our results support the conduct of larger and longer studies of Q-122, with potential use extending to postmenopausal women who require an alternative to menopausal hormone therapy.	
<b>(Borba et al., 2020).</b>	RCT	29 postmenopausal women, aged 47-62  at least a mean of 5 moderate to severe hot flashes per day	sulpiride, 50 mg/d, 8 weeks	placebo	frequency and severity of hot flashes	Sulpiride significantly reduced the total weekly mean of hot flash frequency (GEE, p(interaction)=.019) and the total weekly mean of severity scores (GEE, p(interaction)=.09, p(group)=.006, p(time)≤.0001) after 4 and 8 weeks of treatment.	Treatment with sulpiride 50 mg/d significantly reduced the frequency and severity of hot flashes.	
<b>Non-pharmacological therapies for vasomotor symptoms</b>								
<b>Cognitive behavioural therapy (CBT)</b>								
<b>(Ye et al., 2022)</b>	Review	14 RCTs comprising 1618 patients with a mean sample size of 116. Of these, 14 studies provided post-treatment data, with 11 of these	CTBT - In most studies, interventions were delivered face to face (91.67%), with the remaining studies using web-based interventions (21.43%). The			CTBT had statistically significant effects on core symptoms, which were mainly maintained at a mean follow-up of more than 23 weeks after treatment. CTBT significantly outperformed control groups in terms of a hot flash, night sweats, depression, anxiety, stress, sleep, fatigue, and QoL, with small to medium ESS.	CTBT is an effective psychological treatment for menopausal symptoms, with predominantly small to moderate effects. The efficacy sustains long-	



		<p>providing follow-up data collected at 23 weeks on average. The missing data of two studies were provided after contacting the authors. The severity of menopausal symptoms was an inclusion criterion in 3 studies. The participants of 8 studies were women with NMS, and those of 6 studies were breast cancer survivors. The treatment format of almost all studies was guided-based (85.71%). Assessing the efficacy of CTBT on menopausal symptoms was the primary aim of all studies.</p>	<p>treatment groups were compared to waitlist (n = 9), care-as-usual (n = 3), or menopause education (n = 2) control groups.</p>			<p>Effects of CTBT on HF/NS: For hot flush problem rating, treated groups outperformed the control groups at post-treatment (g = 0.49, 95% CI 0.34–0.64, p &lt; 0.001; I2 47) and follow-up (g = 0.41, 95% CI 0.25–0.57, p &lt; 0.001; I2 51). The ES of hot flush frequency between CTBT and control groups was 0.36 (95% CI 0.21–0.51, p &lt; 0.001; I2 17), and the pooled effect size was decreased at follow-up (g = 0.29, 95% CI 0.12–0.47, p &lt; 0.001; I2 = 39).</p> <p>Effects of CTBT on depression and anxiety: The pooled effect size and heterogeneity of the 12 comparisons of depression between CTBT and control groups were moderate (g = 0.50, 95% CI 0.34–0.66, p &lt; 0.001; I2 = 51), and the effect was maintained at follow-up (g = 0.44, 95% CI 0.29–0.59, p &lt; 0.001; I2 = 34).</p> <p>Effects of CTBT on sleep and QoL: The ES of the 15 comparisons of sleep between CTBT and control was 0.57 (95% CI 0.39–0.74, p &lt; 0.001, I2 = 57), and the pooled effect size was slightly decreased at follow-up (g = 0.50, 95% CI 0.31–0.68, p &lt; 0.001; I2 58).</p> <p>Effects of CTBT on fatigue and other symptoms: Fatigue levels were assessed in 9 trials. The ESs were small at both post-intervention (g = 0.33, 95% CI 0.14–0.53, p &lt; 0.001; I2 48).</p>	<p>term, although it declining somewhat over time. The efficacy is stronger for NMS on HF/NS, compared with TMS, but no differences in other symptoms. These provide support for international guidelines recommending CTBT as the treatment option for menopausal symptoms and could be incorporated into breast cancer survivorship programs.</p>	
<p><b>(Atema et al., 2020)</b></p>	<p>secondary analysis from RCT</p>	<p>235 women and compared the iCBT groups combined (n = 156) with the control group (n = 79).</p>	<p>None - Patient sociodemographic and clinical characteristics were assessed at baseline. Data included, among others, age, educational level and type of BC treatment</p>	<p>Potential moderators: age, education, time since diagnosis, current endocrine treatment, past oophorectomy, baseline frequency of hot flushes and night sweats as assessed by the HFRS frequency subscales, and baseline levels of psychological distress (HADS)</p> <p>Potential mediators: HF/NS Beliefs and Behavior,</p>	<p>Only educational level significantly moderated the relationship between group allocation and changes in perceived impact of HF/NS ((interaction effect (estimate) = 1.38, 99%CI = 0.05 to 2.71)). That is, patients who completed secondary or vocational education showed a significantly greater decrease in perceived impact of HF/NS (unstandardized regression coefficient (B) = -1.49, 99%CI = -2.39 to -0.59) compared to women who completed college or university (B = -0.11, 99%CI = -1.10 to 0.84). Changes in beliefs about hot flushes in a social context and beliefs about coping/control significantly mediated the relationship between group allocation and changes in perceived impact of HF/NS ((partially standardized indirect effect (estimate) = 0.10, 99%CI = 0.01 to 0.24; estimate = 0.19, 99%CI = 0.07 to 0.39, respectively)) and between group allocation and changes in</p>	<p>BC survivors with a high school/vocational training degree benefited most from the iCBT program for treatment-induced HF/NS, and that the positive effects of the iCBT program on the perceived impact of HF/NS overall symptom burden were mediated by the development of healthier HF/NS beliefs. This suggests that the iCBT program should be tailored to the educational level of women, and that more effort be devoted to strengthening</p>	<p>Secondary analysis of (Atema et al., 2019)</p>	



					assessed through the HF/NS Beliefs and Behavior Scale – Short Form	menopausal symptoms (estimate = 0.07,99%CI = 0.00 to 0.19; estimate = 0.17,99%CI = 0.04 to 0.35, respectively). This indicates that the development of healthier beliefs about hot flushes in a social context and beliefs about one's ability to control and cope effectively with hot flushes contribute to lower perceived impact of HF/NS and reduced menopausal symptom burden in the iCBT groups.	the behavioral component of the program	
<b>(Donegan et al., 2022)</b>	secondary analysis from RCT	51 participants therefore completed all cognitive and behavior measures at least at baseline (26 in CBT-Meno and 25 in the waitlist) and were included in the analyses presented here	The CBT-Meno treatment was offered in 12-week sessions in a group format (up to 8 participants per group; range, 5-8).	Waiting list	Hot Flash Related Daily Interference Scale, the vasomotor subscale of the Greene Climacteric Scale, the Beck Depression Inventory II, the Hot Flush Beliefs Scale, the Dysfunctional Attitudes Scale, and the Hot Flash Behavior Scale (HFBehS).	Assessments were conducted at baseline, 12 weeks after baseline, and 3 months after treatment. CBT-Meno participants reported greater improvements than waitlist in menopause-specific beliefs (Hot Flush Beliefs Scale; $\eta^2p = 0.08-0.12$ ), dysfunctional attitudes (Dysfunctional Attitudes Scale; $\eta^2p = 0.09$ ), and menopause-specific behaviors (HFBehS; $\eta^2p = 0.08-0.12$ ). Within-group analyses showed improvements in CBT-Meno on all variables ( $d = 0.38-1.26$ ) except in cooling strategies ( $d = 0.18$ ). Gains in CBT-Meno were maintained from posttreatment to 3-month follow-up, although a decrease in positive coping behaviors was observed (HFBehS—positive behavior subscale; $d = 0.99$ ).	The CBT-Meno protocol is effective in improving menopause-related symptoms and a broader range of outcomes, including problematic beliefs about menopause, dysfunctional attitudes related to depression, and menopause-specific behaviors.	Secondary analysis of (Green et al., 2019)
<b>(Mewes et al., 2015)</b>	Cost-effectiveness analysis		CBT		cost effectiveness	ITCs for achieving a clinically relevant decline on the FACT-ES for one patient were €1,051 for CBT and €1,315 for PE, compared to the WLC. The corresponding value for the HFERS was €1,067 for CBT, while PE was not more effective than the WLC. Incremental cost-utility ratios were €22,502/ QALY for CBT and €28,078/QALY for PE.	CBT is likely the most cost-effective strategy for alleviating treatment-induced menopausal symptoms in this population, followed by PE. The outcomes are sensitive to a reduction of the assumed duration of the treatment effect from 5 to 3 and 1.5 years	
<b>(Verbeek et al., 2019).</b>	Cost-effectiveness analysis	breast cancer survivors with treatment-induced menopausal symptoms	Internet-based cognitive behavioral therapy	Waiting list	Cost-effectiveness	iCBT was slightly more expensive than the waiting list control, but also more effective, resulting in incremental cost-utility ratios of €23,331/QALY and €11,277/QALY for the guided and self-managed formats, resp. A significant reduction in overall levels of menopausal symptoms or perceived impact of HF/NS resulted in incremental costs between €1460 and €1525 for the guided and €500–€753 for the self-managed format. The estimated annual budget impact	Based on the current trial data, the results indicate that both guided and self-managed iCBT are cost-effective with a willingness-to-pay threshold of well below €30,000/QALY. Additionally, self-managed iCBT is the most cost-	



						for the Netherlands was €192,990 for the guided and €74,592 for the self-managed format.	effective strategy and has a lower impact on healthcare budgets.	
<b>Hypnosis</b>								
<b>(Barton et al., 2017)</b>	RCT	women with and without breast cancer	hypnosis	wait list or sham hypnosis controls	vasomotor symptoms (subjective and objective measures)	Hypnosis was similarly effective in reducing vasomotor symptoms to comparators 900mg/ day gabapentin or 75 mg venlafaxine		
<b>(Elkins et al., 2008)</b>								
<b>(Elkins et al., 2013).</b>		13 women	self-guided			thirteen women suggests that self-guided hypnosis may also be helpful		
<b>(Maclaughlan David et al., 2013)</b>		women with and without breast cancer	hypnosis	wait list or sham hypnosis controls	vasomotor symptoms (subjective and objective measures)	Hypnosis was similarly effective in reducing vasomotor symptoms to comparators 900mg/ day gabapentin or 75 mg venlafaxine		
<b>Other</b>								
<b>(Guthrie et al., 2015)</b>								See above
<b>(Lee et al., 2022b)</b>	Text and opinion		Stellate ganglion block (SGB)		VMS complications	<p>Efficacy - 4 studies + 3 RCTs evaluating SGB for VMS in breast cancer survivors 2 RCTs found no significant difference in VMS decrease compared to other treatment (paroxetine/pregabalin), the third RCT reported reduced VMS frequency, significant compared to sham injection.</p> <p>Complications of SGB are rare but can be significant and include central nervous system complications (eg, convulsions), vascular puncture, neural puncture, esophageal and tracheal puncture, spread of local anesthetic, pneumothorax, and allergic reactions. The published incidence of complications, predating the use of imaging guidance, is 1.7 per 1,000 procedures and correlates mostly with the intravascular injection of anesthesia that may lead to temporary seizures. With the increased use of imaging guidance, complications are less likely, although still relevant considering the critical structures in the injection area</p>	SGB is a promising treatment. Based on existing data, it can be considered with caution in patients with severe VMS whose symptoms are refractory to conservative care, who can afford the treatment, and who have access to this service. Although cost data are limited, preliminary analyses indicate that SGB could balance out the cost of hormone therapy, and some insurance companies cover the cost of SGB in VMS.	Dr. Kling reports consulting for Procter & Gamble and for Triangle Insights Group.
<b>(van Driel et al., 2019b)</b>	REVIEW until June 2017	12 RCTs natural or treatment-induced menopause,			frequency of hot flushes, hot flush bother experienced, other	Short-term (<20 weeks) effects of psychological interventions in comparison to no treatment or control were observed for hot flush bother (SMD -0.54, 95% CI -0.74 to -0.35, P < 0.001,	Psychological interventions reduced hot flush bother in the short and medium-term	



					menopausal symptoms and sexual functioning	I(2) = 18%) and menopausal symptoms (SMD -0.34, 95% CI -0.52 to -0.15, P < 0.001, I(2) = 0%). Medium-term (≥20 weeks) effects were observed for hot flush bother (SMD -0.38, 95% CI -0.58 to -0.18, P < 0.001, I(2) = 16%).  Too few studies on sexual functioning for meta-analysis.	and menopausal symptoms in the short-term. These results are especially relevant for breast cancer survivors in whom HRT is contraindicated. There was a lack of studies reporting on the influence on sexual functioning.		
<b>(Sadeghijoola et al., 2022)</b>	RCT	40 eligible postmenopausal women were randomly assigned to face-to-face (n = 20) and phone counseling methods (n = 20).	face-to-face counseling based on cognitive-behavioral therapy (CBT)  Six counseling sessions	Phone CBT	vasomotor symptoms : hot flashes (HF) and night sweats (NS)	Means of weekly hot flashes and night sweats decreased after intervention in both groups (face-to-face group: HF frequency from 31.92 ± 7.98 to 18.83 ± 7.35, HF severity from 2.24 ± 0.28 to 1.21 ± 0.23, HF duration from 4.22 ± 1.17 min to 2.79 ± 0.91 min, NS frequency from 2.34 ± 0.31 to 1.21 ± 0.24 and NS severity from 1.70 ± 0.34 to 1.03 ± 0.29; and also in the phone counseling group: HF frequency from 33.32 ± 7.77 to 19.53 ± 7.7, HF severity from 2.23 ± 0.24 to 1.20 ± 0.18, HF duration from 4.29 ± 1.23 min to 2.68 ± 0.95 min, NS frequency from 2.33 ± 0.31 to 1.14 ± 0.16 and NS severity from 1.59 ± 0.34 to 1.01 ± 0.30).  There was no significant difference between the groups in terms of HF frequency, severity, and duration, as well as NS frequency and severity (p > 0.05).	Face-to-face and phone counseling methods based on CBT had a similar effect on reducing hot flashes and night sweats. Both methods can be used for women with postmenopausal complications such as hot flashes and night sweats.		
<b>Non-hormonal therapies and the effect on other symptoms or quality of life</b>									
<b>(Cheng et al., 2020)</b>	Review up to March 1, 2020	menopausal sleep disturbance  1,949 perimenopausal and postmenopausal women  7 Trials	antidepressants	Placebo	therapeutic benefit and safety	effectiveness against sleep disturbances: small effect size (Hedge g = 0.24, 95% CI = 0.11-0.38). The efficacy remained significantly better than that of placebo for postmenopausal women (Hedge g = 0.25, 95% CI = 0.04-0.45), participants with hot flashes (Hedge g = 0.18, 95% CI = 0.02-0.34), and those without diagnosis of major depressive disorder (Hedge g = 0.23, 95% CI = 0.06-0.40). There was no difference in therapeutic benefit between sedating and nonsedating serotonergic antidepressants.  Dropout rate did not differ between antidepressant and placebo groups.	serotonergic antidepressants were effective against sleep disturbances in perimenopausal and postmenopausal women. The efficacy remained significant for women without major depressive disorder.		
<b>(Caan et al., 2015)</b>	Secondary analysis of RCT	399 women ages 40–62 years with ≥2 (mean 8.07, SD 5.29) daily VMS	low-dose oral 17-beta-estradiol 0.5-mg/day,	placebo	total and domain scores from the Menopause-Specific	Treatment with both estradiol and venlafaxine resulted in significantly greater improvement in total MENQOL scores compared to placebo (MD for ET at 8 weeks of -0.4; 95% CI -0.7 to	Both low-dose estradiol and venlafaxine are effective pharmacologic agents for	Secondary analysis of (Ensrud et al., 2015)	



			venlafaxine XR 75-mg/day,		Quality of Life Questionnaire (MENQOL) and measures of pain (PEG), depression (PHQ-9), anxiety (GAD-7) and perceived stress (PSS).	-0.2; p<0.001 and for venlafaxine of -0.2; 95% CI -0.5 to 0.0; p 0.04).  QOL domain analyses : that ET had beneficial treatment effects in all domains of the MENQOL except psychosocial, while venlafaxine benefits were observed only in the psychosocial domain.  Neither ET nor venlafaxine improved pain, anxiety or depressive symptoms, although baseline symptom levels were low. Modest benefits were observed for perceived stress with venlafaxine.	improving menopause-related quality of life in healthy women with vasomotor symptoms.	INCLUDE D IN REVIEW Azizi 2022
<b>(Chojnacki et al., 2015)</b>	RCT	64 overweight postmenopausal women, aged 54 - 65 years, with increased appetite	I - fluoxetine (20 mg in the morning) and placebo (in the evening) for 24 weeks  (n = 30)	II - fluoxetine (20 mg in the morning) and melatonin (5 mg in the evening) for 24 weeks  (n = 34)	Hamilton anxiety rating scale (HARS), Beck depression scale (BDI), the insomnia severity index (ISI) and body mass index (BMI)	After 24 weeks, comparable and statistically significant reduction in the level of anxiety and depression was obtained in both groups. In group I, the ISI decreased from 14.9 ± 2.5 points to 10.9 ± 1.9 points (P < 0.05) and in group II from 15.8 ± 2.4 points to 7.7 ± 1.5 points (P < 0.001). In group I no reduction in BMI was achieved whereas in group II this index decreased from 30.9 ± 3.1 to 26.3 ± 3.2 (P < 0.05).	combined administration of fluoxetine and melatonin was useful option to treat mood, sleep and appetite disorders in postmenopausal women.	
<b>(Garland et al., 2017)</b>	RCT	58 breast cancer survivors experiencing daily hot flashes.	electro-acupuncture (EA)  8 weeks	gabapentin (GP)  8 weeks (total dose of 900 mg/d)	primary: change in the total Pittsburgh Sleep Quality Index (PSQI) score.  Secondary: specific PSQI domains.	By the end of treatment at week 8, the mean reduction in PSQI total score was significantly greater in the EA group than the GP group (-2.6 vs -0.8, P = 0.044). The EA also had improved sleep latency (-0.5 vs 0.1, P = 0.041) and sleep efficiency (-0.6 vs 0.0, P = 0.05) compared with the GP group. By week 8, the EA group had improved sleep duration, less sleep disturbance, shorter sleep latency, decreased daytime dysfunction, improved sleep efficiency, and better sleep quality (P < 0.05 for all) compared with baseline, whereas the GP group improved in duration and sleep quality only (P < 0.05).	Among women experiencing hot flashes, the effects of EA are comparable with GP for improving sleep quality, specifically in the areas of sleep latency and efficiency. Larger randomized controlled trials with longer follow-ups are needed to confirm this preliminary finding.	
<b>(Singhal and Shullai, 2016)</b>	prospective comparative study	100 patients with complaints of hot flashes	900 mg of gabapentin daily for 3 months	60 mg of isoflavones daily for 3 months	Primary: change in the hot flash score from baseline.  Secondary: improvement in sleep, depression, and lipid profile.	Both groups showed significant improvement in hot flash score at the end of 12 weeks (82% Group I, 74% Group II; P = 0.076). Statistically significant difference was seen at 12 weeks in sleep quality in favor of gabapentin (P = 0.011) and in depression in favor of isoflavones (0.026). Isoflavone had significant improvement in cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides profiles after 12 weeks (P < 0.001, 0.009, 0.024 and <0.001,	Isoflavone and gabapentin are equally effective in the treatment of hot flashes; however, isoflavones have better response in patients who have associated with complaints of depression and gabapentin is better who have associated	



					Scores baseline and after 2, 4, 8, and 12 weeks	respectively) as compared to gabapentin.	sleep disturbance.	
(Li <i>et al.</i> , 2023b)								See above
(Elkins <i>et al.</i> , 2013)								See above
(Abdelaziz <i>et al.</i> , 2022)	RCT	80 eligible menopausal women who fit the criteria of poor sleep quality	Internet-based Cognitive behavioral therapy (CBT)	control group	sleeping difficulties and chronic insomnia  Pittsburgh Sleep Quality Index, Insomnia Severity Index, and sleep diary.	CBT is effective in reducing sleeping difficulties, particularly sleep quality scores (-3.60 ± 2.76) and insomnia index scores (-5.10 ± 3.54) from baseline.  The program induced significant changes in sleep parameters, such as increased total sleep hours (t = 2.734, p = 0.008), increased sleep efficiency ≥85% (t = 3.558, p = 0.001), and decreased sleep latency (t = 2.180, p = 0.033) compared with control	The strong predictors of having very poor sleep quality were short duration since last menopause, severity of hot flashes, and short duration of sleep difficulties.	
(Ye <i>et al.</i> , 2022)								See above
(Liu <i>et al.</i> , 2022a)	REVIEW Up to March 13, 2022	,138 menopausal women participated in 13 studies	Mindfulness-based interventions (MBIs)		anxiety, depression, stress, and scores of mindfulness	Stress; significantly reduced (SMD = -0.84, 95% CI: -1.64 to -0.05, p = 0.04) Anxiety; no statistical differences (SMD = -0.40, 95% CI: -0.81 to 0.01, p = 0.06) Depression; no statistical differences (SMD = -0.19, 95% CI: -0.45 to 0.07, p = 0.16) Mindfulness; no statistical differences (SMD = 0.37, 95% CI: -0.06 to 0.81, p = 0.09)	MBIs may reduce stress in menopausal women, but their effect on improving anxiety, depression, and mindfulness needs further validation.	

### Evidence to recommendations

QUESTION	<b>What non-hormonal therapies are available for POI?</b>
RECOMMENDATION	<b>HCPs could consider non-hormonal pharmacologic and non-pharmacologic therapies for women with POI that are effective in peri-/postmenopausal women, although evidence specific to POI is lacking.</b>
Desirable effects	There is a lack of evidence specific to women with POI regarding the use of non-hormonal therapies. However, there are some data in older women. It is likely that non-hormonal therapies shown to be effective in older peri-and postmenopausal women are effective in POI but differences may exist and need to be identified.
Undesirable effects	
Certainty of evidence	Indirect evidence
Values	Both women and health professionals have increased interest in non-hormonal, complementary and lifestyle alternatives to HT and are interested in both pharmacological and non-pharmacological options to relieve menopausal symptoms and improve quality of life



Balance of effects

Resource use, equity, acceptability and feasibility

Subgroup considerations (if applicable) Some women with POI may choose against HT, while for other women, including those with estrogen sensitive cancer, studies have shown severe adverse events and HT may not be appropriate. Non-hormonal treatments may be a relevant alternative.



## XII.2 Complementary treatments

### PICO QUESTION: WHAT COMPLEMENTARY TREATMENTS ARE EFFECTIVE FOR MANAGING THE SEQUELAE OF POI?

<b>Population</b>	People with POI of any cause including iatrogenic.
<b>Interventions</b>	Complementary therapies (including but not limited to acupuncture and related techniques, nutrient supplements, herbal medicines, whole systems, mind-body practices)
<b>Control</b>	Any control was included as long as there was a direct comparison against the intervention (for RCTs)
<b>Outcomes</b>	vasomotor symptoms, genito-urinary symptoms, life expectancy, bone health, cardiovascular health, quality of life, sexual function, neurological function

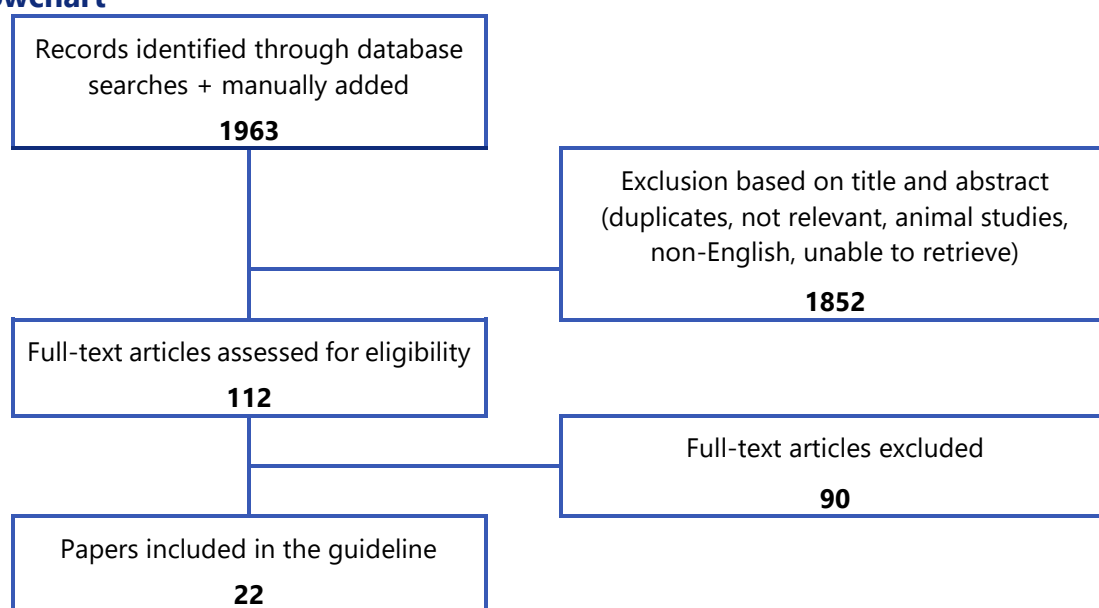
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (botanicals OR "red clover" OR "Trifolium"[Mesh] OR Black cohosh OR "Cimicifuga"[Mesh] OR "Evening primrose oil" OR "Efamol" OR "Chinese herbs" OR "Drugs, Chinese Herbal"[Mesh] OR Ginseng OR "St John's wort" OR "Hypericum"[Mesh] OR "Agnus Castus" OR chasteberry OR "Vitex"[Mesh] OR "Ginkgo biloba" OR "Ginkgo biloba"[Mesh] OR hops OR hop OR "Humulus"[Mesh] OR "sage leaf" OR liquorice OR "Glycyrrhiza"[Mesh] OR "valerian root" OR herbs OR "Traditional Chinese medicine" OR "Medicine, Chinese Traditional"[Mesh] OR Vitamins OR "Vitamins"[Mesh] OR vitamin OR minerals OR "Minerals"[Mesh] OR Acupressure OR acupuncture OR "Acupressure"[Mesh] OR "Acupuncture"[Mesh] OR "Acupuncture Therapy"[Mesh] OR "Alexander technique" OR Ayurveda OR "ayurvedic medicine" OR Osteopathy OR hypnotherapy OR "Psychotherapy"[Mesh] OR "Hypnosis"[Mesh] OR "Mind-Body Therapies"[Mesh] OR reflexology OR "Massage"[Mesh] OR magnetism OR Reiki OR "Therapeutic Touch"[Mesh] OR Phytoestrogens OR "Phytoestrogens"[Mesh] OR pollen OR phytoestrogens OR "Phyto complex" OR Isoflavone OR "Isoflavones"[Mesh] OR nutrient supplements OR probiotic OR "Probiotics"[Mesh] OR Probiotics OR yoga OR "Yoga"[Mesh] OR mindfulness OR "Mindfulness"[Mesh] OR meditation OR "Meditation"[Mesh] OR "Tai Ji"[Mesh] OR "tai chi" OR "Tai Ji" OR relaxation OR "hyaluronic acid" OR "Hyaluronic Acid"[Mesh] OR Hyaluronan OR chiropractic OR "Chiropractic"[Mesh] OR Homeopathy OR Homoeopathy OR "Homeopathy"[Mesh] OR "Complementary therapies" OR "alternative therapies" OR "Complementary Therapies"[Mesh] OR soy OR "Soy Foods"[Mesh])

Literature search was limited to the period between 1/4/2014 and 05/02/2024. Studies and data published prior to 1/4/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 1/4/2014 were retained.



## Flowchart



## Evidence

### Summary of Findings Table

Not applicable

### Evidence table - Chinese herbal medicine

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size + Authors conclusion	Comments
<b>CHM + HT v HT alone</b>							
<b>(Kou et al., 2016)</b>	REVIEW	1352 POI patients from 17 published and unpublished RCTs	TCM combined with HT: variety of CHM formulae including Peikun pills, Yishenkangshuai decoction, and Taijingkangshuai decoction	HT alone	Kupperman Index LH, FSH, E2	3 trials compared Kupperman index scores - TCM combined with HT were better for improvements in perimenopausal syndrome and symptoms (-1.19, 95% CI: -1.77, -0.61, p<0.0001). LH: no significance in reducing LH levels Treatment with a TCM +HT was significantly superior for reducing FSH levels (SMD: -7.08, 95% CI: -9.80,-4.37, P<0.00001). Treatment with a TCM combined with HT was	Compared with HT alone, although no significant effects were observed in the levels of LH, therapy with TCM combined with HT compared to HT alone effectively altered serum hormone levels of FSH (P<0.01) and estradiol (P < 0.01), and improved Kupperman index scores (P<0.01).



						significantly superior for increasing E2 levels (SMD: 3.45, 95% CI: 2.11, 4.79, P < 0.00001).	
<b>(Zhong et al., 2022)</b>	REVIEW	5,675 POI  64 RCTs	patent CHM + HT  12 oral Chinese patent medicines	HT alone	LH, FSH, E2	<p>Total clinical response rate (52 studies, 4702) - total clinical response rate. Among them, GS + HRT, HCDZ + HRT, SW + HRT, KT + HRT, XFZY + HRT, YR + HRT, and LWDH + HRT compared with HRT have statistical significance</p> <p>FSH (59 studies, n=5415). Only KT + HT (MD = -6.78, 95% CrI = -8.47, -5.09), YR + HT (MD = -5.59, 95% CrI = -10.48, -0.92), and LWDH + HT (MD = -5.57, 95% CrI = -9.69, -1.48) had a significant benefit</p> <p>LH (51 studies, 4629). Only GS + HRT (MD = -5.53, 95% CrI = -11.05, -0.03), LWDH+ HRT (MD = -4.17, 95% CrI = -6.65, -1.7), KT + HT (MD = -3.87, 95% CrI = -4.95, -2.72), and YR + HT (MD = -3.03, 95% CrI = -6.27, -0.17) had a significant benefit</p> <p>E2 (58 studies, 5,315). ZHC + HRT (MD = 41.8; 95% CrI = 21.23, 62.41; SUCRA = 95.95%) had the highest rate of impact on</p> <p>A total of 13 studies involving 1,168 patents reported the adverse reactions. Only KT + HRT had a significant benefit compared with HT. KT + HT (OR = 0.44, 95% CrI = 0.21, 0.85, SUCRA = 81.86%) shows the best, and ZHC + HT (OR = 0.45, 95% CrI = 0.03, 4.3, SUCRA = 70.18%) was as follows</p>	
<b>(Liu et al., 2019)</b>	REVIEW	1178 POI patients  12 RCTs	Kuntai capsule + HT	HT alone	total effective treatment rate  lipid parameters  Kupperman Index  LH, FSH, E2	<p>total effective treatment rate was higher for KTC+HT compared to HT-only</p> <p>Lipid Parameters; triglycerides (WMD -0.55; 95% CI -0.67 to -0.43; 3 studies; n=290; I2 0%; p&lt;0.00001; low certainty evidence), total cholesterol (-0.63; 95% CI -0.74 to -0.52; 3 studies; I2 0%; P&lt;0.00001; low certainty evidence), LDL cholesterol (WMD -0.62; 95% CI -0.75 to -0.49; 3 studies; I2 0%; p&lt;0.00001; low certainty evidence) but not for HDL (very low certainty evidence).</p> <p>KI: MD -5.99; 95% CI -8.04 to -3.94; 1 RCT; n=100; p&lt;0.00001)</p> <p>LH : MD -3.47; 95% CI -5.68 to -1.26; 11 trials; n=1100; I<sup>2</sup> 92%; p=0.002</p> <p>FSH : MD -8.15; 95% CI -10.44 to -5.86; 11 trials; n=1100; I<sup>2</sup> 83%; p&lt;0.00001</p> <p>E2 : MD 17.21; 95% CI 10.16 to 24.26; 11 trials; n=1100; I<sup>2</sup> 98%; p&lt;0.00001</p>	



<b>(Ma et al., 2020)</b>	REVIEW		Kuntai capsule + Climen	HT (Climen)	menopausal symptoms (KI)  LH, FSH, E2	KI: MD -3.86, -4.92 to -2.8, I2=83%, 5 trials, n=606, P<0.00001, very low quality evidence).  FSH (MD -8.987, -11.94 to -6.12, I2=74%, 10 trials, n=990, p<0.00001)  LH (-7.01, -10.77 to -3.24, I2=92%, 5 trials, n=460, p=0.0008)  E2 (MD 11.38, 7.11 to 15.64, I2=87%, 10 trials, n=990, p<0.00001)	
<b>CHM versus HT</b>							
<b>(Li et al., 2020b)</b>	REVIEW		Chinese herbal medicine formulae that are designed for the Chinese medicine functions of tonifying the kidney (bushen) and activating blood (huoxue)	HT	KI scores  LH, FSH, E2	KI: MD -0.78, -1.24 to -0.31, I2=81%, 7 trials, n=452, p=0.001, very low certainty evidence).  E2 levels (SMD: 0.70; 95% CI: 0.14, 1.26; P < 0.05, I2 95%),  FSH (SMD: -0.50; 95% CI: -0.81, -0.18; P < 0.05, I2 95%)  LH – no difference	
<b>CHM v placebo</b>							
<b>(Cao et al., 2018)</b>	RCT	146 POI	Chinese herbal formula Yangyin Shugan formula	placebo	Chinese MENQOL  FSH, AMH, AFC, E2	Total score: 38.0 + 7.5 vs 65 +5, Vasomotor 4 + 2 vs 7 +1, Psychosocial 15 + 3 vs 17 + 2, Physical 14 + 4 vs 33 + 3, Sexual 3 + 2.5 vs 7 + 1.5 (P<0.01 for all comparisons)  FSH: 10.11 + 4.63 v 32.66 + 13.81  AMH : 1.76 + 2.11 v 0.73 + 1.61 AFC: 6.97 + 3.35 vs 4.43 vs 3.06  E2: no difference	
<b>CHM + acupuncture v MHT alone</b>							
<b>(Li et al., 2020b)</b>	Review	1030 POI patients, 14 RCTs	Acupoint stimulation and CHM	HT	KI  adverse events  FSH, LH  normalisation of menstrual cycles	KI: 14.41 + 2.97 vs 25.69 + 3.25; p<0.05, 1 RCT, n=56 (after 3 months)  Adverse events : RR 0.31; 95% CI 0.04 to 2.54; 5 trials; n=387; I <sup>2</sup> 42%; p=0.28  FSH : MD -2.88; 95% CI -5.00 to -0.76; 12 trials; n=778; I <sup>2</sup> 0%; p=0.008  LH: no difference  normalisation of menstrual cycles : RR 2.06; 95% CI 1.62 to 2.61; 14 trials; n=1030; I <sup>2</sup> 26%; p<0.00001	
<b>(Yi et al., 2021)</b>	RCT	119 POI patients with deficiency-	Wenjing Decoction and Tiaobu Chongren acupuncture and	HT (3 months)	Chinese medicine syndrome score,	Serum E2 and AMH levels in the two groups increased, while FSH and LH levels decreased compared with before treatment, and the observation group	



		cold syndrome	moxibustion therapy (3 months)		E2, FSH, LH, AMH, AFC  mean ovarian volume, and endometrial thickness	improved significantly compared with the control group (P<0.05). The bilateral AFC, mean ovarian volume, and endometrial thickness of the 2 groups increased compared with before treatment, and the observation group was higher than the control group (P<0.05).	
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### Evidence to recommendations

QUESTION	What complementary treatments are effective for managing the sequelae of POI?
RECOMMENDATION	<b>Women who are considering the use of Chinese herbal medicine for the management of menopausal symptoms and metabolic risk should be informed that the evidence for benefit is limited but the intervention does not appear to cause significant harm in the short term.</b>
Desirable effects	The evidence does not support recommending TCM with or without acupuncture for the management of menopausal symptoms and metabolic risk.
Undesirable effects	Adverse events were included in the MAs with reassuring results.
Certainty of evidence	
Values	It seems relevant to inform women with POI that have an interest in using TCM with or without acupuncture, but this seems not to be of value for all women with POI, and hence it is specified as such in the recommendation
Balance of effects	The evidence for benefit is limited but the intervention appears to not cause significant harm in the short term.
Resource use, equity, acceptability and feasibility	There are general restrictions to the feasibility of applying TCM with or without acupuncture in a Western context, and some of the evaluated TCM may not be available.
Subgroup considerations (if applicable)	NA

### Evidence table - Acupuncture and moxibustion

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>(Jo et al., 2015)</b>	REVIEW	620 participants	Acupuncture + HT (3 RCTs) Acupuncture + CHM (1 RCT)	HT alone	KI  FSH, LH, E2	KI; 2 RCTs Dong et al. reported that mean KI was	Acupuncture significantly lowered serum FSH levels and more women	



		8 RCTs (of which one unpublished)	Other results, see below		resumption of menstruation	<p>reduced in both groups, from 16.65 to 5.43 and from 16.83 to 11.90</p> <p>Li et al. KI reduced in both groups after treatment.</p> <p>After 6 months from the final treatment, there was a significant difference between acupuncture vs control.</p> <p>FSH : MD -11.40; 95% CI -19.61 to -3.2, 3 trials, n=83+78; I<sup>2</sup>=0%, p=0.006</p> <p>resumption of menstruation: RR 1.20; 95% CI 1.03 to 1.39; 4 trials; n=233; I<sup>2</sup> 37%; p=0.02</p> <p>LH: MD -19.81; 95% CI -34.14 to -5.48; 2 trials; n=80; I<sup>2</sup> 0%; p=0.007</p> <p>E2 : no diff (2 trials, n=161).</p>	receiving acupuncture reported resumption of menses. However, the results should be interpreted with caution due to a small number of participants, high risk of bias for blinding, and likely publication bias.	
<b>Acupuncture v HT</b>								
<b>(Jo et al., 2015)</b>	REVIEW	620 participants  8 RCTs (of which one unpublished)	3 acupuncture + HT  1 Acupuncture + CHM  Acupuncture alone (4 RCTs)  Other results, see above	HT alone	KI  FSH, LH, E2  resumption of menstruation	<p>KI: no data</p> <p>FSH: MD -8.60; 95% CI -13.58 to -3.62; 3 trials, n=360; I<sup>2</sup> 23%; p=0.007</p> <p>Resumption of menstruation: RR 1.32; 95% CI 1.10 to 1.59; 4 trials; n=381; I<sup>2</sup> 62%; p=0.003</p> <p>E2 : MD 42.61; 95% CI 6.4 to 78.83; 3 trials; n=318; I<sup>2</sup> 97%; p=0.02</p> <p>LH no diff (2 trials; n=198)</p>		
<b>{Wxu, 2017 #2395}</b>	RCT	80 women	electroacupuncture and moxibustion	HT (Climen)	night sweat score (ranging 0 to 4)  After 6 months treatment	lower night sweat score at end of treatment (1.17 + 0.82 vs 1.53 + 0.65, p<0.05)		



{Chen, 2014 #2399}	Case series	31 women	acupuncture for 3 months	NA	anxiety (Self-Rating Anxiety scale)  KI	Anxiety: reduced from 54±6 to 41±7 (Z=4.82, p= 0.000).  KI reduced from 18±4 to 12±2 (Z=4.71, p= 0.000).		
{Cao et al., 2022}	REVIEW							Same studies as (Jo et al., 2015, Li et al., 2020b)
<b>Moxibustion</b>								
{Wang, 2021 #2394}	RCT	66 women with POI	moxibustion with HT	HT alone for 3 months	AFC ovarian volume  serum estrogen (E2), FSH, interleukin-21 (IL-21) and vascular endothelial growth factor (VEGF)	intervention group compared to control  AFC (3.06±1.2 vs 2.33±0.96), ovarian volume (3.30 + 1.10 vs 2.62 + 0.76 cm3) E2 (77.57±9.21 vs 67.16±9.95pmol/L) FSH (50.31±6.19 vs 59.12±6.82 IU/L) in (p<0.05 for all)		
<b>Korean medicine</b>								
{Jang, 2022 #2401}	case series	3 women with POI (age range 26-39)	Korean herbal medicine, electroacupuncture and moxibustion, and placental acupuncture for at least 3 months		FSH hot flushes pregnancy	All patients experienced a decrease in FSH to < 40. One woman conceived 2 years after starting treatment. Two women had resolution of hot flushes while the third woman had not been experiencing hot flushes at baseline.		

### Evidence to recommendations

QUESTION	<b>What complementary treatments are effective for managing the sequelae of POI?</b>
RECOMMENDATION	<b>Women should be informed that there is limited evidence on the effectiveness of acupuncture for menopausal symptoms in POI, and the evidence does not suggest a benefit from adding acupuncture to HT.</b>
Desirable effects	Evidence is insufficient to support a recommendation for acupuncture in addition to HT for the management of menopausal symptoms. There does not seem to be an added benefit.
Undesirable effects	Adverse events were included in the MAs and reassuring
Certainty of evidence	The evidence is limited to a meta-analysis, a recent study using a non-validated score, and a case series



Values	It seems relevant to inform women with POI that have an interest in using acupuncture, but this seems not to be of value for all women with POI, and hence it is specified as such in the recommendation
Balance of effects	The evidence for benefit is limited but the intervention appears to not cause significant harm in the short term.
Resource use, equity, acceptability and feasibility	
Subgroup considerations	

### Evidence table - Nutrients

Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>{Safiyeh et al., 2021}</b>	RCT	67	selenium and Vitamin E supplements (3 months)	matched placebo	AMH AFC mean ovarian volume	AMH: MD 0.59, 0.48 to 0.71, p<0.001 AFC : MD 5.08, 4.36 to 5.08, p<0.001 mean ovarian volume: MD 2.17, 1.87 to 2.47, P<0.001		
<b>{Goyco Ortiz, 2019 #2400}</b>	Case report	34-year-old woman with POI due to chemotherapy for non Hodgkin's lymphoma, and a history recurrent pregnancy loss and homozygous for MTHFR C677T variant	methylfolate 800 mg daily with a B vitamin supplement (dose and ingredients unspecified).	NA	pregnancy	spontaneous conception after 3 months of treatment.  - vanishing twin at 9 weeks - oligohydramnios / preeclampsia at 36 weeks  Delivery (CS) at 37 weeks. A healthy male baby was delivered weighing 2.69 kg		

### Evidence to recommendations

QUESTION	<b>What complementary treatments are effective for managing the sequelae of POI?</b>
RECOMMENDATION	<b>Women who are considering using other nutrient supplements and herbal medicines should be informed that there is insufficient evidence to support their use.</b>
Desirable effects	Studies focus on AMH/AFC/ovarian volume which are only surrogate marker for fertility. For Selenium/vitamin E treatment, there is one trial shows benefit.  For other nutrients/supplements and herbal medicines, there is no evidence supporting any benefit.
Undesirable effects	There seem to be no harms; but the evidence is too limited to make any conclusion on harms
Certainty of evidence	
Values	Even if no harm was demonstrated, it was suggested to be careful in making a recommendation to avoid overdosing. Furthermore, inappropriate and misuse of Selenium supplements should be avoided if there is insufficient data of efficacy.
Balance of effects	
Resource use, equity, acceptability and feasibility	In theory, nutrient supplements and vitamins should be limited to addressing a deficiency



Subgroup considerations

### Evidence table - Phyto-estrogens

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Cardiovascular health</b>								
<b>(Błaszczyk et al., 2022)</b>	REVIEW	Postmenopausal women  42 RCTs: red clover (n=7), soy protein (n=15), soy isoflavones alone (13), (flaxseed (n=7)	flaxseed, soy protein, soy isoflavones and red clover isoflavone		level of serum lipids	<p><u>Flaxseed</u></p> <p>TC : WMD -0.26; 95% CI: -0.38 -0.13; 7 RCTs; n=452; I<sup>2</sup> 6%; p = 0.0001</p> <p>LDL-C: WMD -0.19; 95% CI: -0.30--0.08; 7 RCTs; n=417; I<sup>2</sup> 0%; p=0.0006</p> <p>HDL-C: WMD -0.06; 95% CI -0.11--0.01; 7 RCTs; n= 418; I<sup>2</sup> 0%; p=0.0150</p> <p>TG: WMD -0.03; 95% CI: -0.12--0.07; 7 RCTs; n=452; I<sup>2</sup> 9%; p =0.5452</p> <p><u>Soy Protein</u> (with/out Isoflavones)</p> <p>TC: WMD -0.15; 95% CI: -0.25--0.05; 18 RCTs, n=1322 I<sup>2</sup> 26%; p = 0.0048</p> <p>LDL-C: WMD= -0.15; 95% CI: -0.25--0.05; 16 RCTs, n=1234; I<sup>2</sup> 17%; p = 0.0067</p> <p>HDL-C: WMD 0.05; 95% CI: 0.02--0.08; 18 RCTs, n=1322; I<sup>2</sup> 0%; p = 0.0034.</p> <p>TG: WMD = -0.08; 95% CI: -0.19 to 0.03; 18 RCTs, n=1322; I<sup>2</sup> 61% p = 0.1462</p> <p><u>Red clover</u></p> <p>TC : WMD = -0.11; 95% CI: -0.18--0.04; 8 RCTs; n=884; I<sup>2</sup> 0%; p = 0.0017</p> <p>LDL-C: WMD = -0.01; 95% CI: -0.13 to 0.10; 8 RCTs; n=884; I<sup>2</sup> 49%; p = 0.8230</p> <p>HDL-C : WMD = 0.04; 95% CI: 0.01 to 0.07; 8 RCTs; n=884; I<sup>2</sup> 0%; p = 0.0165</p> <p>TG : WMD = -0.05; 95% CI: -0.17--0.06; 8 RCTs; n=956; I<sup>2</sup> 76%; p = 0.3713</p>		
<b>Vasomotor symptoms</b>								
<b>(Kanady et al., 2021)</b>	Review	postmenopausal women  12 RCTs, 8 trials (10 comparisons) assessed hot flushes	red clover (most studies: dose of 40–80 mg/d RCIE)	placebo	hot flush frequency	Of the 10 comparisons, 6 showed a reduction in HF, 4 showed no difference.  HF treatment vs placebo: WMD -1.73 HF/d, 95% CI -3.28 to -0.18; 8 RCTs; n=751; I <sup>2</sup> 87%; p = 0.0292		
<b>Sexual function</b>								
<b>(Najaf Najafi and Ghazanfar, 2018)</b>	Review up to 29 September 2017	16 trials in review, only 5 in meta-analysis	Phytoestrogens <ul style="list-style-type: none"> <li>• Soy</li> <li>• Red clover</li> <li>• Korean red ginseng and flaxseed</li> </ul>		sexual disorders and severity of dyspareunia	<u>Soy</u> No effect on sexual function (SMD = 1.099; 95% CI: -3.033 to 0.835, p = 0.265; I <sup>2</sup> 80%; p = 0.006;	Phytoestrogens have various effects on sexual function. Published	



			<ul style="list-style-type: none"> <li>Other phytoestrogens (isolated from <i>Lepidium meyenii</i>, <i>Foeniculum vulgare</i>, and maritime pine bark and <i>Trigonella foenum-graecum</i> L.).</li> </ul>			<p>random-effect model; 3 trials)</p> <p>Improved dyspareunia in 1 study (<math>p &gt; 0.05</math>)</p> <p><u>Red clover</u></p> <p>No effect on sexual function (SMD = -0.087; 95% CI: -0.936 to 0.763, <math>p = 0.842</math>; <math>I^2</math> 0%, <math>p = 0.397</math>; fixed-effect model; 2 trials) and sexual satisfaction (<math>p &gt; 0.05</math>).</p> <p><u>Korean red ginseng and flaxseed</u></p> <p>No significant effect on sexual function.</p> <p><u>Other phytoestrogens</u></p> <p>significantly improved sexual function</p>	<p>reports show that maritime pine bark, <i>T. foenum-graecum</i> L., and <i>F. vulgare</i> could be considered as agents to overcome sexual dysfunctions while soy, red clover, genistein, and flaxseed had no promising effects on these conditions.</p>	
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Evidence table - Black cohosh and other supplements

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Black cohosh</b>								
<b>(Leach Matthew and Moore, 2012)</b>	Review	2027 Women with menopausal symptoms (perimenopausal or postmenopausal)	oral mono-preparations of black cohosh at a median daily dose of 40 mg, for a mean duration of 23 weeks.	placebo, hormone therapy, red clover and fluoxetine	vasomotor symptoms, vulvovaginal symptoms, menopausal symptom scores and adverse effects.	<p>There was no significant difference between black cohosh and placebo in the frequency of hot flushes (mean difference (MD) 0.07 flushes per day; 95% CI -0.43 to 0.56 flushes per day; <math>P=0.79</math>; 393 women; 3 RCTs ; <math>I^2=47%</math>) or in menopausal symptom scores (standardised mean difference (SMD) -0.10; 95% CI -0.32 to 0.11; <math>P = 0.34</math>; 357 women; 4 trials; <math>I^2 = 21%</math>).</p> <p>Compared to black cohosh, hormone therapy significantly reduced daily hot flush frequency (three trials; data not pooled) and menopausal</p>	There is currently insufficient evidence to support the use of black cohosh for menopausal symptoms. However, there is adequate justification for conducting further studies in this area. outcome data.	The quality of included trials was generally unclear, owing to inadequate reporting.



						<p>symptom scores (SMD 0.32; 95%CI 0.13 to 0.51; P=0.0009; 468 women; 5 trials; I2 = 69%).</p> <p>Comparisons of the effectiveness of black cohosh and other interventions were either inconclusive (because of considerable heterogeneity or an insufficient number of studies) or not statistically significant. Similarly, evidence on the safety of black cohosh was inconclusive, owing to poor reporting. There were insufficient data to pool results for health-related quality of life, sexuality, bone health, vulvovaginal atrophic symptoms and night sweats. No trials reported cost-effectiveness data.</p>		
<b>Ginseng</b>								
<b>(Lee et al., 2022a)</b>	Review inception to April 2022	postmenopausal women  15 RCTs	Ginseng (any type)	(any type)	placebo	menopausal symptoms  hot flashes  sexual function  QoL  vaginal maturation index and vaginal pH  endometrial thickness	<p>Ginseng reduced menopausal symptoms in 3 studies (n = 515; SMD: -0.40, 95% CI: -0.73 to -0.07, P = 0.02)</p> <p>lowered hot flashes (n = 515; SMD: -0.34, 95% CI: -0.66 to -0.01, P = 0.04).</p> <p>sexual function – no benefit (n = 491; SMD: 0.31, 95% CI: -0.30 to 0.92, P = 0.32, 3 RCTs).</p>	<p>Ginseng can significantly reduce hot flashes, menopausal symptoms, and quality of life in menopausal women. In contrast, neither KRG nor ginseng appeared to have any direct effect on sexual dysfunction, hormones or biomarkers, or endometrial thickness. More rigorous RCTs are needed to</p>



						quality of life score (3 RCTs, n = 515, SMD: -0.31, 95% CI: -0.61 to -0.01, P = 0.05).	overcome the current limitations.	
						vaginal maturation index / vaginal pH. (no effect, 2 RCTs)		
						No effect of Korean red ginseng (KRG) on endometrial thickness (3 RCTs)		
<b>Fennel</b>								
<b>(Lee et al., 2021)</b>	Review	postmenopausal women  7 RCTs	fennel (Foeniculum vulgare Miller)	placebo	menopausal symptoms  sexual function  QoL  psychological health	menopausal symptoms: benefit (n = 145, 2 RCTs, SMD -1.32 [-1.76, -0.87], p < 0.00001).  No effect on other outcomes  No serious adverse events were reported.	Our review presented evidence for fennel improving menopausal symptoms. However, the effectiveness and safety of fennel in improving QoL, and psychological health remains unclear.	

### Evidence to recommendations

QUESTION	<b>What complementary treatments are effective for managing the sequelae of POI?</b>
GOOD PRACTICE POINT	<b>The guideline group recommends that HCPs should enquire about use of complementary therapies and incorporate individual patient values and preferences into shared decision making about their use.</b> <b>Complementary therapies should not be used to replace HT as there is insufficient evidence on their effectiveness for prevention of long-term sequelae of POI.</b>
Desirable effects	Small – the magnitude of effects are generally small
Undesirable effects	Varies – there is evidence from meta-analyses that adverse events are not increased in the intervention groups compared to control (mostly HT alone) however an indirect undesirable effect is the harm of choosing to use complementary therapies instead of HT and therefore not accessing primary prevention benefits of HT
Certainty of evidence	The certainty of evidence is low to very low and has been downgraded for reasons such as high risk of bias, high heterogeneity and small sample sizes/small number of trials.
Values	Based on non-disclosure in significant proportions of patients, it was considered relevant to formulate a good practice point to enquire on the use of complementary treatments
Balance of effects	More emphasis was put on the prevention of harm - While some interventions could have some benefit for relieving vasomotor symptoms, using them instead of HT could be harmful as the patients are not protected against the longterm sequelae linked to estrogen deficiency



Resource use, equity, acceptability and feasibility	Moderate costs – as complementary therapies require an out of pocket cost - Feasibility varies per region. The interventions are acceptable to patients.
Subgroup considerations	NA

QUESTION	<b>What complementary treatments are effective for managing the sequelae of POI?</b>
RECOMMENDATION	<b>Complementary therapies should not be used to replace HT as there is insufficient evidence on their effectiveness for prevention of long-term sequelae of POI.</b>
Desirable effects	Most studies are looking primarily on vasomotor symptoms, which is relevant for women with natural menopause. In POI patients, however, interventions should be evaluated beyond vasomotor systems and consider all aspects of POI.  The magnitude of effects are generally small
Undesirable effects	Varies – there is evidence from meta-analyses that adverse events are not increased in the intervention groups compared to control (mostly HT alone) however an indirect undesirable effect is the harm of choosing to use complementary therapies instead of HT and therefore not accessing primary prevention benefits of HT
Certainty of evidence	The certainty of evidence is low to very low and has been downgraded for reasons such as high risk of bias, high heterogeneity and small sample sizes/small number of trials.
Values	
Balance of effects	More emphasis was put on the prevention of harm - While some interventions could have some benefit for relieving vasomotor symptoms, using them instead of HT could be harmful as the patients are not protected against the longterm sequelae linked to estrogen deficiency
Resource use, equity, acceptability and feasibility	Moderate costs – as complementary therapies require an out of pocket cost - Feasibility varies per region. The interventions are acceptable to patients.
Subgroup considerations	NA



## XII.3. Lifestyle management options

### PICO QUESTION – WHAT ARE THE LIFESTYLE MANAGEMENT OPTIONS FOR POI?

<b>Population</b>	People with POI of any cause including iatrogenic.
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• Lifestyle modification</li> <li>• diet / Food Habits / Weight loss</li> <li>• exercise</li> <li>• Cooling strategies</li> </ul>
<b>Control</b>	Any control was included as long as there was a direct comparison against the intervention (for RCTs)
<b>Outcomes</b>	vasomotor symptoms, genito-urinary symptoms, life expectancy, bone health, cardiovascular health, quality of life, sexual function, neurological function

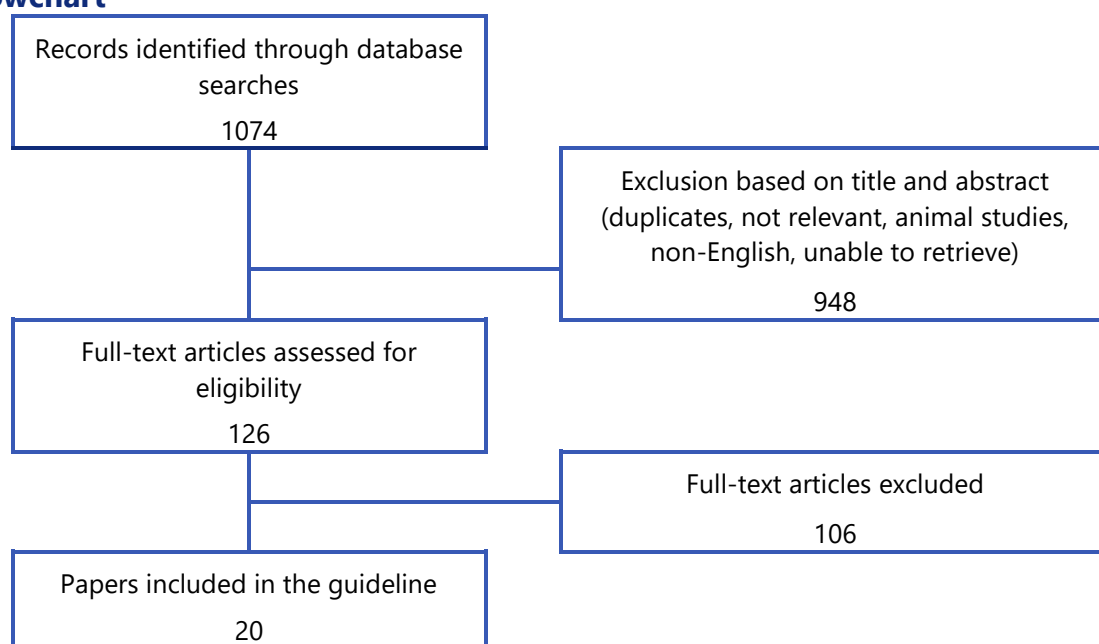
### Search strings

Database	Search String
<b>PUBMED</b>	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency" OR "gonadal dysgenesis" OR "Premature Ovarian Failure" OR "early menopause" OR "premature menopause" OR "hypergonadotropic hypogonadism" OR "Ovarian dysgenesis" OR "Primary ovarian failure" OR "Hypergonadotropic amenorrhea" OR "surgical menopause" OR "Bilateral Salpingo-Oophorectomy" OR "Bilateral Oophorectomy" OR "iatrogenic menopause" OR "radiation menopause") AND (Lifestyle modification OR diet OR "Food Habits"[Mesh] OR "Diet Therapy"[Mesh] OR exercise OR "Exercise Therapy"[Mesh] OR lifestyle OR "Healthy Lifestyle"[Mesh] OR "Life Style"[Mesh] OR "weight loss" OR "Weight Loss"[Mesh] OR "cooling strategies" OR cooling)
<b>PUBMED (FILTER: reviews)</b>	2 ("menopause"[Mesh] OR menopause) AND (Lifestyle modification OR diet OR "Food Habits"[Mesh] OR "Diet Therapy"[Mesh] OR exercise OR "Exercise Therapy"[Mesh] OR lifestyle OR "Healthy Lifestyle"[Mesh] OR "Life Style"[Mesh] OR "weight loss" OR "Weight Loss"[Mesh] OR "cooling strategies" OR cooling)
<b>COCHRANE</b>	

Literature search was limited to the period between 01/01/2014 and 21/10/2022, with an update of the literature searches on 05/02/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Evidence table

Ref.	Study Type	Patients	Intervention	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>Menopause symptoms</b>								
(Noll <i>et al.</i> , 2021)	Systematic review	Postmenopausal women; (> 12 months of amenorrhea caused by ovarian failure);  RCTs and observational studies Sample sizes in the included articles ranged from 91 to 148,93.	nutrition		Menopausal symptoms	Studies evaluating diet quality or dietary patterns showed an association between lower intensity of psychological symptoms, sleep disorders, and vasomotor, urogenital, and somatic symptoms and higher consumption of vegetables, whole grains, and unprocessed foods. Also, the intensity of these symptoms is associated with high-processed foods, saturated fats, and sugars. Regarding nutrient and/or specific food, the studies indicated an association between caffeine intake and type of fat intake and the intensity of menopausal symptoms.	Dietary intake was shown to be associated with intensity of menopausal symptoms. Postmenopausal women with high-quality dietary or health patterns, which included the consumption of vegetables, fruits, and whole grains, generally showed lower intensity of psychological symptoms, somatic symptoms, vasomotor symptoms, sleep disorders, and urogenital symptoms. More severe psychological symptoms, sleep disorders, vasomotor symptoms, and somatic symptoms were shown to be associated with diets high in processed foods.	Most studies were cross-sectional with no comparison group. There was only one RCT with a healthy control group.



							saturated fat, refined grains, fried foods, fatty meats, sweets, and sugar-sweetened beverages.	
<b>(Daley et al., 2014)</b>	Systematic review	Women with surgical or spontaneous menopause, in the perimenopausal or postmenopausal period, experiencing any vasomotor symptoms at baseline and	Exercise was defined as structured exercise and/or physical activity achieved through active living. Trials that compared any type of exercise intervention with no active treatment or with other treatments were included.	no active treatment or other treatments	Primary: vasomotor symptoms, defined as hot flushes and/or night sweats. Vasomotor symptoms assessed using the vasomotor subscale of the Women's Health Questionnaire, Greene Climacteric Scale, Kupperman Index.	Exercise vs no active treatment (3 studies, n = 454 women), no evidence of a difference between groups in frequency or intensity of vasomotor symptoms (SMD -0.10, 95% CI -0.33 to 0.13, 3 RCTs, 454 women, I <sup>2</sup> = 30%, low-quality). No difference between groups in the frequency or intensity of vasomotor symptoms  Exercise vs yoga (SMD -0.03, 95% CI -0.45 to 0.38, 2 studies, n= 279 women, I <sup>2</sup> = 61%, low-quality).  None of the trials found evidence of a difference between groups with respect to adverse effects, but data were very scanty.	Evidence was insufficient to show whether exercise is an effective treatment for vasomotor menopausal symptoms. Evidence was also insufficient to reveal the relative effectiveness of exercise and yoga. One small study suggested that HT is more effective than exercise.	
<b>(Liu et al., 2022b)</b>	Systematic review	Women with spontaneous or iatrogenic menopause;	Exercise intervention involving >1 session of structured exercise (specified frequency, intensity, time or type) where direct effects of exercise could be isolated from other intervention effects	No intervention	Frequency, severity and severity index (severity multiplied by total frequency) of VMS	Compared to no-treatment, exercise significantly improved severity of vasomotor symptoms (10 studies, SMD 0.25; 95% CI: 0.04 to 0.47, p=0.02, very low certainty); the effect size was attenuated when studies with a high risk of bias were excluded (SMD=0.11, 95% CI: 0.03 to 0.26, p=0.13).  No significant changes in vasomotor frequency were found between exercise and control (SMD=0.14, 95% CI 0.03 to 0.31, p=0.12, high certainty)	Exercise training appears to significantly improve VMS severity, but more evidence is needed. Currently, exercise does not alleviate the symptom frequency.	
<b>Quality of life</b>								
<b>(Carcelén-Fraile et al., 2020)</b>	Systematic review	peri- and postmenopausal women	physical exercise intervention	In RCTs, the comparison groups were no intervention/ usual activity or general education material	Primary: sexual function and quality of sexual life related to menopausal symptoms. Secondary: impact of menopausal symptoms on QOL, general and condition-specific health-	The most commonly recommended training programs are based on exercising pelvic floor muscles, as they seem to have the largest impact on sexual function. Mind-body disciplines also helped in managing menopausal symptoms. However, as far as the most traditional programs were concerned, aerobic exercises showed inconsistent results and resistance training did not	The results do not allow for clear conclusions. On the one hand, pelvic floor muscles exercises are the most common type of exercise in these studies and the one that seems most beneficial for sexual function, similarly to how mind-body disciplines improve the impact of menopausal symptoms on the quality of sexual	



					related QOL, and symptoms of depression and anxiety.	seem to convey any benefits.	life. However, concerning the most traditional forms of exercise, aerobic training yielded inconsistent results and resistance training failed to produce any improvement.	
<b>(Shorey et al., 2020)</b>	Systematic review	women in their perimenopausal period (pre-, during, post up to 1year) in Asia  RCTs, clinical trials, intervention studies with at least one control group and quasi-experimental studies  23 studies - 1,812 women	exercise-based interventions including aerobic, strengthening/high impact, walking, Pilates, square dance, stretching, or Rusie Dutton Thai (9 studies)  Aromatherapy (5) yoga (4) Multi-modal interventions (education and exercise-based) (3)  autogenic relaxation (1) qigong (1)  strengthening exercise and high-impact exercise. (1)		Outcomes: quality of life, menopausal symptoms, and/or depression	Significant effects in exercise-based interventions and mind-body therapies were found for quality of life, menopausal symptoms, and depression but not for hot flashes.	Exercise-based interventions and MBTs suggests effectiveness in improving quality of life, menopausal symptoms, and depression among Asian perimenopausal women. However, no significant intervention effect was found for hot flashes.	
<b>(Nguyen et al., 2020)</b>	Systematic review	Women with at least one menopausal symptom due to the natural decline of reproductive hormones, comprehensive cancer treatment program, hysterectomy, and/or POI  Only RCTs  8 RCTs - 882 women	exercise was defined as a planned, structured, repetitive, and purposeful subcategory of physical activity, aimed at the maintenance or improvement of one or more components of physical fitness.  No restrictions on the frequency and duration, instructors or self-delivered.  The effects of pelvic floor muscle training (PFMT), yoga and yoga-like postures, aerobic training, walking, and self-directed exercise programs (e.g., swimming, running, cycling)	No active treatment	Primary: general health  Secondary: menopause-specific QoL scores  Measured by 3 generic and 11 menopause-specific QoL questionnaires.	Positive effects of exercise on physical and psychological QoL scores were found in women with menopausal symptoms. However, there was no evidence for the effects of exercise on general, social, and menopause-specific QoL scores. In meta-analyses, while yoga significantly improved physical QoL, its effects on general, psychological, sexual, and vasomotor symptoms QoL scores as well as the effect of pelvic floor muscle training (PFMT) on general QoL were not significant.	Positive effects of exercise on physical and psychological QoL scores in women with menopausal symptoms. However, there were no evident effects of exercise on general, social, and menopause-specific QoL scores in women after exercise interventions compared with no active interventions. Yoga and PFMT, respectively, were the most common interventions for women with menopausal and urinary symptoms in the included studies. In our meta-analyses, while yoga significantly improved physical QoL, its effects on	



			were investigated.				general, psychological, sexual, and vasomotor symptoms	
<b>(Nguyen et al., 2024)</b>	meta-analysis	5 RCTs including 268 postmenopausal women (mean age 53-67 years) with urinary symptoms	pelvic floor muscle training, commonly known as Kegel's exercise (protocol: 8-12 sessions lasting 20-40 minutes, twice weekly)	non-Kegel's exercise or regular activity	HRQoL	significantly enhanced health-related QoL (HRQoL) (SMD -0.95; 95% CI -1.35 to -0.54; 3 studies; 12.0%)  no significant impact on HRQoL related to sexual symptoms (SMD 1.11; 95% CI -0.25 to 2.47; 2 studies; 12.94%).	Kegel's exercise is an effective intervention for improving HRQoL-related urinary symptoms in postmenopausal women, but there remains insufficient evidence to assess the effectiveness on HRQoL-related genital symptoms.	Most studies exhibited a low risk of bias
<b>(Taebi et al., 2018)</b>	Systematic review	12 interventional studies including 925 women were included in this systematic review.	Physical activity, complementary medicine, and educational programs	Comparison on group included no intervention, placebo or other interventions (low fat milk/vaginal lubricant)	vasomotor symptoms hot flushing, sleep disorders, psychological problems	Exercising and regular physical activity is effective in reducing vasomotor symptoms and improvement of hot flushing, sleep disorders, and psychological problems of menopausal women.  Aerobic and walking exercises are effective in improvement of vasomotor, mental, social, physical, and sexual symptoms and in general the quality of life in premenopausal and menopausal women and could be considered as an effective method for improvement of menopause symptoms in menopausal women.  Studies did not find any significant relation between physical activity and the sexual domain of quality of life.  CAM& QoL: 1 study showed that using licorice can improve QoL life in menopausal women and reported a significant relation between consumption of licorice and vasomotor, mental, social, and physical domains of quality of life and its total score.  Vaginal royal jelly could be effective in improvement of vaginal dryness although it has a weaker performance in comparison with conjugated estrogen, it is an effective in	Results of reviewing the studies showed that using phytoestrogen and isoflavone products along with performing physical exercises and participating in educational and counseling classes have an effective role in the improvement of the quality of life in menopausal women; it is recommended that aerobic exercises and educational classes would be continued	



						improvement of QoL and its domains  fish oil could improve the QoL  Education: increase awareness, and awareness has a positive effect on healthcare and improvement of health behaviors.		
(Zhou <i>et al.</i> , 2023).	systematic review and meta-analysis	16 RCTs - postmenopausal women (n=594)	aquatic exercises	no exercise	physical fitness and QoL	significant improvements in lower limb strength (SMD 1.37; 95% CI 0.53 to 2.21; 11 studies), upper limb strength (SMD 1.86; 95% CI 0.55 to 3.16; 3 studies), agility (SMD -0.67; 95% CI -1.09 to -0.25; 16 studies) and overall QoL (SMD 1.04; 95% CI 0.06 to 2.03; 5 studies)  Subgroup: - resistance exercise showed greater benefits in enhancing physical fitness and QoL than aerobic and multicomponent exercise. The positive effects on physical fitness were particularly evident in postmenopausal women under 65 years, while improvement in overall QoL were observed in women both under and over 65 years	Aquatic exercise can effectively improve physical fitness and overall QoL in postmenopausal women, but has limited effects on aerobic capacity; thus, it is highly recommended in postmenopausal women.	

**Cardiovascular health**

(Sturgeon <i>et al.</i> , 2017)	RCT	BRCA1/2+ breast cancer survivors who underwent prophylactic BSO, 2 or more years prior to study initiation  aged 18-55,  intervention (n=19) and control (n=16) groups.	A 12-month commercially available web-based lifestyle modification program (Precision Nutrition Coaching)  The intervention included 3 daily activities: Workout - completing relative and progressive strength-training and aerobic exercises  Habit - completing a nutritional/lifestyle habit  Lesson - reading lessons on	Not clearly reported. Participants randomized to the control group were waitlisted and enrolled in the program following study activities.	Cardiovascular fitness, dietary intake, leisure-time activity, body composition, bone mineral density, bone structure, and muscle strength were assessed.	Cardiovascular fitness declined in the control group over one year (-4.0% ± 7.7, P = 0.04) compared to baseline while the intervention group maintained cardiovascular fitness levels (1.1% ± 8.1) (Figure 2).  No differences at baseline or at follow up for heart rate recovery following the test, or resting systolic or diastolic blood pressure. Average blood pressure for the cohort at baseline was (SBP: 114.2 ± 13.5, DBP: 74.0 ± 10.9), and follow up (SBP: 111.9 ± 10.9, DBP: 75.2 ± 11.9). At baseline, the intervention group displayed greater upper body strength as measured by bench press	In this population at high risk for detrimental cardiovascular and bone outcomes, a commercially available lifestyle intervention program mitigated a decline in cardiovascular health, improved bone health, and decreased weight through fat loss.	
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			health, nutrition, fitness, or behavior change.  With a coach			(P = 0.02). 12 months later, the intervention group bench-pressed, on average, 6.6 more pounds (P = 0.06) (control on average, 3.7 pounds more). Intervention: enhanced whole body bone area (P = 0.04) compared to the control group that lost whole body bone area.  Increased cortical bone density compared to the control group (P = 0.02). Bone modeling was also observed in the control group, as both endosteal circumference and periosteal circumference increased (P = 0.01 and 0.04, resp). However, the intervention group had greater periosteal circumference at baseline (P = 0.04).	
<b>(Knobf et al., 2017)</b>	RCT	Breast, colorectal, gynecologic cancer or lymphoma diagnosis; ≤3 years since completion of non-endocrine cancer therapy; menopausal, no resistance exercise ≥3 times/week; physically able to participate)  154 (76 in the fitness center and 78 in the home-based group)	Exercise intervention - aerobic-resistance intervention delivered by trained research interventionists at community fitness centers - 3 times per week, supervised for the first 6 months and unsupervised the last 6 months.  The first 4 weeks were designed as progressive training to achieve the intervention target of 30 min of aerobic activity in the subject's target heart rate goal (65%–75%)	home based group - national guidelines for physical activity for adults (30 min moderate level activity most days of the week) were provided	Fasting serum samples were collected at baseline, 6 and 12 months for insulin, glucose, lipids and hemoglobin A-1C. A graded exercise stress test was also performed at baseline and 6 months.	Fitness center group had significantly improved time on treadmill (p = .039), improved heart rate recovery at 1 min (p = .028), greater MET minutes/week (p ≤ .0001), a trend for improved insulin resistance (p = .067) and stable insulin levels (p = .045) compared to the home based physical activity group.	A 12-month aerobic-resistance exercise intervention delivered at a fitness center resulted in significantly better cardiovascular fitness and metabolic risk factors compared to a national guideline home-based physical activity group. There was a 77.4% adherence rate to the supervised thrice weekly exercise intervention at the fitness centers across the first 6 months. However, based on the MET minutes/week, there was a decline in physical activity in the last six months when women were not being supervised
<b>(Ruiz-Rios and Maldonado-Martin, 2022)</b>	Systematic review	RCTs  14 articles were included. Sample size not reported.	Physical activity intervention such as aerobic training, resistance exercises, high-intensity interval training (HIIT), treadmill walking, Zumba fitness, tai chi, or concurrent training. The frequency varied	premenopausal versus postmenopausal state and/or control group comparison	Cardiorespiratory fitness (CRF) and/or cardiovascular risk factors (CVRF)	following intervention, CRF and CVRF (ie, all of those related to lipid and glycemic metabolism, body composition, blood pressure, inflammatory index, and autonomic responses) improved significantly in most of the studies, with positive changes also found in behavioral and psychosocial variables	All the studies analyzed underline the importance and beneficial effects of PA regardless of the menopausal state of women. However, there is great variability concerning the FITT principle (frequency, intensity, type, and



			from 2 to 3 days per week to most days of the week.			leading to emotional well-being. The only article that analyzes premenopausal and postmenopausal women showed significant decreases in total and low-density lipoprotein cholesterol concentrations in both groups, whereas only the postmenopausal women decreased significantly in triglycerides after PA intervention.	time-volume), with only two studies showing good quality	
<b>(Khalafi et al., 2023b).</b>	systematic review	129 studies, including 7141 postmenopausal women with the mean age of 53-90 years	Exercise		cardiorespiratory fitness (CRF), lower- and upper-body muscular strength, and/or handgrip strength	<p>exercise boosts cardiorespiratory fitness (SMD 1.15; 95% CI 0.87 to 1.42; 25 studies), lower-body muscular strength (SMD 1.06; 95% CI 0.90 to 1.22; 90 studies), upper-body muscular strength (SMD 1.11; 95% CI 0.91 to 1.31) and handgrip strength (weighted mean difference (WMD) 1.78 kg; 95% CI 1.24 to 2.32).</p> <p>Sub-group analysis: significant enhancement in CRF and muscle strength among both middle-aged and older individuals and women engaged in medium- and long-term interventions.</p> <p>Resistance exercise increased upper-body strength, while both resistance and combined training enhanced handgrip strength.</p> <p>Aerobic training alone did not affect handgrip strength</p>		there was a significant heterogeneity among studies for all outcomes
<b>(Khalafi et al., 2023a).</b>	meta-analysis	101 RCTs (n=5697 women, mean age 51-89 years).	Exercise training	control	<p>body composition outcomes: muscle mass/volume, muscle and fiber cross-sectional area and fat-free mass, and decreased fat mass, body fat percentage, waist circumference and visceral fat.</p>	<p>effective for improving body composition, leading to increased muscle mass (SMD 0.26; 95% CI 0.13 to 0.39; I2 0%) and decreased fat mass (WMD -1.27 kg; 95% CI -1.93 to -0.62; I2 56%)</p> <p>Aerobic training was found effective for fat loss, while resistance training contributed to muscle gain.</p> <p>favourable outcomes are observed predominantly among middle aged and older women, engaged in</p>	incorporating a combination of aerobic and resistance exercises can promote overall health in postmenopausal women	



						medium- and long-term interventions		
<b>(Nunes et al., 2023).</b>	systematic review and meta-analysis	20 RCTs with a total of 742 obese postmenopausal and older women.	resistance training  RT groups were divided into low-volume RT (LVRT, >44 sets/week) and high-volume RT (HVRT, >77 sets/week).		body adiposity, metabolic risk, and inflammation	Both RT groups presented improved body adiposity, metabolic risk, and inflammation when compared to CG.  However, HVRT demonstrated higher effect sizes than LVRT for glucose (HVRT = -1.19; 95%CI: -1.63 to -0.74; LVRT = -0.78; 95%CI:-1.15 to -0.41) and C-reactive protein (HVRT = -1.00; 95%CI: -1.32 to -0.67; LVRT = -0.34;95%CI,-0.63 to -0.04)) when compared to CG.	The findings demonstrate improvements in body composition and metabolic health, as well as reductions in inflammation, in both low-volume and high-volume RT.  This study suggests the potential benefits of incorporating resistance training, particularly high-volume, into interventions targeting obesity and related metabolic disorders	overall risk of bias: some concerns; GRADE: low to very low
<b>(Ferreira et al., 2024).</b>	systematic review	13 studies (12 RCTs and one retrospective cohort, mostly with fair quality) involving 700 postmenopausal women	different exercise programs (isolated, aerobic, and resistance or combined)  Four studies used only cardiorespiratory exercise, three only resistance, taekwondo class or flexibility exercise, and six combined exercise programs  Most interventions ranged from 3 to 5 days per week.		Arterial stiffness (Pulse Wave Velocity (baPWV)  Cardiorespiratory fitness	Aerobic training and a combined aerobic-resistance training were found to enhance cardiorespiratory fitness and decrease arterial stiffness while also lowering pulse wave velocity. Of these approaches, the combined exercise program exhibited the greatest effectiveness.	combined aerobic and resistance exercise programs, lead to improved cardiorespiratory fitness and AS in postmenopausal women.	the study included participants aged 47 to 88 years, reflecting a diverse range of postmenopausal women
<b>(He et al., 2023)</b>	Review	19 RCTs (mostly with a good quality)	resistance training	placebo	total cholesterol (TC)  high-density lipoprotein cholesterol (HDL-C)  low-density lipoprotein cholesterol (LDL-C)  triglyceride (TG) levels	Reduction in TC (WMD – 11.47 mg/dl; p = 0.002, 95% CI -18.55 to -4.39, n=686 women)  Reduction in LDL-C (WMD – 8.48 mg/dl; p = 0.01, 95% CI -15.05 to -1.91; n=721 women) Reduction in TG (WMD – 6.61 mg/dl; p = 0.043, 95% CI -13.03 to -0.19; n=741 women)  decrease in LDL-C (WMD – 14.38 mg/dl; p = 0.002) levels in patients with LDL-C ≥ 130 mg/dl before trial enrolment.	effects of resistance training on the lipid levels were particularly significant in short term interventions and among women with dyslipidaemia or obesity prior to trial enrolment.	significant heterogeneity was observed



						Reduction in HDL-C (WMD - 2.97 mg/dl; p = 0.01) levels particularly in subjects with obesity.		
<b>(Loaiza-Betancur et al., 2021)</b>	Systematic review	menopausal and postmenopausal women  RCTs  75 studies were included in the qualitative synthesis with a sample of 4,179 participants.  62 studies in the meta analysis.	Exercise training including aerobic training, Dynamic Resistance Training and Combined Training. In some studies exercise training were supervised, some studies did not supervise their interventions and some studies had partial supervision. 15 studies did not report if they had supervised training or not.	non-traditional exercise training (tai-chi, Qi gong and yoga), placebo or non-active groups	BP	Exercise training resulted in clinically significant reductions on SBP (MD -3.43 mmHg; 95% CI, -5.16, -1.71; P <0.0001), DBP (MD, -2.25 mmHg; 95% CI, -3.40, -1.11; P =0.0001) and MAP (MD, -3.48 mmHg; 95% CI, -5.84, -1.11; P =0.004). Aerobic training (AT) did not produce a significant reduction in SBP, DBP and MAP (P >0.05). Combined training (CT) generated larger reductions.	Exercise training generated small clinically relevant reductions in SBP, DBP and mean arterial pressure in menopausal and postmenopausal women, younger or older than 65 years old, with prehypertension or hypertension. CT showed the largest reductions, for this reason, we suggest that this training modality should be the main prescribed in clinical practice as complementary therapy aimed to prevent, control or treat hypertension in this population. Finally, the results show that AT does not lower BP in a clinically relevant way in (post)menopausal women.	
<b>(Yeh et al., 2018)</b>	Systematic review	RCTs (English or Chinese)  at the reproductive stage of menopause, perimenopause, or postmenopause; aged ≤65 years;  17 RCTs - 792 participants	Exercise interventions included aerobic exercise, resistance training, strength training, tai chi, high-impact training, and yoga. The average duration of exercise was 27.12(SD = 15.60) weeks.	Non-exercise controls or other exercises as a placebo (In 14 studies groups did not receive exercise training, and three studies had placebo groups that had received flexibility or deltoid training).	1) BMI 2) body fat 3) waist circumference 4) triglyceride and LDL and high-density lipoprotein levels (HDL; collected after a fasting state of 8–12 h) 5) BMD	Among the 8 RCTs (n=247), a moderate effect size of exercise on body fat (SMD = -0.34, 95% CI: -0.60 to -0.08). In 5 RCTs (n=195), a moderate effect size of exercise on waist circumference (SMD = -0.39, 95% CI: -0.68 to -0.09), in seven RCTs (162 participants), a moderate effect size on triglyceride level (SMD = -0.37, 95% CI: -0.62 to -0.11), and in 5 RCTs (n=311), a moderate effect size on BMD (SMD = 0.38, 95% CI: 0.08-0.68). Subgroup analysis revealed a significant effect of aerobic exercise on body fat (SMD = -0.29, 95% CI: -0.53 to -0.06), and a short-term exercise on body fat (SMD = -0.50, 95% CI: -0.89 to -0.11) and on triglycerides (SMD = -0.42, 95% CI: -0.79 to -0.04).	This study reveals that exercise exerted significant benefits on body fat, waist circumference, triglyceride levels, and lumbar spine BMD (compared with non exercise or placebo groups) in menopausal women. Short-term exercise interventions reduced body fat and triglyceride levels	the methodological flaws of the included studies might compromise the findings of this study and restrict causal inference.
<b>(Jull et al., 2014)</b>	Systematic review	Perimenopausal and early postmenopausal women during the transition to menopause	Exercise with diet or exercise only.	Not clearly reported. One study had no control group	Body weight changes and/or abdominal obesity.	One RCT with lower risk of bias concluded that participation in an exercise program combined with dietary interventions might mitigate body adiposity increases, which	Few studies have measured the effect of exercise and/or dietary interventions on women's body weight or body	



		and up to 6 years post menopause (typical ages from 40 to 65) and BMI range from 20 - 40 kg.m2		(pre-post study design)		is normally observed during the menopause transition. The other two studies with higher risk of bias suggested that exercise might attenuate weight loss or weight gain and change abdominal adiposity patterns.	composition specifically during the menopause transition stage. Evidence from one large higher quality RCT indicates that women should exercise and eat a caloric restricted diet during the menopause transition stage to prevent weight gain and abdominal fat gain.	
		3 studies (2 RCT+1 pre/post) – 612 participants (from 24 to 535 per study)						

### Evidence to recommendations

QUESTION	<b>What are the lifestyle management options for POI?</b>
RECOMMENDATION	<b>Women should be aware that a healthy lifestyle, including physical activity, has metabolic and heart benefits in the general population including postmenopausal women, although specific evidence on lifestyle interventions in POI is limited. STRONG ++00</b>
GOOD PRACTICE POINT	<b>The guideline group recommends women with POI should be encouraged to adopt a healthy lifestyle to improve their overall well-being and mitigate the risk of potential complications.</b>
Desirable effects	exercise interventions have the potential to enhance QoL and alleviate physical and psychological menopause symptoms
Undesirable effects	None
Certainty of evidence	limited research specifically assessing lifestyle interventions in women with POI. More research is needed to explore the specific impact of exercise and dietary interventions during the menopause transition and post menopause stage, particularly in women with POI.
Values	To promote the overall wellbeing of women with POI, it is vital for them to adhere to general population healthy lifestyle guidelines. This entails adopting a healthy diet and engaging in regular physical activity. These practices offer a broad range of health benefits and are particularly important due to the increased risks associated with POI. By prioritizing a healthy lifestyle, women with POI can enhance their overall health and mitigate potential complications effectively.
Balance of effects	Benefits of healthy lifestyle guidelines, at least similar as for the general population
Resource use, equity, acceptability and feasibility	Accessible, feasible and acceptable



*Research recommendation.*

- **Due to limited evidence available for POI, ongoing research is essential to explore the specific effect of lifestyle interventions on the features of menopause, QoL and cardiovascular outcomes for women with this condition.**



## XIII. Puberty Induction

### PICO QUESTION : HOW SHOULD PUBERTY BE INDUCED?

<b>Population</b>	Children and adolescents diagnosed with POI	Turners syndrome
<b>Interventions</b>	Estrogen replacement therapy (preparations, dose, start, treatment effects) Androgen replacement	Ethinyl estradiol Medroxyprogesterone acetate / other progestogens Estrogen replacement therapy (preparations, dose, start, treatment effects) Androgen replacement
<b>Control</b>	/	/
<b>Outcomes</b>	Induction of puberty Breast development Uterine size	Induction of puberty Growth Breast development Uterine size

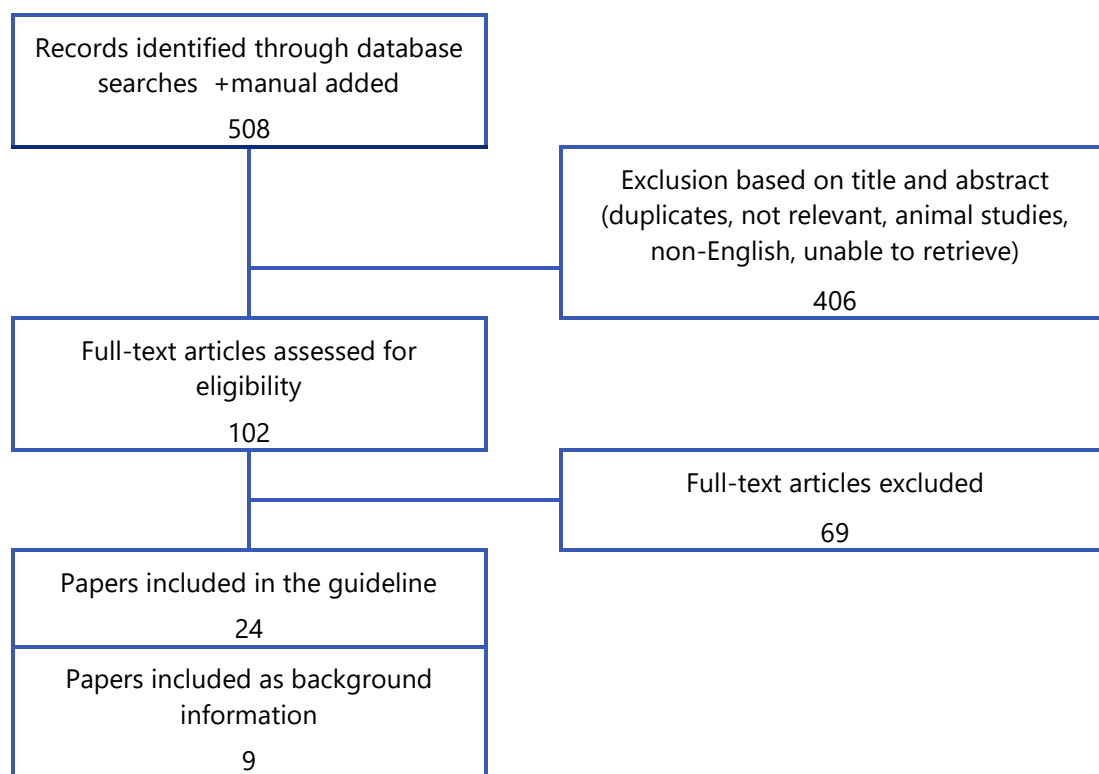
### Search strings

Database	Search String
PUBMED	((“Primary Ovarian Insufficiency”[Mesh] OR “Primary Ovarian Insufficiency” OR “gonadal dysgenesis” OR “Premature Ovarian Failure” OR “early menopause” OR “premature menopause” OR “hypergonadotropic hypogonadism” OR “Ovarian dysgenesis” OR “Primary ovarian failure” OR “Hypergonadotropic amenorrhea” OR “surgical menopause” OR “Bilateral Salpingo-Oophorectomy” OR “Bilateral Oophorectomy” OR “iatrogenic menopause” OR “radiation menopause” OR “Turner syndrome”) AND (“Induction of puberty” OR “inducing puberty” OR “puberty induction” OR “pubertal induction” OR puberty))OR ((“Medroxyprogesterone acetate” OR MPA OR norethisterone OR dydrogesterone OR “growth hormone” OR Androgen OR androgens OR estradiol OR “Ethinyl estradiol” OR Ethinylestradiol OR “Ethinyl Estradiol”[Mesh] OR “Estrogen replacement therapy” OR Progesterone OR “Progesterone”[Mesh] OR “Conjugated estrogen”) AND (“Induction of puberty” OR “inducing puberty” OR “puberty induction” OR “pubertal induction”))
COCHRANE	

Literature search was limited to the period between 01/01/2014 and 01/04/2024. Studies and data published prior to 01/01/2014 were assessed in the development of the POI Guideline 2015. Where still relevant, and in absence of newer data, the studies and data published prior to 01/01/2014 were retained.



## Flowchart



## Evidence

### Evidence table

Ref.	Study Type	Patients	Intervention / Diagnostic test	Control	Outcome measures	Effect size	Authors conclusion	Comments
<b>When to start estrogens?</b>								
<b>(Chemau sek et al., 2000)</b>	RCT	60 patients from a large (n=117), previously unreported, clinical trial of GH treatment - all less than 11 yr of age at entry (mean, 9.5 yr) and received 0.375 mg/kg*week of GH for nearly 6 yr on a daily or 3 times weekly regimen)	start conjugated estrogens at either 12 vs 15 yr of age		Height gain	Patients in whom estrogen treatment was delayed until age 15 yr gained an average of 8.4 ± 4.3 cm over their projected height, whereas those starting estrogen at 12 yr gained only 5.1±3.6 cm, on the average (P < 0.01). Analysis of the interval data showed that growth was stimulated for approximately 2 yr after estrogen initiation, but then declined in association with bone age advancement.  Patients > 11 yr at entry (n = 57) all initiated estrogen 1 yr after beginning GH and showed a mean gain in adult height of 4.7 cm, similar to those given estrogen at age 12 yr.		



<b>(Ross et al., 2011).</b>	RCT	149 TS girls, 5.0 to 12.5 years of age	<p>4 Groups:</p> <p>1= double placebo (placebo injection plus childhood oral placebo, 39 patients)</p> <p>2= estrogen alone (placebo injection plus childhood oral low-dose estrogen,40),</p> <p>3= growth hormone alone (GH injection plus childhood oral placebo, 35),</p> <p>4= GH–estrogen (GH injection plus childhood oral low-dose estrogen, 35).</p> <p>GH Dose; 0.1 mg/kg; three times per week.</p> <p>Ethinyl estradiol (or placebo) dose: were adjusted for chronologic age and pubertal status.</p>	Height	<p>The mean SD scores for adult height, attained at an average age of 17.0±1.0 years, after an average study period of 7.2±2.5 years were -2.81±0.85, -3.39±0.74, -2.29±1.10, and -2.10±1.02 for the groups, resp (P&lt;0.001).</p> <p>The overall effect of GH (vs. placebo) on adult height was a 0.78±0.13 increase in the height SD score (5.0 cm) (P&lt;0.001); adult height was greater in the GH–estrogen vs GH–alone group, by 0.32±0.17 SD score (2.1 cm) (P = 0.059),</p>	growth hormone treatment increases adult height in TS. In addition, the data suggest that combining childhood ultra-low-dose estrogen with growth hormone may improve growth and provide other potential benefits		
<b>What preparations, mode of delivery and doses of estrogen should be used?</b>								
<b>(Cameroon-Pimblett et al., 2019).</b>	Study	799 women with TS, 624 had primary amenorrhea and 599 had accurate maintenance ERT	ERT subgroups [combined oral contraceptive pill (OCP), oral estrogen (OE), and transdermal estradiol (TE)]			Estrogen start age was negatively correlated with adult bone density (spine: r = -0.20 and hip: r = -0.20; P # 0.001). OCP users had higher blood pressure and an adverse lipid profile compared with other ERT subgroups. TE was associated with elevated liver enzymes and hemoglobin A1c compared with OE (P # 0.01).	An earlier age of induction of puberty may be beneficial for adult bone density. Given the high prevalence of hypertension in TS, the use of OCP for ERT should be limited. OE may be a benefit for steatohepatitis.	associations between age of induction of puberty and type of ERT on adult health outcomes
<b>(Torres-Santiago et al., 2013).</b>	RCT	40 TS girls, mean age 16.7 ± 1.7 years,	Oral 17β-estradiol  E2 concentrations were titrated to normal range in both groups	TD 17β-estradiol  E2 concentrations were titrated to normal range in	Changes in body composition and lipid oxidation	After 6 and 12 months, fat-free mass and percent fat mass, bone mineral density accrual, lipid oxidation, and resting energy expenditure rates were similar between groups.	When E(2) concentrations are titrated to the normal range, the route of delivery of 17β-estradiol does not affect	Oral ethinyl estradiol is no longer recommended for puberty induction with



			<p>Mean oral dose was 2 mg</p> <p>both groups</p> <p>Mean TD dose was 0.1 mg</p>		<p>IGF-1 concentrations were lower on oral 17β-E2, but suppression of gonadotropins was comparable with no significant changes in lipids, glucose, osteocalcin, or highly sensitive C-reactive protein between groups. However, E1, E1S, SHBG, and bioestrogen concentrations were significantly higher in the oral group.</p>	<p>differentially body composition, lipid oxidation, and lipid concentrations in hypogonadal girls with TS. However, total estrogen exposure (E(1), E(1)S, and total bioestrogen) is significantly higher after oral 17β-E(2). TD 17β-E(2) results in a more physiological estrogen milieu than oral 17β-E(2) administration in girls with TS.</p>	<p>oral or transdermal estradiol showing similar effects on metabolic parameters</p>
<p><b>(Ankarberg-Lindgren et al., 2019).</b></p>	<p>Study</p>		<p>Estraderm MX 50 µg, System 50 µg and Oesclim 25 µg matrix</p> <p>patches were cut into eight pieces while Estradot 50 µg small patches were cut in half.</p> <p>The cut patches were stored in their respective pouches at +21°C or at +35°C for up to 1 month. The estradiol drug was extracted from the patch by ethyl acetate</p>		<p>Storage at +21°C or +35°C up to 1 month did not reduce the estradiol concentration in Estraderm MX, System and Oesclim patches. However, although the estradiol in Estradot patches was not affected by storage at +21°C, at +35°C, estradiol decreased by 57% (±1%) in cut pieces.</p>		<p>assess 1-month stability of cut estradiol patches from four different manufacturers in the laboratory at room temperature (+21°C) and at an elevated temperature (+35°C).</p>



			n-hexane and determined by radioimmunoassay.					
<b>(Shim et al, 2023).</b>	retrospective chart review	45 TS patients	Transdermal estrogen.		Incidence of abnormal uterine bleeding (AUB) during pubertal induction	16 (35%) experienced AUB. Individuals with AUB most commonly experienced prolonged (44%), prolonged and heavy (25%), and intermenstrual (19%) bleeding. Individuals who experienced AUB were more likely to experience spontaneous bleeding (69% vs 28%) and a duration of unopposed estrogen greater than 18 months (63% vs 41%), undergo progestin cycling less often than monthly (69% vs 0%), use a micronized progestin dose of less than 200 mg (25% vs 14%), and be non-compliant with HRT (19% vs 0%) compared with those who did not experience AUB.	There is a relatively high incidence of AUB among individuals with TS undergoing pubertal induction with transdermal estrogen.	
<b>Effects of estrogen therapy: Breast and pubic hair</b>								
<b>(Bannink et al, 2009)</b>	Prospective cohort study	68 TS girls (6 spont pub, 56 analysis)  Girls with TS in a dose-response GH study, puberty induction is also studied  Follow-up: 4.8 (2.0) years after	oral micronized 17b-estradiol in increasing doses start age 12 and over after at least 4 yrs of GH.start dose 5 microg/kg/day for 2 yr, 7.5 third yr, later 10 microg/kg/d progestagen 5mg/day 14days/month After GH Rx E2 1 -2 mg/day,		breast development and hormones  uterine volume, length and shape	Breast dev. Similar but 2 yrs later than normal, . Pubic hair developed normally up to P5, whereas delayed.  P6 not reached  E2 levels increased with higher E2 dose LH decrease-increase FSH decrease. SHBG no change  Follow-up: uterine dimensions in women aged nearly 20 were	With low dose E2 started at appropriate age breast dev. Normal up to B5 with 2 yrs delay. Pubic hair normal to p5 although delayed and P6 not observed.  Serum hormone levels do	



		the end of GH therapy. Assessment of pubertal stages and US internal genitals 7:1 (2:2) years after start of oestrogen Age at FU: 19.9 ± 2.2 (15.0-23.4)	Cyclic progesterone 10 mg/d. blood samples were taken 4-6 hours after estrogen administration			subnormal streaks or no ovaries  uterine volume, length and shape of the TS girls were suboptimal at age 19.9 (±2.2) years, after on average 7.1 (± 2.2) years of oral estrogen therapy compared to women of the same age	not provide additional information for evaluating the progression through puberty in a clinical setting. At follow-up uterine dimensions subnormal	
<b>(Nabhan et al., 2009)</b>	RCT	12 prepubertal GH-treated girls with TS (14.0 ± 1.7 yr)	conjugated oral estrogen for 1 year.	transdermal estrogen	DXA, pelvic ultrasound, Tanner staging, growth velocity, IGF-I, and lipid profile.	TD E2 resulted in a significantly greater change in spine bone density at 12m compared with oral estrogen (bone mineral content 9.0 +/- 0.9 vs. 5.8 +/- 0.9 g, P = 0.04; BMD 0.12 +/- 0.01 vs. 0.06 +/- 0.01 g/cm <sup>2</sup> , P = 0.004; Z-score 0.7 +/- 0.1 vs. 0.3 +/- 0.1, P = 0.03). Greater increases in uterine length (4.13 +/- 0.39 vs. 1.98 +/- 0.39 cm, P = 0.003) and volume (22.2 +/- 4.4 vs. 4.0 +/- 4.4 ml, P = 0.02) were also found in the TD vs. the oral group at 1 yr. At study end, 66% of subjects in the TD group had a mature uterus vs. 0% in the oral group. No significant differences in other parameters examined were seen.	In girls with TS, TD E2 resulted in faster bone accrual at the spine and increased uterine growth compared with conjugated oral estrogen.	
<b>Effects of estrogen therapy: Uterine size</b>								
<b>(Nabhan et al., 2009)</b>								See above
<b>(Obara-Moszyns)</b>	Cohort study	40 girls with TS	17β-estradiol with a dose		uterine volume (UV) and	The average age of TS patients at estrogen introduction and at the last control visit, when the uterus		



<b>ka et al., 2021).</b>			escalation regime uterine		fundocervical antero-posterior ratio (FCR)  before, after 6-12 months,, after ≥36 or ≥ 12 months after menarche.	was considered mature, was 12.9 years and 16.1 years, respectively. The UV in patients with TS at the beginning of ERT was 1.55 ± 1.22 cm(3) and was not significantly different from the UV in the prepubertal controls. The mature UV in patients with TS was 31.04 ± 11.78 cm(3) and was significantly smaller than the UV of the postpubertal controls (45.68 ± 12.51 cm(3), p<0.001). The FCR in girls with TS did not differ significantly from that in the prepubertal and postpubertal control groups, resp. No prognostic factors could be established for the final UV.		
<b>(Bannink et al., 2009)</b>							See above	
<b>(Snajderova et al., 2003)</b>	multicenter cross-sectional study	57 TS women, aged 18.1–41.5 years	estrogen for puberty induction		uterine length, endometrium thickness, and Tanner breast stage	In 21 women (37%), the uterus developed to >65 mm in length. The daily estrogen dose correlated with both uterine length (r = 0.29; p < 0.05) and Tanner breast stage (r = 0.44; p < 0.001).  A negative correlation between age at artificial menarche and uterine length was found (r = -0.29; p < 0.05). The endometrium thickness was greater in women with an uterus length >65 mm (p < 0.05). In 50% of the women (18 were evaluated), an adult-shaped uterus developed. Previous GH (n = 32) had no impact on the uterus length.	uterine volume, length and shape of the TS girls were suboptimal	
<b>(Paterson et al., 2002).</b>	STUDY	96 TS patients – Pelvic ultrasound data	Patients were classified into three groups: (1) untreated (n = 48); (2) complete spontaneous puberty (n = 10); and (3) treated with ethinyl oestradiol (n = 38).		Uterine length, fundal-cervical ratio (FCR) and shape, presence or absence of ovaries	In untreated girls up to age 10 years there was a variable distribution of uterine length and FCR about the mean. Thereafter, the uterus failed to grow and mature normally. Girls with complete spontaneous puberty had morphologically normal ovaries and uteri, but of 7 girls who attained menarche, 3 subsequently developed secondary oligomenorrhoea or	current E2 treatment regimen for TS girls gives rise to satisfactory pubertal induction and maintenance, but failed to induce a fully mature uterus in half the cohort. In view of the high risk of miscarriage	uterine volume, length and shape of the TS girls were suboptimal



						amenorrhoea. In the treated group, in general, breast development and uterine length progressed with increasing E2 dose. However, only 50% of girls with complete secondary sexual development had a mature heart-shaped uterine configuration.	in TS in both spontaneous and assisted pregnancies, the effect of more physiological methods of E2 replacement on uterine development should be investigated.	
<b>(McDonnell et al., 2003).</b>	prospective study	18 GH-treated girls with TS (5 with spontaneous puberty and 13 receiving estrogen therapy from age 14.6 (± 2.2) years),  Karyotype was 45XO in 6/18, mosaic in 12/18. Spontaneous pubertal onset occurred in 5/18.	Pubertal induction with oestrogen was used in 13/18 girls.			A total of 15/18 girls have either achieved spontaneous menarche or are using adult doses of oestrogen and progestogen with regular withdrawal bleeds. All 18 girls have achieved a uterine length of 5.8-8.6 cm (mean 7.04 cm) within the normal adult range (5-8 cm). Mean uterine volume was 30.23 cm <sup>3</sup> .	adequate oestrogen replacement in early to mid adolescence mimicking spontaneous timing of puberty results in normal uterine growth and adult uterine dimensions.	all girls had normal uterine length and volume at final assessment at age 17.1 (± 2.8) years
<b>(Lindsay Mart et al., 2024).</b>	cross-sectional study	29 TS (age, 15-26 years) with POI who reached adult estrogen dosing (100 mcg transdermal or 2 mg oral 17β-estradiol)	estrogen dosing (100 mcg transdermal or 2 mg oral 17β-estradiol)		Uterine length, volume, and fundal-cervical ratio (FCR)	There was no evidence of compromise of the uterine size/configuration in the TS cohort compared with the controls; in fact, uterine length- mean 7.7 cm (+/-1.3) vs. 7.2 cm (+/-1.0) (p = 0.03) and volume- mean 60.6 cm <sup>3</sup> (+/-26.6) vs. 50.5 cm <sup>3</sup> (+/-20.5) (p = 0.02), were both larger in TS individuals.	Current international guidelines for hormone replacement using 17β-estradiol in TS individuals appear adequate to allow for normal uterine growth by the end of pubertal induction.	normal uterine size comparable to normative data
<b>(Cleeman et al., 2011).</b>	cross-sectional study	41 TS (17.0 ± 3.3 years, range 11-24.9 years), 50 healthy age-matched controls (16.9 ± 3.2 years, range 12.5-25.0 years) and	2 mg versus 4 mg 17β-estradiol orally		Uterine and ovarian volume by US and MRI	Ovaries were detected in 37% in TS by US and in 55% in TS by MRI (P = 0.1). Total ovarian volume was lower in TS compared to both groups of controls (TS vs C-US: median 1.1 ml (range 0.1-29.3) vs 11.52 ml (1.9-77.9), P = 0.001, TS vs C-MRI:	A larger ovarian volume was detected by MRI in TS compared to US. This finding is important with the advancements of	TS females in the high dose group achieved a normal adult uterine size



		107 Tanner-stage-matched controls (15.0 ± 3.2 years, range 10.1-24.2)				1.0 ml (0.1-34.2) vs 13.2 ml (2.4-30.1), P < 0.0005). Mean difference in total ovarian volume measured by MRI and US in patients with TS was 2.3 ± 3.8 ml (P = 0.01). Mean uterine volume by MRI was lower in TS compared to controls (29.5 ± 25.1 vs 54.3 ± 23.3 ml, P < 0.0005). Uterine volume by US was lower in TS at Tanner stage B5 compared to controls (TS vs C: 33.6 ± 18.2 vs 50.2 ± 18.0 ml, P = 0.007).	performing ovarian biopsies for cryopreservation and later reimplantation. Mean uterine volumes by MRI and US in fully matured TS were lower compared to controls despite appropriate hormonal replacement therapy in TS.	
<b>(Guo et al, 2019).</b>	retrospective, longitudinal study	TS girls (n=71)	oral estradiol valerate using a standard protocol for pubertal induction		uterine size	the interval of each stage was significantly longer (P < 0.001) in the girls with TS than that in the normal Chinese girls, except for B2-3 (P = 0.011). The uterine volumes of the girls with TS in stages B2 and 3 were greater than those of the control group (P = 0.046), whereas the uterine volume of the control group was inversely greater than that of the TS group among those who reached stages B4 and 5 (P = 0.034). During HRT, the uterine volume grew significantly from all previous stages except for breast stage 5 (B3 vs.2): Z = -2.031; P = 0.042; B(4 vs. 3): Z = -2.273; P = 0.023; B(5 vs. 4): Z = -1.368; P = 0.171). The paired data of 27 girls with TS showed that the uterine volume (17.93 +/- 9.31 ml vs. 13.75 +/- 6.67 ml) and width (2.54 +/- 0.66 cm vs. 2.22 +/- 0.36 cm) increased significantly during artificial cycles compared with before artificial cycles (t = -2.79 and -2.51, P = 0.01 and 0.018).	HRT led to normal breast development in girls with TS; half of the girls with TS in our study reached Tanner stage B5, although the uterus ultimately developed suboptimally. The girls' breasts and uteruses grew quickly at the beginning of HRT (stages B2-4). An optimal HRT regimen for girls with TS may specifically focus on Tanner stages B2-4 and artificial cycles.	many did not achieve a normal uterine size
<b>(Burt et al, 2019)</b>	retrospective study	mixed group of females (n=95) with	mixed, with some being treated with oral contraceptive		Pelvic ultrasound	Those with hypogonadism had significantly reduced uterine dimensions	Despite standard oestrogen therapy,	lower average



		TS, POI, and gonadotropin deficiency, all needing pubertal induction	pill, some with transdermal E2 and some with low dose ethinyl estradiol, and no direct comparison was performed.			compared with the reference group (uterine length 64 mm vs 71 mm P = <.05, uterine volume 28.9 mL vs 43.9 mL P = <.05). All women in the reference group attained a mature uterine configuration with a FCR >1, compared with 84% of those with hypogonadism (P = .01). A total of 24% and 48% of the diagnostic group had total uterine length and uterine volume measurements less than the 5th percentile of the reference group, respectively. In a subgroup of 22 women in whom serum oestradiol concentrations could be analysed, there was a positive correlation between this parameter and uterine volume.	uterine growth is often compromised in those with hypogonadism. Uterine health has historically been overlooked in pubertal induction protocols; however, with increasing options for fertility treatment, adequate uterine development is crucial. Given the variation in uterine size witnessed, a more tailored approach to treatment with regular monitoring of uterine dimensions should be advocated.	uterine volume
<b>(Rodari et al, 2023).</b>	retrospective study	mixed group of females (n=95), including POI and hypogonadotropic hypogonadism of all causes (chronological age > 10.9 years, Tanner stage ≤ 2)	transdermal 17β-oestradiol patches for at least 1 year. Induction was started at a median dose of 0.14 mcg/kg/day with a 6-monthly increase and was considered completed for 49/95 patients who started progesterone with a concomitant oestrogen adult dose		Auxological, biochemical, and radiological data at baseline and during follow-up	At the end of induction, the achievement of the complete breast maturation was associated with a 17β-oestradiol dose at progesterone introduction. ULD showed a significant correlation with a 17β-oestradiol dosage. Final ULD was >65 mm in only 17/45 girls. At multiple regression analysis, pelvic irradiation represented the major determinant of reduced final ULD. After correction for uterine irradiation, ULD was associated with the 17β-oestradiol dose at progesterone introduction. Final ULD was not significantly different from the one assessed after	Our results provide evidence that progestins, hampering further changes in uterine volume and breast development, should be introduced only in the presence of a concomitant adequate 17β-oestradiol dose and an appropriate clinical response.	



						progesterone introduction.		
<b>Effects of estrogen therapy : Metabolic actions and bone</b>								
<b>(Mauras et al, 2007).</b>	RCT	11 girls with TS, mean age 13.4 +/- 0.5 (se) yr treated with GH for at least 6 months.	17beta-estradiol orally (0.5, 1, and 2 mg for 2 wk each) and TD (0.025, 0.0375, and 0.05 mg for 2 wk each), and studies were repeated after each 6-wk course with 4 wk washout in between.		[(13)C]leucine and d5-glycerol infusions, indirect calorimetry, DXA, and hormone and substrate measurements.	Rates of whole-body protein turnover, oxidation and synthesis, lipolysis, lipid and carbohydrate oxidation, and resting energy expenditure were unaffected by either form of estrogen; nor were lipids, insulin, and fibrinogen concentrations affected. Plasma IGF-I concentrations did not change clinically significantly with either form of estrogen, despite higher estrogen concentrations after oral estrogen. Estradiol concentrations did not correlate with any variables measured.	these data suggest that the route of delivery of estrogen does not adversely affect these metabolic effects of GH in young girls with Turner syndrome.	route of delivery does not adversely affect the metabolic effects of GH in young girls with TS
<b>(Nabhan et al, 2009)</b>								See above
<b>(Torres-Santiago et al, 2013).</b>								See above
<b>(Cleeman et al, 2017).</b>	RCT	20 TS females, age 15–25 years and current treatment with 2 mg oral estradiol daily	low-dose (LD) group : 2 mg 17B-estradiol/day orally and placebo	high-dose (HD) group : 2 mg + 2 mg 17B-estradiol/day orally	whole body and regional BMD, lean body mass (LBM), fat mass (FM) measured yearly by DXA scan and the resorptive and formative bone markers in serum.	BMD, whole body and regional, increased over time with an attenuation toward the end of the study, and bone turnover markers decreased over time, both with no differences between the treatment groups (P = 0.2–0.9). LBM increased significantly more in the HD group (P = 0.02). FM remained stable in both groups.	A steady increase in BMD over time in TS was found similar to healthy young women. The higher estrogen dose did not differentially affect BMD or bone markers.	
<b>Effects of estrogen therapy : Cardiovascular actions</b>								
<b>(Viuff et al, 2020).</b>	epidemiological study	1156 TS + 1157 age-matched female controls.	treated compared with untreated  (Among 32945,X women, 44 had never been HRT treated, and 285 had been treated at some point.)		morbidity, mortality and medicinal use	Endocrine and cardiovascular mortality and morbidity were significantly increased in TS compared with the matched controls. Comparing HRT treated with nontreated	Women with TS have an increased overall mortality and morbidity. HRT seems to have a beneficial effect on	lower risk of being prescribed antihypertensives, antidiabetics and thyroid medications, and



						women, we found a similar mortality (hazard ratio 0.83, 95% confidence interval 0.38-1.79). Among the HRT-treated 45,X women, we found a significantly lower use of antihypertensives, antidiabetics, and thyroid hormones and significantly reduced hospitalization rates for stroke and osteoporotic fractures.	endocrine conditions, hypertension, and stroke	stroke was also less frequent, results pointing towards a protective effect of HRT
<b>(Brun et al, 2019).</b>	secondary analysis from trial	20 TS females around 15 years at start of treatment	2 and 4 mg of 17β-estradiol given orally		Cardiovascular health (5 year follow up): blood pressure (BP) and heart rate	Systolic and diastolic BPs increased regardless of estradiol dose (P=0.005 and P=0.009) in TS patients, whereas heart rate decreased (P=0.05). Neither body mass index, height, weight, nor lipids contributed significant to the changes. There was no difference in BP, heart rate, or lipids because of treatment. At the end of the study, diastolic BP and heart rate were significantly higher in TS during day, night, and over 24 hours. Systolic BP increased insignificantly. Lipids did not change during the study period, but body mass index determined individual levels.	Systolic and diastolic BPs increase significantly in late adolescence and early adulthood in TS.	similar development in blood pressure, irrespective of the 17β-estradiol dosing
<b>Effects of estrogen therapy : Cognitive function</b>								
<b>(Li et al, 2019)</b>	study	23 adolescent girls with TS	estradiol for pubertal induction  hormonally subnormal group and an abnormal subgroup		MRI - Brain structural (i.e., gray matter [GM] morphology and white matter [WM] connectivity) and functional phenotypes	Statistical analyses revealed significant effects of the "group-by-age" interaction on GM volume around the left medial orbitofrontal cortex and WM diffusion parameters around the bilateral corticospinal tract, anterior thalamic radiation, left superior longitudinal fasciculus, and cingulum bundle, but no significant "group-by-age" or group differences were observed in resting-	estrogen deficiency has a nontrivial impact on the development of the brain structure during adolescence in girls with TS.	expected maturational changes in brain development



						state functional measures.		
(O'Donoghue <i>et al.</i> , 2020)	Study	55 girls with TS and 53 typically developing girls	estradiol for pubertal induction		MRI	Parieto-occipital gray and white matter regions showed slower growth during typical pubertal timing in girls with TS relative to typically developing girls. In contrast, some basal ganglia, cerebellar, and limited cortical areas showed enhanced volume growth with peaks around 10 years of age.	particular brain regions are more vulnerable to TS genetic and hormonal effects during puberty. These specific alterations in neurodevelopment may be more likely to affect long-term cognitive behavioral outcomes in young girls with this common genetic condition.	expected maturational changes in brain development

### Evidence to recommendations

QUESTION	<b>How should puberty be induced?</b>
RECOMMENDATION	<b>Puberty should be induced or progressed with estradiol, starting with low dose at the age of 11 years with a gradual increase over 2–3 years.</b> <b>In cases of late diagnosis and for those girls in whom growth is not a concern, HCPs can consider a modified regimen of estradiol therapy.</b>
Desirable effects	normal breast and pubic hair development There are many options for HRT for puberty induction. However, systemic administration of increasing doses estradiol, preferably by transdermal application, is the most used form of therapy to achieve natural levels of estradiol in blood and mimic normal estradiol physiology in adolescence and adulthood With increasing doses of oral / transdermal 17β-estradiol normal breast and pubic hair development can be achieved (Gravholt <i>et al.</i> , 2017, Klein <i>et al.</i> , 2018). In cases of later diagnosis of pubertal failure and for those girls in whom growth is not a consideration, estrogens may be started at somewhat higher doses and escalated more rapidly
Undesirable effects	With higher starting doses of E2 and/or more rapid dose escalation, breast development should be monitored for stretch marks and asymmetry.
Certainty of evidence	Few data, mainly based on clinical expertise
Values	
Balance of effects	
Resource use, equity, acceptability and feasibility	



Subgroup considerations (if applicable)	Almost all the literature concerning puberty induction deals with Turner syndrome and the recommendations are based on knowledge from this area. It is thought that one can extrapolate data from this arena, but the reader should of course be cautious that one may not be able to extrapolate all conclusions to other conditions with POI.
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QUESTION	<b>How should puberty be induced?</b>
RECOMMENDATION	<b>Evidence for the optimum mode of administration (oral or transdermal) is inconclusive.</b>
RECOMMENDATION	<b>HCPs may prefer transdermal estradiol as it results in more physiological estrogen concentrations</b>
RECOMMENDATION	<b>A combined oral contraceptive should not be used for puberty induction</b>
Desirable effects	mimic normal estradiol physiology/normal development: systemic administration of increasing doses estradiol, preferably by transdermal application, is the most used form of therapy to achieve natural levels of estradiol in blood and mimic normal estradiol physiology in adolescence and adulthood (Ankarberg-Lindgren <i>et al.</i> , 2019, Donaldson <i>et al.</i> , 2019).
Undesirable effects	We suggest E2 transdermal (TD) route when possible, with oral E2 as second choice. Ethinyl estradiol has more risks but is better than no treatment
Certainty of evidence	inconclusive
Values	
Balance of effects	
Resource use, equity, acceptability and feasibility	NA
Subgroup considerations (if applicable)	Almost all the literature concerning puberty induction deals with Turner syndrome and the recommendations are based on knowledge from this area. It is thought that one can extrapolate data from this arena, but the reader should of course be cautious that one may not be able to extrapolate all conclusions to other conditions with POI.

QUESTION	<b>How should puberty be induced?</b>
GOOD PRACTICE POINT	<b>The guideline group recommends starting cyclical progestogens after ~2 years of estrogen therapy or when breakthrough bleeding occurs.</b>
Desirable effects	It is suggested to use unopposed estradiol for at least 18-24 months before adding a progestogen to allow for regular menstrual periods (Gravholt <i>et al.</i> , 2017, Klein <i>et al.</i> , 2018). Benefits of progesterone are described above – re. avoiding the known risk of endometrial hyperplasia/cancer with unopposed estrogen therapy
Undesirable effects	Undesirable effects of progesterone are described above - re. possible risk of breast cancer (unclear)
Certainty of evidence	NA
Values	
Balance of effects	Protection against endometrial hyperplasia/cancer was considered the most important aspect



Resource use, equity, NA  
acceptability and  
feasibility

### Research recommendations.

- **Research concerning the optimal age for induction of puberty is still needed, with increased focus on cognitive function, sexual function, uterine development, cardiovascular status, development of a normal body composition including bone acquisition and other areas.**
- **Likewise, in induction of puberty, there is a need to establish the optimal route of delivery of first estradiol at escalating doses and then progesterone, when sequential therapy is needed.**
- **Establishing the long-term outcome of appropriate puberty induction using both a clinical and an epidemiological approach is also needed.**
- **The fundamental understanding of why POI develops in conditions like Turner syndrome remains an enigma and should also be investigated.**



## References

- Abadi O, Cheraghi MA, Tirgari B, Nayeri ND, Rayyani M. Feeling an Invisible Wall: The Experience of Iranian Women's Marital Relationship After Surgical Menopause: A Qualitative Content Analysis Study. *Journal of sex & marital therapy* 2018;44: 627-640.
- Abdelaziz EM, Elsharkawy NB, Mohamed SM. Efficacy of Internet-based cognitive behavioral therapy on sleeping difficulties in menopausal women: A randomized controlled trial. *Perspectives in psychiatric care* 2022;58: 1907-1917.
- Achimaş-Cadariu PA, Păun DL, Paşca A. Impact of Hormone Replacement Therapy on the Overall Survival and Progression Free Survival of Ovarian Cancer Patients: A Systematic Review and Meta-Analysis. *Cancers* 2023;15.
- ACOG. Committee opinion no. 605: primary ovarian insufficiency in adolescents and young women. *Obstetrics and gynecology* 2014;124: 193-197.
- Alexandre M, Black J, Whicker M, Minkin MJ, Ratner E. The management of sexuality, intimacy, and menopause symptoms (SIMS) after prophylactic bilateral salpingo-oophorectomy: How to maintain sexual health in "previvors". *Maturitas* 2017;105: 46-51.
- Allen-Brady K, Moore B, Verrilli LE, Alvord MA, Kern M, Camp N, Kelley K, Letourneau J, Cannon-Albright L, Yandell M. Breast Cancer Is Increased in Women With Primary Ovarian Insufficiency. *The Journal of Clinical Endocrinology & Metabolism* 2024: dgae480.
- Allen EG, Charen K, Hipp HS, Shubeck L, Amin A, He W, Hunter JE, Sherman SL. Clustering of comorbid conditions among women who carry an FMR1 premutation. *Genetics in medicine : official journal of the American College of Medical Genetics* 2020;22: 758-766.
- Allshouse AA, Semple AL, Santoro NF. Evidence for prolonged and unique amenorrhea-related symptoms in women with premature ovarian failure/primary ovarian insufficiency. *Menopause* 2015;22: 166-174.
- Alvaro Mercadal B, Imbert R, Demeestere I, Englert Y, Delbaere A. Pregnancy outcome after oocyte donation in patients with Turner's syndrome and partial X monosomy. *Human reproduction (Oxford, England)* 2011;26: 2061-2068.
- Alves-Nogueira AC, Melo D, Carona C, Figueiredo-Dias M. The Psychosocial Impact of the Decision to Undergo Risk-Reducing Salpingo-Oophorectomy Surgery in BRCA Mutation Carriers and the Role of Physician-Patient Communication. *Current oncology (Toronto, Ont)* 2023;30: 2429-2440.
- Anderson RA, Amant F, Braat D, D'Angelo A, Chuva de Sousa Lopes SM, Demeestere I, Dwek S, Frith L, Lambertini M, Maslin C *et al*. ESHRE guideline: female fertility preservation. *Human reproduction open* 2020;2020: hoaa052.
- Anderson RA, Cameron D, Clatot F, Demeestere I, Lambertini M, Nelson SM, Peccatori F. Anti-Müllerian hormone as a marker of ovarian reserve and premature ovarian insufficiency in children and women with cancer: a systematic review. *Human reproduction update* 2022;28: 417-434.
- Anderson RA, Mansi J, Coleman RE, Adamson DJA, Leonard RCF. The utility of anti-Müllerian hormone in the diagnosis and prediction of loss of ovarian function following chemotherapy for early breast cancer. *European journal of cancer (Oxford, England : 1990)* 2017;87: 58-64.
- Ankarberg-Lindgren C, Gawlik A, Kriström B, Mazzanti L, Ruijgrok EJ, Sas TCJ. Estradiol matrix patches for pubertal induction: stability of cut pieces at different temperatures. *Endocrine connections* 2019;8: 360-366.
- Arif S, Underhill JA, Donaldson P, Conway GS, Peakman M. Human leukocyte antigen-DQB1\* genotypes encoding aspartate at position 57 are associated with 3beta-hydroxysteroid dehydrogenase autoimmunity in premature ovarian failure. *The Journal of clinical endocrinology and metabolism* 1999;84: 1056-1060.
- Atema V, van Leeuwen M, Kieffer JM, Oldenburg HSA, van Beurden M, Gerritsma MA, Kuenen MA, Plaisier PW, Lopes Cardozo AMF, van Riet YEA *et al*. Efficacy of Internet-Based Cognitive Behavioral Therapy for Treatment-Induced Menopausal Symptoms in Breast Cancer Survivors: Results of a Randomized Controlled Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2019;37: 809-822.
- Atema V, van Leeuwen M, Kieffer JM, Oldenburg HSA, van Beurden M, Hunter MS, Aaronson NK. Internet-based cognitive behavioral therapy aimed at alleviating treatment-induced menopausal symptoms in breast cancer survivors: Moderators and mediators of treatment effects. *Maturitas* 2020;131: 8-13.



- Ates S, Aydın S, Özcan P, Bakar RZ, Cetin C. Sleep, depression, anxiety and fatigue in women with premature ovarian insufficiency. *Journal of psychosomatic obstetrics and gynaecology* 2022; 1-6.
- Azizi M, Khani S, Kamali M, Elyasi F. The Efficacy and Safety of Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors in the Treatment of Menopausal Hot Flashes: A Systematic Review of Clinical Trials. *Iranian journal of medical sciences* 2022;47: 173-193.
- Baber RJ, Panay N, Fenton A. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. *Climacteric : the journal of the International Menopause Society* 2016;19: 109-150.
- Bachelot A, Nicolas C, Bidet M, Dulon J, Leban M, Golmard JL, Polak M, Touraine P. Long-term outcome of ovarian function in women with intermittent premature ovarian insufficiency. *Clinical endocrinology* 2017;86: 223-228.
- Bachelot A, Nicolas C, Gricourt S, Dulon J, Leban M, Golmard JL, Touraine P. Poor Compliance to Hormone Therapy and Decreased Bone Mineral Density in Women with Premature Ovarian Insufficiency. *PLoS one* 2016;11: e0164638.
- Bakalov VK, Anasti JN, Calis KA, Vanderhoof VH, Premkumar A, Chen S, Furmaniak J, Smith BR, Merino MJ, Nelson LM. Autoimmune oophoritis as a mechanism of follicular dysfunction in women with 46,XX spontaneous premature ovarian failure. *Fertility and sterility* 2005;84: 958-965.
- Bakhsh H, Dei M, Bucciantini S, Balzi D, Bruni V. Premature ovarian insufficiency in young girls: repercussions on uterine volume and bone mineral density. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2015;31: 65-69.
- Balen AH, Harris SE, Chambers EL, Picton HM. Conservation of fertility and oocyte genetics in a young woman with mosaic Turner syndrome. *BJOG : an international journal of obstetrics and gynaecology* 2010;117: 238-242.
- Bannink EM, van Sassen C, van Buuren S, de Jong FH, Lequin M, Mulder PG, de Muinck Keizer-Schrama SM. Puberty induction in Turner syndrome: results of oestrogen treatment on development of secondary sexual characteristics, uterine dimensions and serum hormone levels. *Clinical endocrinology* 2009;70: 265-273.
- Bansal N, Hazim CF, Badillo S, Shyam S, Wolfe D, Bortnick AE, Garcia MJ, Rodriguez CJ, Zhang L. Maternal Cardiovascular Outcomes of Pregnancy in Childhood, Adolescent, and Young Adult Cancer Survivors. *Journal of cardiovascular development and disease* 2022;9.
- Bar J, Davidi O, Goshen Y, Hod M, Yaniv I, Hirsch R. Pregnancy outcome in women treated with doxorubicin for childhood cancer. *American journal of obstetrics and gynecology* 2003;189: 853-857.
- Barakat RR, Bundy BN, Spirtos NM, Bell J, Mannel RS. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006;24: 587-592.
- Baronchelli S, Conconi D, Panzeri E, Bentivegna A, Redaelli S, Lissoni S, Saccheri F, Villa N, Crosti F, Sala E *et al.* Cytogenetics of premature ovarian failure: an investigation on 269 affected women. *Journal of biomedicine & biotechnology* 2011;2011: 370195.
- Barton DL, Schroeder KCF, Banerjee T, Wolf S, Keith TZ, Elkins G. Efficacy of a biobehavioral intervention for hot flashes: a randomized controlled pilot study. *Menopause* 2017;24: 774-782.
- Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, King K, Kvaskoff M, Nap A, Petersen K *et al.* ESHRE guideline: endometriosis. *Human reproduction open* 2022;2022: hoac009.
- Benetti-Pinto CL, Brancalion MF, Assis LH, Tinois E, Giraldo HP, Cabello C, Yela DA. Mammographic breast density in women with premature ovarian failure: a prospective analysis. *Menopause* 2014;21: 933-937.
- Benetti-Pinto CL, Ferreira VB, Yela DA. Long-term follow-up of bone density in women with primary ovarian insufficiency. *Menopause* 2015a;22: 946-949.
- Benetti-Pinto CL, Menezes C, Yela DA, Cardoso TM. Sleep quality and fatigue in women with premature ovarian insufficiency receiving hormone therapy: a comparative study. *Menopause* 2019;26: 1141-1145.
- Benetti-Pinto CL, Soares PM, Giraldo HP, Yela DA. Role of the different sexuality domains on the sexual function of women with premature ovarian failure. *J Sex Med* 2015b;12: 685-689.
- Berglund A, Viuff MH, Skakkebaek A, Chang S, Stochholm K, Gravholt CH. Changes in the cohort composition of Turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: a nationwide cohort study. *Orphanet journal of rare diseases* 2019;14: 16.
- Bernard V, Donadille B, Zenaty D, Courtillot C, Salenave S, Brac de la Perrière A, Albarel F, Fèvre A, Kerlan V, Brue T *et al.* Spontaneous fertility and pregnancy outcomes amongst 480 women with Turner syndrome. *Human reproduction (Oxford, England)* 2016;31: 782-788.



- Berreni N, Salerno J, Chevalier T, Alonso S, Mares P. Evaluation of the effect of multipoint intra-mucosal vaginal injection of a specific cross-linked hyaluronic acid for vulvovaginal atrophy: a prospective bi-centric pilot study. *BMC women's health* 2021;21: 322.
- Betterle C, Coco G, Zanchetta R. Adrenal cortex autoantibodies in subjects with normal adrenal function. *Best practice & research Clinical endocrinology & metabolism* 2005;19: 85-99.
- Bidet M, Bachelot A, Bissauge E, Golmard JL, Gricourt S, Dulon J, Coussieu C, Badachi Y, Touraine P. Resumption of ovarian function and pregnancies in 358 patients with premature ovarian failure. *The Journal of clinical endocrinology and metabolism* 2011;96: 3864-3872.
- Bıldırcın FD, Özdeş EK, Karlı P, Özdemir AZ, Kökçü A. Does Type of Menopause Affect the Sex Lives of Women? *Medical science monitor : international medical journal of experimental and clinical research* 2020;26: e921811.
- Birkebaek NH, Crüger D, Hansen J, Nielsen J, Bruun-Petersen G. Fertility and pregnancy outcome in Danish women with Turner syndrome. *Clin Genet* 2002;61: 35-39.
- Birkhaeuser M, Bitzer J, Braat S, Ramos Y. Esmirtazapine treatment of postmenopausal vasomotor symptoms: two randomized controlled trials. *Climacteric : the journal of the International Menopause Society* 2019;22: 312-322.
- Błaszczuk A, Barańska A, Kanadys W, Malm M, Jach ME, Religioni U, Wróbel R, Herda J, Polz-Dacewicz M. Role of Phytoestrogen-Rich Bioactive Substances (Linum usitatissimum L., Glycine max L., Trifolium pratense L.) in Cardiovascular Disease Prevention in Postmenopausal Women: A Systematic Review and Meta-Analysis. *Nutrients* 2022;14.
- Blizzard RM, Chee D, Davis W. The incidence of adrenal and other antibodies in the sera of patients with idiopathic adrenal insufficiency (Addison's disease). *Clin Exp Immunol* 1967;2: 19-30.
- Blümel JE, Arteaga E, Vallejo MS, Ojeda E, Meza P, Martino M, Rodriguez-Vidal D, Nãñez M, Tserotas K, Rojas J *et al.* Association of bilateral oophorectomy and menopause hormone therapy with mild cognitive impairment: the REDLINC X study. *Climacteric : the journal of the International Menopause Society* 2022;25: 195-202.
- Bober SL, Recklitis CJ, Bakan J, Garber JE, Patenaude AF. Addressing sexual dysfunction after risk-reducing salpingo-oophorectomy: effects of a brief, psychosexual intervention. *J Sex Med* 2015;12: 189-197.
- Bodri D, Vernaev V, Figueras F, Vidal R, Guillen JJ, Coll O. Oocyte donation in patients with Turner's syndrome: a successful technique but with an accompanying high risk of hypertensive disorders during pregnancy. *Human reproduction (Oxford, England)* 2006;21: 829-832.
- Bondy C. Pregnancy and cardiovascular risk for women with Turner syndrome. *Women's health (London, England)* 2014;10: 469-476.
- Borba CM, Ferreira CF, Ferreira FV, Pérez-López FR, Wender MCO. Effect of sulpiride on menopausal hot flashes: a randomized, double-blind, placebo-controlled clinical trial. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2020;36: 247-251.
- Borgstrom B, Hreinsson J, Rasmussen C, Sheikhi M, Fried G, Keros V, Fridstrom M, Hovatta O. Fertility preservation in girls with turner syndrome: prognostic signs of the presence of ovarian follicles. *The Journal of clinical endocrinology and metabolism* 2009;94: 74-80.
- Bosze P, Toth A, Torok M. Hormone replacement and the risk of breast cancer in Turner's syndrome. *The New England journal of medicine* 2006;355: 2599-2600.
- Both S, Lew-Starowicz M, Luria M, Sartorius G, Maseroli E, Tripodi F, Lowenstein L, Nappi RE, Corona G, Reisman Y, Vignozzi L. Hormonal Contraception and Female Sexuality: Position Statements from the European Society of Sexual Medicine (ESSM). *J Sex Med* 2019;16: 1681-1695.
- Bove R, Secor E, Chibnik LB, Barnes LL, Schneider JA, Bennett DA, De Jager PL. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. *Neurology* 2014;82: 222-229.
- Brand JS, Onland-Moret NC, Eijkemans MJ, Tjonneland A, Roswall N, Overvad K, Fagherazzi G, Clavel-Chapelon F, Dossus L, Lukanova A *et al.* Diabetes and onset of natural menopause: results from the European Prospective Investigation into Cancer and Nutrition. *Human reproduction (Oxford, England)* 2015;30: 1491-1498.
- Bräuner EV, Wilson LF, Koch T, Christensen J, Dehlendorff C, Duun-Henriksen AK, Priskorn L, Abildgaard J, Simonsen MK, Jørgensen JT *et al.* The long-term association between bilateral oophorectomy and depression: a prospective cohort study. *Menopause* 2022;29: 276-283.
- Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA, Bachman G, Aguirre OA, Lucas JD, Rodenberg C *et al.* Safety and efficacy of a testosterone patch for the treatment of hypoactive



sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Archives of internal medicine* 2005;165: 1582-1589.

Brozzetti A, Alimohammadi M, Morelli S, Minarelli V, Hallgren Å, Giordano R, De Bellis A, Perniola R, Kämpe O, Falorni A. Autoantibody response against NALP5/MATER in primary ovarian insufficiency and in autoimmune Addison's disease. *The Journal of clinical endocrinology and metabolism* 2015;100: 1941-1948.

Brun S, Cleemann L, Holm K, Salskov G, Erlandsen M, Berglund A, Andersen NH, Gravholt CH. Five-Year Randomized Study Demonstrates Blood Pressure Increases in Young Women With Turner Syndrome Regardless of Estradiol Dose. *Hypertension* 2019;73: 242-248.

Bryman I, Sylven L, Berntorp K, Innala E, Bergstrom I, Hanson C, Oxholm M, Landin-Wilhelmsen K. Pregnancy rate and outcome in Swedish women with Turner syndrome. *Fertility and sterility* 2011;95: 2507-2510.

Bullington BW, Edmonds A, Ramirez C, Rahangdale L, Neal-Perry G, Konkle-Parker D, Weiss DJ, Moran C, Golub ET, Cejtin H *et al*. Premature and early menopause among US women with or at risk for HIV. *Menopause* 2022;29: 741-747.

Bundred NJ, Kenemans P, Yip CH, Beckmann MW, Foidart JM, Sismondi P, Schoultz B, Vassilopoulou-Sellin R, Galta RE, Lieshout EV *et al*. Tibolone increases bone mineral density but also relapse in breast cancer survivors: LIBERATE trial bone substudy. *Breast Cancer Res* 2012;14: R13.

Burgos N, Cintron D, Latortue-Albino P, Serrano V, Rodriguez Gutierrez R, Faubion S, Spencer-Bonilla G, Erwin PJ, Murad MH. Estrogen-based hormone therapy in women with primary ovarian insufficiency: a systematic review. *Endocrine* 2017;58: 413-425.

Burt E, Davies MC, Yasmin E, Cameron-Pimblett A, Mavrelou D, Talaulikar V, Conway GS. Reduced uterine volume after induction of puberty in women with hypogonadism. *Clinical endocrinology* 2019;91: 798-804.

Bustami M, Matalka KZ, Elyyan Y, Hussein N, Hussein N, Abu Safieh N, Thekrallah F, Mallah E, Abu-Qatouseh L, Arafat T. Age of Natural Menopause Among Jordanian Women and Factors Related to Premature and Early Menopause. *Risk management and healthcare policy* 2021;14: 199-207.

Buster JE, Kingsberg SA, Aguirre O, Brown C, Breaux JG, Buch A, Rodenberg CA, Wekselman K, Casson P. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstetrics and gynecology* 2005;105: 944-952.

Caan B, LaCroix AZ, Joffe H, Guthrie KA, Larson JC, Carpenter JS, Cohen LS, Freeman EW, Manson JE, Newton K *et al*. Effects of estrogen and venlafaxine on menopause-related quality of life in healthy postmenopausal women with hot flashes: a placebo-controlled randomized trial. *Menopause* 2015;22: 607-615.

Cakiroglu Y, Saltik A, Yuceturk A, Karaosmanoglu O, Kopuk SY, Scott RT, Tiras B, Seli E. Effects of intraovarian injection of autologous platelet rich plasma on ovarian reserve and IVF outcome parameters in women with primary ovarian insufficiency. *Ageing* 2020;12: 10211-10222.

Cakmak E, Karakus S, Demirpençe O, Demet Coskun B. Ovarian Reserve Assessment in Celiac Patients of Reproductive Age. *Medical science monitor : international medical journal of experimental and clinical research* 2018;24: 1152-1157.

Cameron-Pimblett A, Davies MC, Burt E, Talaulikar VS, La Rosa C, King TFJ, Conway GS. Effects of Estrogen Therapies on Outcomes in Turner Syndrome: Assessment of Induction of Puberty and Adult Estrogen Use. *The Journal of clinical endocrinology and metabolism* 2019;104: 2820-2826.

Canonica M, Plu-Bureau G, O'Sullivan MJ, Stefanick ML, Cochrane B, Scarabin PY, Manson JE. Age at menopause, reproductive history, and venous thromboembolism risk among postmenopausal women: the Women's Health Initiative Hormone Therapy clinical trials. *Menopause* 2014;21: 214-220.

Cao M, Pan W, Shen X, Li C, Zhou J, Liu J. Urinary levels of phthalate metabolites in women associated with risk of premature ovarian failure and reproductive hormones. *Chemosphere* 2020;242: 125206.

Cao X, Sun ML, Qin YN, Zhang JJ, Bai YF, Zhang Y, Ai YK, Liu J. Overview of the systematic reviews of premature ovarian insufficiency treated with acupuncture. *World Journal of Acupuncture - Moxibustion* 2022;32: 287-297.

Cao XJ, Huang X, Liu J, Ma F, Zeng Y, Chen C, Wang JJ, Nie G, Wang XY. A randomized, double-blind, placebo-controlled trial of Chinese herbal medicine capsules for the treatment of premature ovarian insufficiency. *Menopause* 2018;25: 918-926.

Carcelén-Fraile MDC, Aibar-Almazán A, Martínez-Amat A, Cruz-Díaz D, Díaz-Mohedo E, Redecillas-Peiró MT, Hita-Contreras F. Effects of Physical Exercise on Sexual Function and Quality of Sexual



- Life Related to Menopausal Symptoms in Peri- and Postmenopausal Women: A Systematic Review. *International journal of environmental research and public health* 2020;17.
- Cardona Attard C, Cameron-Pimblett A, Puri D, Elliot J, Wilson JC, Talaulikar VS, Davies MC, Conway GS. Fracture rate in women with oestrogen deficiency - Comparison of Turner syndrome and premature ovarian insufficiency. *Clinical endocrinology* 2019;91: 743-749.
- Cardona Attard C, Cameron-Pimblett A, Puri D, La Rosa C, Talaulikar VS, Davies MC, Learner HI, Liao LM, Conway GS. Relationship and sexual experiences in women with early-onset oestrogen deficiency: Comparison between women with Turner syndrome and premature ovarian insufficiency. *Clinical endocrinology* 2020;93: 473-481.
- Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density. *The Journal of clinical endocrinology and metabolism* 2016;101: 3497-3505.
- Castronovo C, Rossetti R, Rusconi D, Recalcati MP, Cacciatori C, Beccaria E, Calcaterra V, Invernizzi P, Larizza D, Finelli P, Persani L. Gene dosage as a relevant mechanism contributing to the determination of ovarian function in Turner syndrome. *Human reproduction (Oxford, England)* 2014;29: 368-379.
- Chaker L, Razvi S, Bensenor IM, Azizi F, Pearce EN, Peeters RP. Hypothyroidism. *Nat Rev Dis Primers* 2022;8: 30.
- Chemaitilly W, Li Z, Krasin MJ, Brooke RJ, Wilson CL, Green DM, Klosky JL, Barnes N, Clark KL, Farr JB *et al.* Premature Ovarian Insufficiency in Childhood Cancer Survivors: A Report From the St. Jude Lifetime Cohort. *The Journal of clinical endocrinology and metabolism* 2017;102: 2242-2250.
- Chen M, Jiang H, Zhang C. Selected Genetic Factors Associated with Primary Ovarian Insufficiency. *International journal of molecular sciences* 2023;24.
- Chen S, Sawicka J, Betterle C, Powell M, Prentice L, Volpato M, Rees Smith B, Furmaniak J. Autoantibodies to steroidogenic enzymes in autoimmune polyglandular syndrome, Addison's disease, and premature ovarian failure. *The Journal of clinical endocrinology and metabolism* 1996;81: 1871-1876.
- Chen TL, Chang SC, Huang CY, Wang HH. Effectiveness of mindfulness-based interventions on quality of life and menopausal symptoms in menopausal women: A meta-analysis. *Journal of psychosomatic research* 2021;147: 110515.
- Cheng YS, Sun CK, Yeh PY, Wu MK, Hung KC, Chiu HJ. Serotonergic antidepressants for sleep disturbances in perimenopausal and postmenopausal women: a systematic review and meta-analysis. *Menopause* 2020;28: 207-216.
- Chernausek SD, Attie KM, Cara JF, Rosenfeld RG, Frane J. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. Genentech, Inc., Collaborative Study Group. *The Journal of clinical endocrinology and metabolism* 2000;85: 2439-2445.
- Chojnacki C, Walecka-Kapica E, Klupinska G, Pawlowicz M, Blonska A, Chojnacki J. Effects of fluoxetine and melatonin on mood, sleep quality and body mass index in postmenopausal women. *Journal of physiology and pharmacology : an official journal of the Polish Physiological Society* 2015;66: 665-671.
- Christ JP, Gunning MN, Palla G, Eijkemans MJC, Lambalk CB, Laven JSE, Fauser B. Estrogen deprivation and cardiovascular disease risk in primary ovarian insufficiency. *Fertility and sterility* 2018;109: 594-600.e591.
- Christmas MM, Iyer S, Daisy C, Maristany S, Letko J, Hickey M. Menopause hormone therapy and urinary symptoms: a systematic review. *Menopause* 2023;30: 672-685.
- Chu K, Wang Y, He Y, Tang Y, Gu J, Wu S, Zhang H, Sun N, Li Z, Zhang Q, Li W. The psychosocial impact of premature ovarian insufficiency on male partners and their perceptions of the disease. *Psychology, health & medicine* 2021;26: 1248-1257.
- Cleemann L, Holm K, Fallentin E, Skouby SO, Smedegaard H, Møller N, Borch-Christensen H, Jeppesen EM, Wieslander SB, Andersson AM *et al.* Uterus and ovaries in girls and young women with Turner syndrome evaluated by ultrasound and magnetic resonance imaging. *Clinical endocrinology* 2011;74: 756-761.
- Cleemann L, Holm K, Kobbarnagel H, Kristensen B, Skouby SO, Jensen AK, Gravholt CH. Dosage of estradiol, bone and body composition in Turner syndrome: a 5-year randomized controlled clinical trial. *European journal of endocrinology / European Federation of Endocrine Societies* 2017;176: 233-242.



Coelingh Bennink HJT, van Gennip FAM, Gerrits MGF, Egberts JFM, Gemzell-Danielsson K, Kopp-Kallner H. Health benefits of combined oral contraceptives - a narrative review. *Eur J Contracept Reprod Health Care* 2024; 1-13.

Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *The Lancet Oncology* 2012;13: 1141-1151.

Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet* 2019;394: 1159-1168.

Comba C, Comba A, Yilmaz H, Erdogan SV, Demir O. Celiac disease does not influence markers of ovarian reserve in adolescent girls. *Archives of gynecology and obstetrics* 2020;302: 1263-1269.

Comini ACM, Carvalho BM, Moreira MJB, Reis PCA, Colapietro L, Northern J, Batalini F. Safety and Serum Estradiol Levels in Hormonal Treatments for Vulvovaginal Atrophy in Breast Cancer Survivors: A Systematic Review and Meta-Analysis. *Clinical breast cancer* 2023;23: 835-846.

Conrad KP, von Versen-Höynck F, Baker VL. Potential role of the corpus luteum in maternal cardiovascular adaptation to pregnancy and preeclampsia risk. *American journal of obstetrics and gynecology* 2022;226: 683-699.

Conway GS. Premature ovarian failure. *British medical bulletin* 2000;56: 643-649.

Coughlan GT, Betthausen TJ, Boyle R, Kosciak RL, Klinger HM, Chibnik LB, Jonaitis EM, Yau WW, Wenzel A, Christian BT *et al.* Association of Age at Menopause and Hormone Therapy Use With Tau and  $\beta$ -Amyloid Positron Emission Tomography. *JAMA neurology* 2023;80: 462-473.

Coulam CB. The prevalence of autoimmune disorders among patients with primary ovarian failure. *American journal of reproductive immunology : AJRI : official journal of the American Society for the Immunology of Reproduction and the International Coordination Committee for Immunology of Reproduction* 1983;4: 63-66.

Coulam CB, Ryan RJ. Prevalence of circulating antibodies directed toward ovaries among women with premature ovarian failure. *Am J Reprod Immunol Microbiol* 1985;9: 23-24.

Cox P, Panay N. Non-hormonal treatments for managing vulvovaginal atrophy/genitourinary syndrome of menopause. *Climacteric : the journal of the International Menopause Society* 2023;26: 367-372.

Cramer DW, Xu H, Harlow BL. Family history as a predictor of early menopause. *Fertility and sterility* 1995;64: 740-745.

Crean-Tate KK, Faubion SS, Pederson HJ, Vencill JA, Batur P. Management of genitourinary syndrome of menopause in female cancer patients: a focus on vaginal hormonal therapy. *American journal of obstetrics and gynecology* 2020;222: 103-113.

Critchley HO, Wallace WH, Shalet SM, Mamtora H, Higginson J, Anderson DC. Abdominal irradiation in childhood; the potential for pregnancy. *British journal of obstetrics and gynaecology* 1992;99: 392-394.

Cucinella L, Tiranini L, Cassani C, Martella S, Nappi RE. Genitourinary Syndrome of Menopause in Breast Cancer Survivors: Current Perspectives on the Role of Laser Therapy. *International journal of women's health* 2023;15: 1261-1282.

Cui Y, Deming-Halverson SL, Beeghly-Fadiel A, Lipworth L, Shrubsole MJ, Fair AM, Shu XO, Zheng W. Interactions of hormone replacement therapy, body weight, and bilateral oophorectomy in breast cancer risk. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2014;20: 1169-1178.

Cusimano MC, Chiu M, Ferguson SE, Moineddin R, Aktar S, Liu N, Baxter NN. Association of bilateral salpingo-oophorectomy with all cause and cause specific mortality: population based cohort study. *BMJ (Clinical research ed)* 2021;375: e067528.

Dal Pra C, Chen S, Furmaniak J, Smith BR, Pedini B, Moscon A, Zanchetta R, Betterle C. Autoantibodies to steroidogenic enzymes in patients with premature ovarian failure with and without Addison's disease. *European journal of endocrinology / European Federation of Endocrine Societies* 2003;148: 565-570.

Daley A, Stokes-Lampard H, Thomas A, MacArthur C. Exercise for vasomotor menopausal symptoms. *The Cochrane database of systematic reviews* 2014: Cd006108.

Davis SM, Soares K, Howell S, Cree-Green M, Buyers E, Johnson J, Tartaglia NR. Diminished Ovarian Reserve in Girls and Adolescents with Trisomy X Syndrome. *Reprod Sci* 2020;27: 1985-1991.

Davis SR. Androgens in premenopausal women and women with premature ovarian insufficiency. *Climacteric : the journal of the International Menopause Society* 2021;24: 459-465.



- Davis SR, Baber R, Panay N, Bitzer J, Perez SC, Islam RM, Kaunitz AM, Kingsberg SA, Lambrinoudaki I, Liu J *et al*. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. *The Journal of clinical endocrinology and metabolism* 2019;104: 4660-4666.
- Davis SR, Hirschberg AL, Wagner LK, Lodhi I, von Schoultz B. The effect of transdermal testosterone on mammographic density in postmenopausal women not receiving systemic estrogen therapy. *The Journal of clinical endocrinology and metabolism* 2009;94: 4907-4913.
- Davis SR, Jane F. Sex and perimenopause. *Australian family physician* 2011;40: 274-278.
- Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, Braunstein GD, Hirschberg AL, Rodenberg C, Pack S *et al*. Testosterone for low libido in postmenopausal women not taking estrogen. *The New England journal of medicine* 2008;359: 2005-2017.
- Davis SR, Robinson PJ, Jane F, White S, White M, Bell RJ. Intravaginal Testosterone Improves Sexual Satisfaction and Vaginal Symptoms Associated With Aromatase Inhibitors. *The Journal of clinical endocrinology and metabolism* 2018;103: 4146-4154.
- Davis SR, van der Mooren MJ, van Lunsen RH, Lopes P, Ribot C, Rees M, Moufारेge A, Rodenberg C, Buch A, Purdie DW. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Menopause* 2006;13: 387-396.
- De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. *Lancet* 2010;376: 911-921.
- Dedden SJ, Werner MA, Steinweg J, Lissenberg-Witte BI, Huirne JAF, Geomini P, Maas JWM. Hysterectomy and sexual function: a systematic review and meta-analysis. *J Sex Med* 2023;20: 447-466.
- Deeks AA, Gibson-Helm M, Teede H, Vincent A. Premature menopause: a comprehensive understanding of psychosocial aspects. *Climacteric : the journal of the International Menopause Society* 2011;14: 565-572.
- Del Pilar Larosa M, Chen S, Steinmaus N, Macrae H, Guo L, Masiero S, Garelli S, Costa MD, Bossowski A, Furmaniak J *et al*. A new ELISA for autoantibodies to steroid 21-hydroxylase. *Clinical chemistry and laboratory medicine* 2018;56: 933-938.
- Dendrinios ML, Smorgick N, Marsh CA, Smith YR, Quint EH. Occurrence of Gonadoblastoma in Patients with 45,X/46,XY Mosaicism. *Journal of pediatric and adolescent gynecology* 2015;28: 192-195.
- Dhakate M, Goswami D, Goswami R, Saha S, Kandasamy D, Arora M. Bone mineral density, vertebral fractures and trabecular bone score in primary ovarian insufficiency. *Journal of endocrinological investigation* 2023;46: 1865-1874.
- Diem SJ, LaCroix AZ, Reed SD, Larson JC, Newton KM, Ensrud KE, Woods NF, Guthrie KA. Effects of pharmacologic and nonpharmacologic interventions on menopause-related quality of life: a pooled analysis of individual participant data from four MsFLASH trials. *Menopause* 2020;27: 1126-1136.
- Ding N, Harlow SD, Randolph JF, Calafat AM, Mukherjee B, Batterman S, Gold EB, Park SK. Associations of Perfluoroalkyl Substances with Incident Natural Menopause: The Study of Women's Health Across the Nation. *The Journal of clinical endocrinology and metabolism* 2020;105: e3169-3182.
- Donaldson M, Kriström B, Ankarberg-Lindgren C, Verlinde S, van Alfen-van der Velden J, Gawlik A, van Gelder M, Sas T. Optimal Pubertal Induction in Girls with Turner Syndrome Using Either Oral or Transdermal Estradiol: A Proposed Modern Strategy. *Hormone research in paediatrics* 2019;91: 153-163.
- Donegan E, Frey BN, McCabe RE, Streiner DL, Fedorkow DM, Furtado M, Green SM. Impact of the CBT-Meno protocol on menopause-specific beliefs, dysfunctional attitudes, and coping behaviors. *Menopause* 2022;29: 963-972.
- Dorman JS, Steenkiste AR, Foley TP, Strotmeyer ES, Burke JP, Kuller LH, Kwok CK. Menopause in type 1 diabetic women: is it premature? *Diabetes* 2001;50: 1857-1862.
- Driscoll MA, Davis MC, Aiken LS, Yeung EW, Sterling EW, Vanderhoof V, Calis KA, Popat V, Covington SN, Nelson LM. Psychosocial Vulnerability, Resilience Resources, and Coping with Infertility: A Longitudinal Model of Adjustment to Primary Ovarian Insufficiency. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2016;50: 272-284.
- Dutta D, Dharmshaktu P, Aggarwal A, Gaurav K, Bansal R, Devru N, Garga UC, Kulshreshtha B. Severity and pattern of bone mineral loss in endocrine causes of osteoporosis as compared to age-related bone mineral loss. *Journal of postgraduate medicine* 2016;62: 162-169.
- Ehrhardt MJ, Leerink JM, Mulder RL, Mavinkurve-Groothuis A, Kok W, Nohria A, Nathan PC, Merks R, de Baat E, Asogwa OA *et al*. Systematic review and updated recommendations for



cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *The Lancet Oncology* 2023;24: e108-e120.

Elkins G, Johnson A, Fisher W, Sliwinski J, Keith T. A pilot investigation of guided self-hypnosis in the treatment of hot flashes among postmenopausal women. *The International journal of clinical and experimental hypnosis* 2013;61: 342-350.

Elkins G, Marcus J, Stearns V, Perfect M, Rajab MH, Ruud C, Palamara L, Keith T. Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008;26: 5022-5026.

Engberg H, Strandqvist A, Berg E, Nordenskjöld A, Nordenström A, Frisén L, Hirschberg AL. Sexual Function in Women With Differences of Sex Development or Premature Loss of Gonadal Function. *J Sex Med* 2022;19: 249-256.

Ensrud KE, Guthrie KA, Hohensee C, Caan B, Carpenter JS, Freeman EW, LaCroix AZ, Landis CA, Manson J, Newton KM *et al*. Effects of estradiol and venlafaxine on insomnia symptoms and sleep quality in women with hot flashes. *Sleep* 2015;38: 97-108.

Ewertz M, Mellekjær L, Poulsen AH, Friis S, Sørensen HT, Pedersen L, McLaughlin JK, Olsen JH. Hormone use for menopausal symptoms and risk of breast cancer. A Danish cohort study. *British journal of cancer* 2005;92: 1293-1297.

Fahlen M, Fornander T, Johansson H, Johansson U, Rutqvist LE, Wilking N, von Schoultz E. Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. *European journal of cancer (Oxford, England : 1990)* 2013;49: 52-59.

Falorni A, Laureti S, Candeloro P, Perrino S, Coronella C, Bizzarro A, Bellastella A, Santeusano F, De Bellis A. Steroid-cell autoantibodies are preferentially expressed in women with premature ovarian failure who have adrenal autoimmunity. *Fertility and sterility* 2002;78: 270-279.

Fante JF, Brito LGO, Teatin-Juliato CR, Benetti-Pinto CL. Can hormone therapy modify pelvic floor muscle assessment and symptoms within women with premature ovarian insufficiency? *European journal of obstetrics, gynecology, and reproductive biology* 2020;252: 624-625.

Farland LV, Rice MS, Degnan WJ, 3rd, Rexrode KM, Manson JE, Rimm EB, Rich-Edwards J, Stewart EA, Cohen Rassier SL, Robinson WR, Missmer SA. Hysterectomy With and Without Oophorectomy, Tubal Ligation, and Risk of Cardiovascular Disease in the Nurses' Health Study II. *Journal of women's health (2002)* 2023;32: 747-756.

Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *The New England journal of medicine* 2000;342: 1077-1084.

Fernández-Pena A, Navas-Sánchez FJ, de Blas DM, Marcos-Vidal L, Desco M, Carmona S. Previous pregnancies might mitigate cortical brain differences associated with surgical menopause. *Human brain mapping* 2024;45: e26538.

Ferreira L, Abrantes C, Alves ME, Moreira C, Moreira H. Effects of exercise programs on cardiorespiratory fitness and arterial stiffness on postmenopausal women: A systematic review study. *Maturitas* 2024;181: 107917.

Fitzpatrick D, Pirie K, Reeves G, Green J, Beral V. Combined and progestagen-only hormonal contraceptives and breast cancer risk: A UK nested case-control study and meta-analysis. *PLoS medicine* 2023;20: e1004188.

Forges T, Monnier-Barbarino P, Faure GC, Bene MC. Autoimmunity and antigenic targets in ovarian pathology. *Human reproduction update* 2004;10: 163-175.

Foudila T, Soderstrom-Anttila V, Hovatta O. Turner's syndrome and pregnancies after oocyte donation. *Human reproduction (Oxford, England)* 1999;14: 532-535.

Fraison E, Crawford G, Casper G, Harris V, Ledger W. Pregnancy following diagnosis of premature ovarian insufficiency: a systematic review. *Reproductive biomedicine online* 2019;39: 467-476.

Francés-Herrero E, Lopez R, Hellström M, de Miguel-Gómez L, Herraiz S, Brännström M, Pellicer A, Cervelló I. Bioengineering trends in female reproduction: a systematic review. *Human reproduction update* 2022;28: 798-837.

Franić-Ivanišević M, Franić D, Ivočić M, Tančić-Gajić M, Marina L, Barac M, Vujović S. Genetic Etiology of Primary Premature Ovarian Insufficiency. *Acta clinica Croatica* 2016;55: 629-635.

Frederick AB, Zinsli AM, Carlock G, Conneely K, Fridovich-Keil JL. Presentation, progression, and predictors of ovarian insufficiency in classic galactosemia. *Journal of inherited metabolic disease* 2018;41: 785-790.



- Freeman JR, Whitcomb BW, Purdue-Smithe AC, Manson JE, Langton CR, Hankinson SE, Rosner BA, Bertone-Johnson ER. Is Alcohol Consumption Associated With Risk of Early Menopause? *American journal of epidemiology* 2021;190: 2612-2617.
- Fu C, Hao W, Shrestha N, Virani SS, Mishra SR, Zhu D. Association of reproductive factors with dementia: A systematic review and dose-response meta-analyses of observational studies. *EClinicalMedicine* 2022;43: 101236.
- Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *The Cochrane database of systematic reviews* 2012;2012: Cd000402.
- Gaba F, Manchanda R. Systematic review of acceptability, cardiovascular, neurological, bone health and HRT outcomes following risk reducing surgery in BRCA carriers. *Best practice & research Clinical obstetrics & gynaecology* 2020;65: 46-65.
- Gao J, Jiao X, Dang Y, Li J, Li G, Han T, Liu Y, Qin Y, Chen ZJ. Identification of patients with primary ovarian insufficiency caused by autoimmunity. *Reproductive biomedicine online* 2017;35: 475-479.
- Garelli S, Dalla Costa M, Sabbadin C, Barollo S, Rubin B, Scarpa R, Masiero S, Fierabracci A, Bizzarri C, Crinò A *et al.* Autoimmune polyendocrine syndrome type 1: an Italian survey on 158 patients. *Journal of endocrinological investigation* 2021;44: 2493-2510.
- Garland SN, Xie SX, Li Q, Seluzicki C, Basal C, Mao JJ. Comparative effectiveness of electro-acupuncture versus gabapentin for sleep disturbances in breast cancer survivors with hot flashes: a randomized trial. *Menopause* 2017;24: 517-523.
- Georgakis MK, Beskou-Kontou T, Theodoridis I, Skalkidou A, Petridou ET. Surgical menopause in association with cognitive function and risk of dementia: A systematic review and meta-analysis. *Psychoneuroendocrinology* 2019;106: 9-19.
- Georgakis MK, Kalogirou EI, Diamantaras AA, Daskalopoulou SS, Munro CA, Lyketsos CG, Skalkidou A, Petridou ET. Age at menopause and duration of reproductive period in association with dementia and cognitive function: A systematic review and meta-analysis. *Psychoneuroendocrinology* 2016;73: 224-243.
- Gibson-Helm M, Teede H, Vincent A. Symptoms, health behavior and understanding of menopause therapy in women with premature menopause. *Climacteric : the journal of the International Menopause Society* 2014;17: 666-673.
- Giri R, Vincent AJ. Prevalence and Risk Factors of Premature Ovarian Insufficiency/Early Menopause. *Seminars in reproductive medicine* 2020;38: 237-246.
- Gleason CE, Dowling NM, Wharton W, Manson JE, Miller VM, Atwood CS, Brinton EA, Cedars MI, Lobo RA, Merriam GR *et al.* Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. *PLoS medicine* 2015;12: e1001833; discussion e1001833.
- Gold D, Nicolay L, Avian A, Greimel E, Balic M, Pristauz-Telsnigg G, Tamussino K, Trutnovsky G. Vaginal laser therapy versus hyaluronic acid suppositories for women with symptoms of urogenital atrophy after treatment for breast cancer: A randomized controlled trial. *Maturitas* 2023;167: 1-7.
- Gold EB, Crawford SL, Avis NE, Crandall CJ, Matthews KA, Waetjen LE, Lee JS, Thurston R, Vuga M, Harlow SD. Factors related to age at natural menopause: longitudinal analyses from SWAN. *American journal of epidemiology* 2013;178: 70-83.
- Gonçalves CR, Vasconcellos AS, Rodrigues TR, Comin FV, Reis FM. Hormone therapy in women with premature ovarian insufficiency: a systematic review and meta-analysis. *Reproductive biomedicine online* 2022;44: 1143-1157.
- Gong J, Harris K, Peters SAE, Woodward M. Reproductive factors and the risk of incident dementia: A cohort study of UK Biobank participants. *PLoS medicine* 2022;19: e1003955.
- Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M, Murad MH, Santoro NF, Warren MP. Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. *The Journal of clinical endocrinology and metabolism* 2017;102: 1413-1439.
- Gosden RG, Treloar SA, Martin NG, Cherkas LF, Spector TD, Faddy MJ, Silber SJ. Prevalence of premature ovarian failure in monozygotic and dizygotic twins. *Human reproduction (Oxford, England)* 2007;22: 610-615.
- Gosset A, Claeys JM, Huyghe E, Tremollieres F. Sexual function and quality of life in women with idiopathic premature ovarian insufficiency. *J Sex Med* 2023;20: 626-632.
- Goswami D, Conway GS. Premature ovarian failure. *Human reproduction update* 2005;11: 391-410.
- Gottschalk MS, Eskild A, Hofvind S, Bjelland EK. The relation of number of childbirths with age at natural menopause: a population study of 310 147 women in Norway. *Human reproduction (Oxford, England)* 2022;37: 333-340.



- Gottschau M, Rosthøj S, Settnes A, Aalborg GL, Viuff JH, Munk C, Jensen A, Kjær SK, Mellempkjær L. Long-Term Health Consequences After Ovarian Removal at Benign Hysterectomy : A Nationwide Cohort Study. *Annals of internal medicine* 2023;176: 596-604.
- Gravholt CH, Andersen NH, Christin-Maitre S, Davis SM, Duijnhouwer A, Gawlik A, Maciel-Guerra AT, Gutmark-Little I, Fleischer K, Hong D *et al*. Clinical practice guidelines for the care of girls and women with Turner syndrome. *Eur J Endocrinol* 2024;190: G53-G151.
- Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, Lin AE, Mauras N, Quigley CA, Rubin K *et al*. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *European journal of endocrinology / European Federation of Endocrine Societies* 2017;177: G1-g70.
- Gravholt CH, Viuff M, Just J, Sandahl K, Brun S, van der Velden J, Andersen NH, Skakkebaek A. The Changing Face of Turner Syndrome. *Endocrine reviews* 2023;44: 33-69.
- Green SM, Donegan E, Frey BN, Fedorkow DM, Key BL, Streiner DL, McCabe RE. Cognitive behavior therapy for menopausal symptoms (CBT-Meno): a randomized controlled trial. *Menopause* 2019;26: 972-980.
- Grindler NM, Allsworth JE, Macones GA, Kannan K, Roehl KA, Cooper AR. Persistent organic pollutants and early menopause in U.S. women. *PloS one* 2015;10: e0116057.
- Grossmann B, Saur S, Rall K, Pecher AC, Hubner S, Henes J, Henes M. Prevalence of autoimmune disease in women with premature ovarian failure. *Eur J Contracept Reprod Health Care* 2020;25: 72-75.
- Grynberg M, Jacquesson L, Sifer C. In vitro maturation of oocytes for preserving fertility in autoimmune premature ovarian insufficiency. *Fertility and sterility* 2020;114: 848-853.
- Gulbahar A, Akgun Kavurmaci S. Comparison of sexual function between women with iatrogenic and natural menopause. *Revista internacional de andrologia* 2022;20: 121-127.
- Guo S, Zhang J, Li Y, Ma H, Chen Q, Chen H, Du M. The pubertal development mode of Chinese girls with turner syndrome undergoing hormone replacement therapy. *BMC Endocr Disord* 2019;19: 72.
- Guo T, Qin Y, Jiao X, Li G, Simpson JL, Chen ZJ. FMR1 premutation is an uncommon explanation for premature ovarian failure in Han Chinese. *PloS one* 2014;9: e103316.
- Guthrie KA, LaCroix AZ, Ensrud KE, Joffe H, Newton KM, Reed SD, Caan B, Carpenter JS, Cohen LS, Freeman EW *et al*. Pooled Analysis of Six Pharmacologic and Nonpharmacologic Interventions for Vasomotor Symptoms. *Obstetrics and gynecology* 2015;126: 413-422.
- Ha J, Park SS, Park S, Yoon JH, Baek KH, Kim HJ, Lee S, Kim MR, Kang MI, Lee JW. Effects of Hormone Replacement Therapy on Bone Mass After Allogeneic Hematopoietic Stem Cell Transplantation. *The Journal of clinical endocrinology and metabolism* 2020;105.
- Hadnott TN, Gould HN, Gharib AM, Bondy CA. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the U.S. National Institutes of Health experience. *Fertility and sterility* 2011;95: 2251-2256.
- Hagman A, Loft A, Wennerholm UB, Pinborg A, Bergh C, Aittomaki K, Nygren KG, Bente Romundstad L, Hazekamp J, Soderstrom-Anttila V. Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study. *Human reproduction (Oxford, England)* 2013;28: 1598-1609.
- Hall E, Finch A, Jacobson M, Rosen B, Metcalfe K, Sun P, Narod SA, Kotsopoulos J. Effects of bilateral salpingo-oophorectomy on menopausal symptoms and sexual functioning among women with a BRCA1 or BRCA2 mutation. *Gynecol Oncol* 2019;152: 145-150.
- Hamoda H. British Menopause Society tools for clinicians: Progestogens and endometrial protection. *Post reproductive health* 2022;28: 40-46.
- Hao W, Fu C, Dong C, Zhou C, Sun H, Xie Z, Zhu D. Age at menopause and all-cause and cause-specific dementia: a prospective analysis of the UK Biobank cohort. *Human reproduction (Oxford, England)* 2023;38: 1746-1754.
- Hardy R, Kuh D, Wadsworth M. Smoking, body mass index, socioeconomic status and the menopausal transition in a British national cohort. *International journal of epidemiology* 2000;29: 845-851.
- Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *The Journal of clinical endocrinology and metabolism* 2012;97: 1159-1168.
- Hassan H, Allen I, Sofianopoulou E, Walburga Y, Turnbull C, Eccles DM, Tischkowitz M, Pharoah P, Antoniou AC. Long-term outcomes of hysterectomy with bilateral salpingo-oophorectomy: a



- systematic review and meta-analysis. *American journal of obstetrics and gynecology* 2024;230: 44-57.
- He M, Hu S, Wang J, Wang J, Găman MA, Hariri Z, Tian Y. Effect of resistance training on lipid profile in postmenopausal women: A systematic review and meta-analysis of randomized controlled trials. *European journal of obstetrics, gynecology, and reproductive biology* 2023;288: 18-28.
- Heddar A, Ogur C, Da Costa S, Braham I, Billaud-Rist L, Findlinki N, Beneteau C, Reynaud R, Mahmoud K, Legrand S *et al*. Genetic landscape of a large cohort of Primary Ovarian Insufficiency: New genes and pathways and implications for personalized medicine. *EBioMedicine* 2022;84: 104246.
- Henderson VW, St John JA, Hodis HN, McCleary CA, Stanczyk FZ, Shoupe D, Kono N, Dustin L, Allayee H, Mack WJ. Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. *Neurology* 2016;87: 699-708.
- Hickey I, Jha S, Wyld L. The psychosexual effects of risk-reducing bilateral salpingo-oophorectomy in female BRCA1/2 mutation carriers: A systematic review of qualitative studies. *Gynecol Oncol* 2021a;160: 763-770.
- Hickey M, Baber R, Eden J, Brennan J, Bateson D, Goldman M, Rockweiler H, Dreon D. Safety and effectiveness of a novel home-use therapeutic ultrasound device for the treatment of vaginal dryness in postmenopausal women: a pilot study. *Menopause* 2023;30: 383-392.
- Hickey M, Moss KM, Krejany EO, Wrede CD, Brand A, Kirk J, Symecko HL, Domchek SM, Tejada-Berges T, Trainer A, Mishra GD. What happens after menopause? (WHAM): A prospective controlled study of vasomotor symptoms and menopause-related quality of life 12 months after premenopausal risk-reducing salpingo-oophorectomy. *Gynecol Oncol* 2021b;163: 148-154.
- Hickey M, Trainer A, Braat S, Davey MA, Krejany E, Wark J. What Happens After Menopause? (WHAM): protocol for a prospective, multicentre, age-matched cohort trial of risk-reducing bilateral salpingo-oophorectomy in high-risk premenopausal women. *BMJ open* 2017;7: e018758.
- Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. *Endocrine reviews* 1997;18: 107-134.
- Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *The Journal of clinical endocrinology and metabolism* 2002;87: 489-499.
- Honigberg MC, Zekavat SM, Aragam K, Finneran P, Klarin D, Bhatt DL, Januzzi JL, Jr., Scott NS, Natarajan P. Association of Premature Natural and Surgical Menopause With Incident Cardiovascular Disease. *Jama* 2019;322: 2411-2421.
- Hsieh Y-T, Ho JYP. Thyroid autoimmunity is associated with higher risk of premature ovarian insufficiency—a nationwide Health Insurance Research Database study. *Human Reproduction* 2021;36: 1621-1629.
- Huan L, Deng X, He M, Chen S, Niu W. Meta-analysis: Early Age at Natural Menopause and Risk for All-Cause and Cardiovascular Mortality. *BioMed research international* 2021;2021: 6636856.
- Huang J, Zhang W, Liu Y, Liu Y, Wang J, Jiang H. Association between the FMR1 CGG repeat lengths and the severity of idiopathic primary ovarian insufficiency: a meta analysis. *Artificial cells, nanomedicine, and biotechnology* 2019;47: 3116-3122.
- Huang Y, Qi T, Ma L, Li D, Li C, Lan Y, Chu K, Chen P, Xu W, Cao Y *et al*. Menopausal symptoms in women with premature ovarian insufficiency: prevalence, severity, and associated factors. *Menopause* 2021;28: 529-537.
- Huber D, Seitz S, Kast K, Emons G, Ortmann O. Hormone replacement therapy in BRCA mutation carriers and risk of ovarian, endometrial, and breast cancer: a systematic review. *Journal of cancer research and clinical oncology* 2021;147: 2035-2045.
- Hunter MS. Cognitive behavioral therapy for menopausal symptoms. *Climacteric : the journal of the International Menopause Society* 2021;24: 51-56.
- Huo N, Smith CY, Gazzuola Rocca L, Rocca WA, Mielke MM. Association of Premenopausal Bilateral Oophorectomy With Restless Legs Syndrome. *JAMA network open* 2021;4: e2036058.
- Husebye ES, Anderson MS, Kampe O. Autoimmune Polyendocrine Syndromes. *The New England journal of medicine* 2018;378: 1132-1141.
- Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. *Lancet* 2021;397: 613-629.
- Hynes JS, Kuller JA, Goldstein SA, Ward CC, Muasher SJ. Increased Risk of Aortic Dissection Associated With Pregnancy in Women With Turner Syndrome: A Systematic Review. *Obstetrical & gynecological survey* 2020;75: 566-575.



- Ibarra-Ramírez M, Campos-Acevedo LD, Martínez de Villarreal LE. Chromosomal Abnormalities of Interest in Turner Syndrome: An Update. *Journal of pediatric genetics* 2023;12: 263-272.
- Ibrahim AA, Abdelazim IA, Hagra AM. The risk of Parkinson's disease in women who underwent hysterectomy before the age of menopause. *Przeegląd menopauzalny = Menopause review* 2022;21: 185-190.
- Isaza PG. Use of Growth Factors for Vulvo/Vaginal Bio-Stimulation. *Surgical technology international* 2019;34: 269-273.
- Ishizuka B. Current Understanding of the Etiology, Symptomatology, and Treatment Options in Premature Ovarian Insufficiency (POI). *Frontiers in endocrinology* 2021;12: 626924.
- Islam RM, Bell RJ, Green S, Page MJ, Davis SR. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. *The lancet Diabetes & endocrinology* 2019;7: 754-766.
- Islam RM, Davis SR, Bell RJ, Tejada-Berges T, Wrede CD, Domchek SM, Meiser B, Kirk J, Krejany EO, Hickey M. A prospective controlled study of sexual function and sexually related personal distress up to 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy. *Menopause* 2021;28: 748-755.
- Iwase A, Asada Y, Sugishita Y, Osuka S, Kitajima M, Kawamura K, from the subcommittee "Survey of Amh measurement in Japan" in Reproductive Endocrinology Committee JSoO, Gynecology. Anti-Mullerian hormone for screening, diagnosis, evaluation, and prediction: A systematic review and expert opinions. *The journal of obstetrics and gynaecology research* 2024;50: 15-39.
- Jacoby VL, Grady D, Wactawski-Wende J, Manson JE, Allison MA, Kuppermann M, Sarto GE, Robbins J, Phillips L, Martin LW *et al.* Oophorectomy vs ovarian conservation with hysterectomy: cardiovascular disease, hip fracture, and cancer in the Women's Health Initiative Observational Study. *Archives of internal medicine* 2011;171: 760-768.
- Jang YC, Leung CY, Huang HL. Comparison of Severity of Genitourinary Syndrome of Menopause Symptoms After Carbon Dioxide Laser vs Vaginal Estrogen Therapy: A Systematic Review and Meta-analysis. *JAMA network open* 2022;5: e2232563.
- Javadpour S, Sharifi N, Mosallanezhad Z, Rasekhjahromi A, Jamali S. Assessment of premature menopause on the sexual function and quality of life in women. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2021;37: 307-311.
- Jiao X, Qin C, Li J, Qin Y, Gao X, Zhang B, Zhen X, Feng Y, Simpson JL, Chen ZJ. Cytogenetic analysis of 531 Chinese women with premature ovarian failure. *Human reproduction (Oxford, England)* 2012;27: 2201-2207.
- Jiao X, Zhang H, Ke H, Zhang J, Cheng L, Liu Y, Qin Y, Chen ZJ. Premature Ovarian Insufficiency: Phenotypic Characterization Within Different Etiologies. *The Journal of clinical endocrinology and metabolism* 2017;102: 2281-2290.
- Jin J, Ruan X, Hua L, Mueck AO. Prevalence of metabolic syndrome and its components in Chinese women with premature ovarian insufficiency. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2023;39: 2254847.
- Jo J, Lee YJ, Lee H. Effectiveness of Acupuncture for Primary Ovarian Insufficiency: A Systematic Review and Meta-Analysis. *Evid Based Complement Alternat Med* 2015;2015: 842180.
- Johnson KA, Martin N, Nappi RE, Neal-Perry G, Shapiro M, Stute P, Thurston RC, Wolfman W, English M, Franklin C *et al.* Efficacy and Safety of Fezolinetant in Moderate to Severe Vasomotor Symptoms Associated With Menopause: A Phase 3 RCT. *The Journal of clinical endocrinology and metabolism* 2023;108: 1981-1997.
- Jolly A, Bayram Y, Turan S, Aycan Z, Tos T, Abali ZY, Hacıhamdioglu B, Coban Akdemir ZH, Hijazi H, Bas S *et al.* Exome Sequencing of a Primary Ovarian Insufficiency Cohort Reveals Common Molecular Etiologies for a Spectrum of Disease. *The Journal of clinical endocrinology and metabolism* 2019;104: 3049-3067.
- Jull J, Stacey D, Beach S, Dumas A, Strychar I, Ufholz LA, Prince S, Abdunour J, Prud'homme D. Lifestyle interventions targeting body weight changes during the menopause transition: a systematic review. *Journal of obesity* 2014;2014: 824310.
- Jungari SB, Chauhan BG. Prevalence and Determinants of Premature Menopause among Indian Women: Issues and Challenges Ahead. *Health & social work* 2017;42: 79-86.
- Kalantari H, Madani T, Zari Moradi S, Mansouri Z, Almadani N, Gourabi H, Mohseni Meybodi A. Cytogenetic analysis of 179 Iranian women with premature ovarian failure. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2013;29: 588-591.



- Kalantaridou SN, Naka KK, Papanikolaou E, Kazakos N, Kravariti M, Calis KA, Paraskevaïdis EA, Sideris DA, Tsatsoulis A, Chrousos GP, Michalis LK. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. *The Journal of clinical endocrinology and metabolism* 2004;89: 3907-3913.
- Kalra R, Cameron M, Stern C. Female fertility preservation in DSD. *Best practice & research Clinical endocrinology & metabolism* 2019;33: 101289.
- Kanadys W, Baranska A, Blaszczyk A, Polz-Dacewicz M, Drop B, Kanecki K, Malm M. Evaluation of Clinical Meaningfulness of Red Clover (*Trifolium pratense* L.) Extract to Relieve Hot Flashes and Menopausal Symptoms in Peri- and Post-Menopausal Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients* 2021;13.
- Karamitrou EK, Anagnostis P, Vaitsi K, Athanasiadis L, Goulis DG. Early menopause and premature ovarian insufficiency are associated with increased risk of dementia: A systematic review and meta-analysis of observational studies. *Maturitas* 2023;176: 107792.
- Kato I, Toniolo P, Akhmedkhanov A, Koenig KL, Shore R, Zeleniuch-Jacquotte A. Prospective study of factors influencing the onset of natural menopause. *Journal of clinical epidemiology* 1998;51: 1271-1276.
- Kaunitz AM, Kapoor E, Faubion S. Treatment of Women After Bilateral Salpingo-oophorectomy Performed Prior to Natural Menopause. *Jama* 2021;326: 1429-1430.
- Ke H, Tang S, Guo T, Hou D, Jiao X, Li S, Luo W, Xu B, Zhao S, Li G *et al.* Landscape of pathogenic mutations in premature ovarian insufficiency. *Nat Med* 2023;29: 483-492.
- Kearley-Shiers K, Holloway D, Janice R, Bruce D. Intravaginal dehydroepiandrosterone for genitourinary symptoms of the menopause: Is the evidence sufficient? *Post reproductive health* 2022;28: 237-243.
- Kelkar RL, Meherji PK, Kadam SS, Gupta SK, Nandedkar TD. Circulating auto-antibodies against the zona pellucida and thyroid microsomal antigen in women with premature ovarian failure. *Journal of reproductive immunology* 2005;66: 53-67.
- Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, Vassilopoulou-Sellin R, Yip CH, Egberts J, Mol-Arts M *et al.* Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *The Lancet Oncology* 2009;10: 135-146.
- Kershaw V, Hickey I, Wyld L, Jha S. The impact of risk reducing bilateral salpingo-oophorectomy on sexual function in BRCA1/2 mutation carriers and women with Lynch syndrome: A systematic review and meta-analysis. *European journal of obstetrics, gynecology, and reproductive biology* 2021;265: 7-17.
- Keukens A, van Wely M, van der Meulen C, Mochtar MH. Pre-eclampsia in pregnancies resulting from oocyte donation, natural conception or IVF: a systematic review and meta-analysis. *Human reproduction (Oxford, England)* 2022;37: 586-599.
- Khalafi M, Habibi Maleki A, Sakhaei MH, Rosenkranz SK, Pourvagher MJ, Ehsanifar M, Bayat H, Korivi M, Liu Y. The effects of exercise training on body composition in postmenopausal women: a systematic review and meta-analysis. *Frontiers in endocrinology* 2023a;14: 1183765.
- Khalafi M, Sakhaei MH, Habibi Maleki A, Rosenkranz SK, Pourvagher MJ, Fang Y, Korivi M. Influence of exercise type and duration on cardiorespiratory fitness and muscular strength in post-menopausal women: a systematic review and meta-analysis. *Frontiers in cardiovascular medicine* 2023b;10: 1190187.
- Khastgir G, Abdalla H, Studd JW. The case against ovarian biopsy for the diagnosis of premature menopause. *British journal of obstetrics and gynaecology* 1994;101: 96-98.
- Khizroeva J, Nalli C, Bitsadze V, Lojaco A, Zatti S, Andreoli L, Tincani A, Shoenfeld Y, Makatsariya A. Infertility in women with systemic autoimmune diseases. *Best practice & research Clinical endocrinology & metabolism* 2019;33: 101369.
- Kim C, Cleary PA, Cowie CC, Braffett BH, Dunn RL, Larkin ME, Gatcomb PM, Wessells HB, Nathan DM, Sarma AV. Effect of glycemic treatment and microvascular complications on menopause in women with type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. *Diabetes care* 2014;37: 701-708.
- Kim H, Jung JH, Han K, Lee D-Y, Fava M, Mischoulon D, Jeon HJ. Ages at menarche and menopause, hormone therapy, and the risk of depression. *General hospital psychiatry* 2023;83: 35-42.
- Kingsberg SA, Althof S, Simon JA, Bradford A, Bitzer J, Carvalho J, Flynn KE, Nappi RE, Reese JB, Rezaee RL *et al.* Female Sexual Dysfunction-Medical and Psychological Treatments, Committee 14. *J Sex Med* 2017;14: 1463-1491.



- Kingsberg SA, Simon JA. Female Hypoactive Sexual Desire Disorder: A Practical Guide to Causes, Clinical Diagnosis, and Treatment. *Journal of women's health* (2002) 2020;29: 1101-1112.
- Kirshenbaum M, Orvieto R. Premature ovarian insufficiency (POI) and autoimmunity-an update appraisal. *Journal of assisted reproduction and genetics* 2019;36: 2207-2215.
- Klasa Ł, Sadowska-Klasa A, Piekarska A, Wydra D, Zaucha JM. The management of gynecological complications in long-term survivors after allogeneic hematopoietic cell transplantation-a single-center real-life experience. *Annals of hematology* 2020;99: 1361-1368.
- Klein KO, Rosenfield RL, Santen RJ, Gawlik AM, Backeljauw PF, Gravholt CH, Sas TCJ, Mauras N. Estrogen Replacement in Turner Syndrome: Literature Review and Practical Considerations. *The Journal of clinical endocrinology and metabolism* 2018;103: 1790-1803.
- Knauff EA, Eijkemans MJ, Lambalk CB, ten Kate-Booij MJ, Hoek A, Beerendonk CC, Laven JS, Goverde AJ, Broekmans FJ, Themmen AP *et al.* Anti-Mullerian hormone, inhibin B, and antral follicle count in young women with ovarian failure. *The Journal of clinical endocrinology and metabolism* 2009;94: 786-792.
- Knobf MT, Jeon S, Smith B, Harris L, Thompson S, Stacy MR, Insogna K, Sinusas AJ. The Yale Fitness Intervention Trial in female cancer survivors: Cardiovascular and physiological outcomes. *Heart & lung : the journal of critical care* 2017;46: 375-381.
- Kokcu A. Premature ovarian failure from current perspective. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2010;26: 555-562.
- Kotsopoulos J, Gronwald J, Karlan BY, Huzarski T, Tung N, Moller P, Armel S, Lynch HT, Senter L, Eisen A *et al.* Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among BRCA1 Mutation Carriers. *JAMA oncology* 2018;4: 1059-1065.
- Kotsopoulos J, Gronwald J, Lubinski J, McCuaig J, Lynch HT, Neuhausen SL, Foulkes WD, Weitzel JN, Senter L, Tung N *et al.* Does preventive oophorectomy increase the risk of depression in BRCA mutation carriers? *Menopause* 2020;27: 156-161.
- Kotze LMS. Gynecologic and Obstetric Findings Related to Nutritional Status and Adherence to a Gluten-Free Diet in Brazilian Patients with Celiac Disease. *Journal of Clinical Gastroenterology* 2004;38: 567-574.
- Kou MJ, Ding XF, Chen JX, Liu Y, Liu YY. TRADITIONAL CHINESE MEDICINE COMBINED WITH HORMONE THERAPY TO TREAT PREMATURE OVARIAN FAILURE: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. *African journal of traditional, complementary, and alternative medicines : AJTCAM* 2016;13: 160-169.
- Koysombat K, McGown P, Nyunt S, Abbara A, Dhillon WS. New advances in menopause symptom management. *Best practice & research Clinical endocrinology & metabolism* 2024;38: 101774.
- Krul IM, Opstal-van Winden AWJ, Aleman BMP, Janus CPM, van Eggermond AM, De Bruin ML, Hauptmann M, Krol ADG, Schaapveld M, Broeks A *et al.* Breast Cancer Risk After Radiation Therapy for Hodgkin Lymphoma: Influence of Gonadal Hormone Exposure. *International journal of radiation oncology, biology, physics* 2017;99: 843-853.
- Kundu S, Acharya SS. Linkage of premature and early menopause with psychosocial well-being: a moderated multiple mediation approach. *BMC psychology* 2023;11: 228.
- La Marca A, Brozzetti A, Sighinolfi G, Marzotti S, Volpe A, Falorni A. Primary ovarian insufficiency: autoimmune causes. *Current opinion in obstetrics & gynecology* 2010;22: 277-282.
- La Marca A, Marzotti S, Brozzetti A, Stabile G, Artensio AC, Bini V, Giordano R, De Bellis A, Volpe A, Falorni A, Italian Addison N. Primary ovarian insufficiency due to steroidogenic cell autoimmunity is associated with a preserved pool of functioning follicles. *The Journal of clinical endocrinology and metabolism* 2009;94: 3816-3823.
- Lakhal B, Braham R, Berguigua R, Bouali N, Zaouali M, Chaieb M, Veitia RA, Saad A, Elghezal H. Cytogenetic analyses of premature ovarian failure using karyotyping and interphase fluorescence in situ hybridization (FISH) in a group of 1000 patients. *Clin Genet* 2010;78: 181-185.
- Lambrinoudaki I. Progestogens in postmenopausal hormone therapy and the risk of breast cancer. *Maturitas* 2014;77: 311-317.
- Langrish JP, Mills NL, Bath LE, Warner P, Webb DJ, Kelnar CJ, Critchley HO, Newby DE, Wallace WH. Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure. *Hypertension* 2009;53: 805-811.
- Langton CR, Whitcomb BW, Purdue-Smithe AC, Sievert LL, Hankinson SE, Manson JE, Rosner BA, Bertone-Johnson ER. Association of Parity and Breastfeeding With Risk of Early Natural Menopause. *JAMA network open* 2020;3: e1919615.



- Lara LA, Cartagena-Ramos D, Figueiredo JB, Rosa ESACJ, Ferriani RA, Martins WP, Fuentealba-Torres M. Hormone therapy for sexual function in perimenopausal and postmenopausal women. *The Cochrane database of systematic reviews* 2023;8: Cd009672.
- Larsen EC, Loft A, Holm K, Muller J, Brocks V, Andersen AN. Oocyte donation in women cured of cancer with bone marrow transplantation including total body irradiation in adolescence. *Human reproduction (Oxford, England)* 2000;15: 1505-1508.
- Lasa JS, Zubiaurre I, Soifer LO. Risk of infertility in patients with celiac disease: a meta-analysis of observational studies. *Arquivos de gastroenterologia* 2014;51: 144-150.
- Lau NM, Huang JY, MacDonald S, Elizur S, Gidoni Y, Holzer H, Chian RC, Tulandi T, Tan SL. Feasibility of fertility preservation in young females with Turner syndrome. *Reproductive biomedicine online* 2009;18: 290-295.
- Leach Matthew J, Moore V. Black cohosh (*Cimicifuga* spp.) for menopausal symptoms *Cochrane Database of Systematic Reviews*. 2012. John Wiley & Sons, Ltd.
- Lederman S, Ottery FD, Cano A, Santoro N, Shapiro M, Stute P, Thurston RC, English M, Franklin C, Lee M, Neal-Perry G. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet* 2023;401: 1091-1102.
- Lee GB, Nam GE, Kim W, Han B, Cho KH, Kim SM, Choi YS, Kim DH, Park YG, Jung JH *et al*. Association Between Premature Menopause and Cardiovascular Diseases and All-Cause Mortality in Korean Women. *Journal of the American Heart Association* 2023: e030117.
- Lee HW, Ang L, Kim E, Lee MS. Fennel (*Foeniculum vulgare* Miller) for the management of menopausal women's health: A systematic review and meta-analysis. *Complementary therapies in clinical practice* 2021;43: 101360.
- Lee HW, Ang L, Lee MS. Using ginseng for menopausal women's health care: A systematic review of randomized placebo-controlled trials. *Complementary therapies in clinical practice* 2022a;48: 101615.
- Lee YS, Wie C, Pew S, Kling JM. Stellate ganglion block as a treatment for vasomotor symptoms: Clinical application. *Cleveland Clinic journal of medicine* 2022b;89: 147-153.
- Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. *The Cochrane database of systematic reviews* 2016;2016: Cd001500.
- Li C, Cao M, Ma L, Ye X, Song Y, Pan W, Xu Z, Ma X, Lan Y, Chen P *et al*. Pyrethroid Pesticide Exposure and Risk of Primary Ovarian Insufficiency in Chinese Women. *Environmental science & technology* 2018;52: 3240-3248.
- Li F, Lu H, Huang Y, Wang X, Zhang Q, Li X, Qiang L, Yang Q. A systematic review and meta-analysis of the association between Hashimoto's thyroiditis and ovarian reserve. *Int Immunopharmacol* 2022;108: 108670.
- Li FG, Maheux-Lacroix S, Deans R, Nesbitt-Hawes E, Budden A, Nguyen K, Lim CY, Song S, McCormack L, Lyons SD *et al*. Effect of Fractional Carbon Dioxide Laser vs Sham Treatment on Symptom Severity in Women With Postmenopausal Vaginal Symptoms: A Randomized Clinical Trial. *Jama* 2021a;326: 1381-1389.
- Li M, Zhao C, Xie S, Liu X, Zhao Q, Zhang Z, Gong G. Effects of hypogonadism on brain development during adolescence in girls with Turner syndrome. *Human brain mapping* 2019;40: 4901-4911.
- Li S, Ma L, Huang H, Lou Z, Qi T, Huang Y, Zou Y, Zhou J. Loss of muscle mass in women with premature ovarian insufficiency as compared with healthy controls. *Menopause* 2023a;30: 122-127.
- Li XT, Li PY, Liu Y, Yang HS, He LY, Fang YG, Liu J, Liu BY, Chaplin JE. Health-related quality-of-life among patients with premature ovarian insufficiency: a systematic review and meta-analysis. *Qual Life Res* 2020a;29: 19-36.
- Li Y, Chang J, Shi G, Zhang W, Wang H, Wei L, Liu X, Zhang W. Effects of stellate ganglion block on perimenopausal hot flashes: a randomized controlled trial. *Frontiers in endocrinology* 2023b;14: 1293358.
- Li Y, Xia G, Tan Y, Shuai J. Acupoint stimulation and Chinese herbal medicines for the treatment of premature ovarian insufficiency: A systematic review and meta-analysis. *Complementary therapies in clinical practice* 2020b;41: 101244.
- Li Y, Zhao D, Wang M, Sun JY, Liu J, Qi Y, Hao YC, Deng QJ, Liu J, Liu J, Liu M. Combined effect of menopause and cardiovascular risk factors on death and cardiovascular disease: a cohort study. *BMC cardiovascular disorders* 2021b;21: 109.
- Lindsay Mart F, Gutmark-Little I, Streich-Tilles T, Trout AT, Khoury J, Bowers K, Casnellie L, Backeljauw P. Current Recommended Estrogen Dosing for Pubertal Induction in Turner Syndrome



Results in Normal Uterine Growth. *The Journal of clinical endocrinology and metabolism* 2024;109: e1040-e1047.

Liu AX, Shi HY, Cai ZJ, Liu A, Zhang D, Huang HF, Jin HM. Increased risk of gonadal malignancy and prophylactic gonadectomy: a study of 102 phenotypic female patients with Y chromosome or Y-derived sequences. *Human reproduction (Oxford, England)* 2014;29: 1413-1419.

Liu H, Cai K, Wang J, Zhang H. The effects of mindfulness-based interventions on anxiety, depression, stress, and mindfulness in menopausal women: A systematic review and meta-analysis. *Front Public Health* 2022a;10: 1045642.

Liu J, Jin X, Liu W, Chen W, Wang L, Feng Z, Huang J. The risk of long-term cardiometabolic disease in women with premature or early menopause: A systematic review and meta-analysis. *Frontiers in cardiovascular medicine* 2023;10: 1131251.

Liu T, Chen S, Mielke GI, McCarthy AL, Bailey TG. Effects of exercise on vasomotor symptoms in menopausal women: a systematic review and meta-analysis. *Climacteric : the journal of the International Menopause Society* 2022b;25: 552-561.

Liu W, Nguyen TN, Tran Thi TV, Zhou S. Kuntai Capsule plus Hormone Therapy vs. Hormone Therapy Alone in Patients with Premature Ovarian Failure: A Systematic Review and Meta-Analysis. *Evid Based Complement Alternat Med* 2019;2019: 2085804.

Loaiza-Betancur AF, Chulvi-Medrano I, Díaz-López VA, Gómez-Tomás C. The effect of exercise training on blood pressure in menopause and postmenopausal women: A systematic review of randomized controlled trials. *Maturitas* 2021;149: 40-55.

Luborsky J, Llanes B, Davies S, Binor Z, Radwanska E, Pong R. Ovarian autoimmunity: greater frequency of autoantibodies in premature menopause and unexplained infertility than in the general population. *Clin Immunol* 1999;90: 368-374.

Luo W, Ke H, Tang S, Jiao X, Li Z, Zhao S, Zhang F, Guo T, Qin Y. Next-generation sequencing of 500 POI patients identified novel responsible monogenic and oligogenic variants. *Journal of ovarian research* 2023;16: 39.

Luo X, Cheng R, Zhang J, Ma Y, Zhang J, Luo Y, Xu L. Evaluation of body composition in POF and its association with bone mineral density and sex steroid levels. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2018;34: 1027-1030.

Lutjen P, Trounson A, Leeton J, Findlay J, Wood C, Renou P. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. *Nature* 1984;307: 174-175.

Lv M, Zhang Y, Chen GC, Li G, Rui Y, Qin L, Wan Z. Reproductive factors and risk of Parkinson's disease in women: A meta-analysis of observational studies. *Behavioural brain research* 2017;335: 103-110.

Ma Q, Tan Y, Mo G. Effectiveness of Cotreatment with Kuntai Capsule and Climen for Premature Ovarian Failure: A Meta-Analysis. *Evid Based Complement Alternat Med* 2020;2020: 4367359.

Ma X, Pan W, Zhu Z, Ye X, Li C, Zhou J, Liu J. A case-control study of thallium exposure with the risk of premature ovarian insufficiency in women. *Archives of environmental & occupational health* 2022;77: 468-477.

Maclaughlan David S, Salzillo S, Bowe P, Scuncio S, Malit B, Raker C, Gass JS, Granai CO, Dizon DS. Randomised controlled trial comparing hypnotherapy versus gabapentin for the treatment of hot flashes in breast cancer survivors: a pilot study. *BMJ open* 2013;3: e003138.

Mamsen LS, Charkiewicz K, Anderson RA, Telfer EE, McLaughlin M, Kelsey TW, Kristensen SG, Gook DA, Ernst E, Andersen CY. Characterization of follicles in girls and young women with Turner syndrome who underwent ovarian tissue cryopreservation. *Fertility and sterility* 2019;111: 1217-1225 e1213.

Mamsen LS, Kelsey TW, Ernst E, Macklon KT, Lund AM, Andersen CY. Cryopreservation of ovarian tissue may be considered in young girls with galactosemia. *Journal of assisted reproduction and genetics* 2018;35: 1209-1217.

Manchanda R, Gaba F, Talaulikar V, Pundir J, Gessler S, Davies M, Menon U. Risk-Reducing Salpingo-Oophorectomy and the Use of Hormone Replacement Therapy Below the Age of Natural Menopause: Scientific Impact Paper No. 66 October 2021: Scientific Impact Paper No. 66. *BJOG : an international journal of obstetrics and gynaecology* 2022;129: e16-e34.

Manson JE, Aragaki AK, Bassuk SS, Chlebowski RT, Anderson GL, Rossouw JE, Howard BV, Thomson CA, Stefanick ML, Kaunitz AM *et al.* Menopausal Estrogen-Alone Therapy and Health Outcomes in Women With and Without Bilateral Oophorectomy: A Randomized Trial. *Annals of internal medicine* 2019;171: 406-414.



- Marchetti C, De Felice F, Boccia S, Sassu C, Di Donato V, Perniola G, Palaia I, Monti M, Muzii L, Tombolini V, Benedetti Panici P. Hormone replacement therapy after prophylactic risk-reducing salpingo-oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers: A meta-analysis. *Critical reviews in oncology/hematology* 2018;132: 111-115.
- Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. *The Cochrane database of systematic reviews* 2017;1: Cd004143.
- Matsumoto F, Matsuyama S, Matsui F, Yazawa K, Matsuoka K. Variation of Gonadal Dysgenesis and Tumor Risk in Patients With 45,X/46,XY Mosaicism. *Urology* 2020;137: 157-160.
- Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in Turner syndrome. *Circulation* 2007;116: 1663-1670.
- Mauras N, Shulman D, Hsiang HY, Balagopal P, Welch S. Metabolic effects of oral versus transdermal estrogen in growth hormone-treated girls with turner syndrome. *The Journal of clinical endocrinology and metabolism* 2007;92: 4154-4160.
- McDonald IR, Welt CK, Dwyer AA. Health-related quality of life in women with primary ovarian insufficiency: a scoping review of the literature and implications for targeted interventions. *Human reproduction (Oxford, England)* 2022;37: 2817-2830.
- McDonnell CM, Coleman L, Zacharin MR. A 3-year prospective study to assess uterine growth in girls with Turner's syndrome by pelvic ultrasound. *Clinical endocrinology* 2003;58: 446-450.
- McKinlay SM, Bifano NL, McKinlay JB. Smoking and age at menopause in women. *Annals of internal medicine* 1985;103: 350-356.
- Menezes C, Pravata GR, Yela DA, Benetti-Pinto CL. Women with premature ovarian failure using hormone therapy do not experience increased levels of depression, anxiety and stress compared to controls. *Journal of affective disorders* 2020;273: 562-566.
- Mension E, Alonso I, Anglès-Acedo S, Ros C, Otero J, Villarino Á, Farré R, Saco A, Vega N, Castrejón N *et al.* Effect of Fractional Carbon Dioxide vs Sham Laser on Sexual Function in Survivors of Breast Cancer Receiving Aromatase Inhibitors for Genitourinary Syndrome of Menopause: The LIGHT Randomized Clinical Trial. *JAMA network open* 2023;6: e2255697.
- Mercier J, Dumoulin C, Carrier-Noreau G. Pelvic floor muscle rehabilitation for genitourinary syndrome of menopause: why, how and when? *Climacteric : the journal of the International Menopause Society* 2023;26: 302-308.
- Mewes JC, Steuten LM, Duijts SF, Oldenburg HS, van Beurden M, Stuiver MM, Hunter MS, Kieffer JM, van Harten WH, Aaronson NK. Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients. *Journal of cancer survivorship : research and practice* 2015;9: 126-135.
- Meziou N, Scholfield C, Taylor CA, Armstrong HL. Hormone therapy for sexual function in perimenopausal and postmenopausal women: a systematic review and meta-analysis update. *Menopause* 2023;30: 659-671.
- Michels KA, Brinton LA, Pfeiffer RM, Trabert B. Oral Contraceptive Use and Risks of Cancer in the NIH-AARP Diet and Health Study. *American journal of epidemiology* 2018;187: 1630-1641.
- Michelsen TM, Rosland TE, Åsvold BO, Pripp AH, Liavaag AH, Johansen N. All-cause and cardiovascular mortality after hysterectomy and oophorectomy in a large cohort (HUNT2). *Acta obstetrica et gynecologica Scandinavica* 2023;102: 465-472.
- Mirkin S, Goldstein SR, Archer DF, Pickar JH, Graham S, Bernick B. Endometrial safety and bleeding profile of a 17 $\beta$ -estradiol/progesterone oral softgel capsule (TX-001HR). *Menopause* 2020;27: 410-417.
- Mishra GD, Pandeya N, Dobson AJ, Chung HF, Anderson D, Kuh D, Sandin S, Giles GG, Bruinsma F, Hayashi K *et al.* Early menarche, nulliparity and the risk for premature and early natural menopause. *Human reproduction (Oxford, England)* 2017;32: 679-686.
- Mittal M, McEniery C, Supramaniam PR, Cardozo L, Savvas M, Panay N, Hamoda H. Impact of micronised progesterone and medroxyprogesterone acetate in combination with transdermal oestradiol on cardiovascular markers in women diagnosed with premature ovarian insufficiency or an early menopause: a randomised pilot trial. *Maturitas* 2022;161: 18-26.
- Moncayo H, Moncayo R, Benz R, Wolf A, Lauritzen C. Ovarian failure and autoimmunity. Detection of autoantibodies directed against both the unoccupied luteinizing hormone/human chorionic gonadotropin receptor and the hormone-receptor complex of bovine corpus luteum. *The Journal of clinical investigation* 1989;84: 1857-1865.



- Monteleone P, Parrini D, Faviana P, Carletti E, Casarosa E, Uccelli A, Cela V, Genazzani AR, Artini PG. Female infertility related to thyroid autoimmunity: the ovarian follicle hypothesis. *American journal of reproductive immunology (New York, NY : 1989)* 2011;66: 108-114.
- Morga A, Ajmera M, Gao E, Patterson-Lomba O, Zhao A, Mancuso S, Siddiqui E, Kagan R. Systematic review and network meta-analysis comparing the efficacy of fezolinetant with hormone and nonhormone therapies for treatment of vasomotor symptoms due to menopause. *Menopause* 2024;31: 68-76.
- Morgan O, Belda R, Schnur J, Montgomery G, Parmar S, Chirivella I, Cano A. Prophylactic mastectomy and bilateral salpingo-oophorectomy in patients with breast cancer: a systematic review of postsurgical sexual function and menopausal hormone therapy symptom mitigation. *Sexual medicine reviews* 2023;12: 3-13.
- Morris DH, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. Familial concordance for age at natural menopause: results from the Breakthrough Generations Study. *Menopause* 2011;18: 956-961.
- Moss KM, Mishra GD, Krejany EO, Hickey M. What happens after menopause? (WHAM): A prospective controlled study of symptom profiles up to 12 months after pre-menopausal risk-reducing salpingo-oophorectomy. *Gynecol Oncol* 2022.
- Movaghar A, Page D, Brilliant M, Baker MW, Greenberg J, Hong J, DaWalt LS, Saha K, Kuusisto F, Stewart R *et al*. Data-driven phenotype discovery of FMR1 premutation carriers in a population-based sample. *Science advances* 2019;5: eaaw7195.
- Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH. Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis. *JAMA cardiology* 2016;1: 767-776.
- Murray A, Schoemaker MJ, Bennett CE, Ennis S, Macpherson JN, Jones M, Morris DH, Orr N, Ashworth A, Jacobs PA, Swerdlow AJ. Population-based estimates of the prevalence of FMR1 expansion mutations in women with early menopause and primary ovarian insufficiency. *Genetics in medicine : official journal of the American College of Medical Genetics* 2014;16: 19-24.
- Nabhan ZM, Dimeglio LA, Qi R, Perkins SM, Eugster EA. Conjugated oral versus transdermal estrogen replacement in girls with Turner syndrome: a pilot comparative study. *The Journal of clinical endocrinology and metabolism* 2009;94: 2009-2014.
- Naessén S, Bergström I, Ljungman P, Landgren BM. Long-term follow-up of bone density, general and reproductive health in female survivors after treatment for haematological malignancies. *Eur J Haematol* 2014;93: 137-142.
- Najaf Najafi M, Ghazanfarpour M. Effect of phytoestrogens on sexual function in menopausal women: a systematic review and meta-analysis. *Climacteric : the journal of the International Menopause Society* 2018;21: 437-445.
- Nakamura T, Tsuburai T, Tokinaga A, Nakajima I, Kitayama R, Imai Y, Nagata T, Yoshida H, Hirahara F, Sakakibara H. Efficacy of estrogen replacement therapy (ERT) on uterine growth and acquisition of bone mass in patients with Turner syndrome. *Endocrine journal* 2015;62: 965-970.
- Naletto L, Frigo AC, Ceccato F, Sabbadin C, Scarpa R, Presotto F, Dalla Costa M, Faggian D, Plebani M, Censi S *et al*. The natural history of autoimmune Addison's disease from the detection of autoantibodies to development of the disease: a long-term follow-up study on 143 patients. *European journal of endocrinology / European Federation of Endocrine Societies* 2019;180: 223-234.
- Naleway AL, Mittendorf KF, Irving SA, Henninger ML, Crane B, Smith N, Daley MF, Gee J. Primary Ovarian Insufficiency and Adolescent Vaccination. *Pediatrics* 2018;142.
- Nappi RE, Cucinella L, Martini E, Cassani C. The role of hormone therapy in urogenital health after menopause. *Best practice & research Clinical endocrinology & metabolism* 2021;35: 101595.
- Nappi RE, Cucinella L, Martini E, Rossi M, Tiranini L, Martella S, Bosoni D, Cassani C. Sexuality in premature ovarian insufficiency. *Climacteric : the journal of the International Menopause Society* 2019;22: 289-295.
- Nappi RE, Martella S, Albani F, Cassani C, Martini E, Landoni F. Hyaluronic Acid: A Valid Therapeutic Option for Early Management of Genitourinary Syndrome of Menopause in Cancer Survivors? *Healthcare (Basel, Switzerland)* 2022a;10.
- Nappi RE, Tiranini L, Martini E, Bosoni D, Righi A, Cucinella L. Medical Treatment of Female Sexual Dysfunction. *The Urologic clinics of North America* 2022b;49: 299-307.
- Nappi RE, Tiranini L, Sacco S, De Matteis E, De Icco R, Tassorelli C. Role of Estrogens in Menstrual Migraine. *Cells* 2022c;11.
- Nebgen DR, Domchek SM, Kotsopoulos J, de Hullu JA, Crosbie EJ, Paramanandam VS, Brood-van Zanten MMA, Norquist BM, Guise T, Rozenberg S *et al*. Care after premenopausal risk-reducing



- salpingo-oophorectomy in high-risk women: Scoping review and international consensus recommendations. *BJOG: an international journal of obstetrics and gynaecology* 2023;130: 1437-1450.
- Nelson LM. Clinical practice. Primary ovarian insufficiency. *The New England journal of medicine* 2009;360: 606-614.
- Nelson SM, Davis SR, Kalantaridou S, Lumsden MA, Panay N, Anderson RA. Anti-Müllerian hormone for the diagnosis and prediction of menopause: a systematic review. *Human reproduction update* 2023;29: 327-346.
- Nguyen HH, Wong P, Strauss BJ, Jones G, Ebeling PR, Milat F, Vincent A. Delay in estrogen commencement is associated with lower bone mineral density in Turner syndrome. *Climacteric: the journal of the International Menopause Society* 2017;20: 436-441.
- Nguyen TM, Do TTT, Tran TN, Kim JH. Exercise and Quality of Life in Women with Menopausal Symptoms: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *International journal of environmental research and public health* 2020;17.
- Nguyen TTB, Hsu YY, Sari YP. The Effect of Pelvic Floor Muscle Training on Health-Related Quality of Life in Postmenopausal Women With Genitourinary Syndrome: A Systematic Review and Meta-Analysis. *The journal of nursing research: JNR* 2024;32: e316.
- NICE. Menopause: diagnosis and management. NICE guideline [NG23] <https://www.nice.org.uk/guidance/ng23> 2015;Published: 12 November 2015 Last updated: 05 December 2019.
- NICE. Summary of evidence for 2019 surveillance of menopause (2015) NICE guideline NG23. <https://www.nice.org.uk/consultations/672/10/diagnosing-and-managing-premature-ovarian-insufficiency#diagnosing-and-managing-premature-ovarian-insufficiency> 2019.
- Nolan M, Oikonomou EK, Silversides CK, Hines MR, Thompson KA, Campbell BA, Amir E, Maxwell C, Thavendiranathan P. Impact of Cancer Therapy-Related Cardiac Dysfunction on Risk of Heart Failure in Pregnancy. *JACC CardioOncology* 2020;2: 153-162.
- Noll P, Campos CAS, Leone C, Zangirolami-Raimundo J, Noll M, Baracat EC, Júnior JMS, Sorpreso ICE. Dietary intake and menopausal symptoms in postmenopausal women: a systematic review. *Climacteric: the journal of the International Menopause Society* 2021;24: 128-138.
- Novosad JA, Kalantaridou SN, Tong ZB, Nelson LM. Ovarian antibodies as detected by indirect immunofluorescence are unreliable in the diagnosis of autoimmune premature ovarian failure: a controlled evaluation. *BMC women's health* 2003;3: 2.
- Nunes PRP, Castro ESP, de Oliveira AA, Camilo BF, Cristina-Souza G, Vieira-Souza LM, Carneiro M. Effect of resistance training volume on body adiposity, metabolic risk, and inflammation in postmenopausal and older females: Systematic review and meta-analysis of randomized controlled trials. *Journal of sport and health science* 2023.
- O'Donnell RL, Warner P, Lee RJ, Walker J, Bath LE, Kelnar CJ, Wallace WH, Critchley HO. Physiological sex steroid replacement in premature ovarian failure: randomized crossover trial of effect on uterine volume, endometrial thickness and blood flow, compared with a standard regimen. *Human reproduction (Oxford, England)* 2012;27: 1130-1138.
- O'Donoghue S, Green T, Ross JL, Hallmayer J, Lin X, Jo B, Huffman LC, Hong DS, Reiss AL. Brain Development in School-Age and Adolescent Girls: Effects of Turner Syndrome, Estrogen Therapy, and Genomic Imprinting. *Biological psychiatry* 2020;87: 113-122.
- Obara-Moszynska M, Dzialach L, Rabska-Pietrzak B, Niedziela M, Kapczuk K. Uterine Development During Induced Puberty in Girls with Turner Syndrome. *Frontiers in endocrinology* 2021;12: 707031.
- Oboni JB, Marques-Vidal P, Bastardot F, Vollenweider P, Waeber G. Impact of smoking on fertility and age of menopause: a population-based assessment. *BMJ open* 2016;6: e012015.
- Ornello R, Frattale I, Caponnetto V, Pistoia F, Sacco S. Cerebral vascular reactivity and the migraine-stroke relationship: A narrative review. *Journal of the neurological sciences* 2020;414: 116887.
- Osuka S, Iwase A, Goto M, Takikawa S, Nakamura T, Murase T, Kato N, Kotani T, Kikkawa F. Thyroid Autoantibodies do not Impair the Ovarian Reserve in Euthyroid Infertile Women: A Cross-Sectional Study. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et métabolisme* 2018;50: 537-542.
- Otero UB, Chor D, Carvalho MS, Faerstein E, Lopes Cde S, Werneck GL. Lack of association between age at menarche and age at menopause: Pro-Saude Study, Rio de Janeiro, Brazil. *Maturitas* 2010;67: 245-250.
- Oyesanya OA, Olufowobi O, Ross W, Sharif K, Afnan M. Prognosis of oocyte donation cycles: a prospective comparison of the in vitro fertilization-embryo transfer cycles of recipients who used shared oocytes versus those who used altruistic donors. *Fertility and sterility* 2009;92: 930-936.



- Palacios S, Hood S, Abakah-Phillips T, Savania N, Krychman M. A randomized trial on the effectiveness and safety of 5 water-based personal lubricants. *J Sex Med* 2023;20: 498-506.
- Pan ML, Chen LR, Tsao HM, Chen KH. Polycystic ovarian syndrome and the risk of subsequent primary ovarian insufficiency: a nationwide population-based study. *Menopause* 2017;24: 803-809.
- Pan W, Ye X, Yin S, Ma X, Li C, Zhou J, Liu W, Liu J. Selected persistent organic pollutants associated with the risk of primary ovarian insufficiency in women. *Environment international* 2019;129: 51-58.
- Pan W, Ye X, Zhu Z, Li C, Zhou J, Liu J. A case-control study of arsenic exposure with the risk of primary ovarian insufficiency in women. *Environmental science and pollution research international* 2020;27: 25220-25229.
- Pan W, Ye X, Zhu Z, Li C, Zhou J, Liu J. Urinary cadmium concentrations and risk of primary ovarian insufficiency in women: a case-control study. *Environmental geochemistry and health* 2021;43: 2025-2035.
- Panay N, Al-Azzawi F, Bouchard C, Davis SR, Eden J, Lodhi I, Rees M, Rodenberg CA, Rymer J, Schwenkhausen A, Sturdee DW. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. *Climacteric : the journal of the International Menopause Society* 2010;13: 121-131.
- Panay N, Anderson RA, Nappi RE, Vincent AJ, Vujovic S, Webber L, Wolfman W. Premature ovarian insufficiency: an International Menopause Society White Paper. *Climacteric : the journal of the International Menopause Society* 2020;23: 426-446.
- Panay N, Nappi RE, Stute P, Palacios S, Paszkowski T, Kagan R, Archer DF, Héroux J, Boolell M. Oral estradiol/micronized progesterone may be associated with lower risk of venous thromboembolism compared with conjugated equine estrogens/medroxyprogesterone acetate in real-world practice. *Maturitas* 2023;172: 23-31.
- Parker WH, Feskanich D, Broder MS, Chang E, Shoupe D, Farquhar CM, Berek JS, Manson JE. Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. *Obstetrics and gynecology* 2013;121: 709-716.
- Paterson WF, Hollman AS, Donaldson MD. Poor uterine development in Turner syndrome with oral oestrogen therapy. *Clinical endocrinology* 2002;56: 359-365.
- Pellicer N, Cozzolino M, Diaz-Garcia C, Galliano D, Cobo A, Pellicer A, Herraiz S. Ovarian rescue in women with premature ovarian insufficiency: facts and fiction. *Reproductive biomedicine online* 2023;46: 543-565.
- Persani L, Rossetti R, Cacciato C, Bonomi M. Primary Ovarian Insufficiency: X chromosome defects and autoimmunity. *J Autoimmun* 2009;33: 35-41.
- Pesce G, Artaud F, Roze E, Degaey I, Portugal B, Nguyen TTH, Fournier A, Boutron-Ruault MC, Severi G, Elbaz A, Canonico M. Reproductive characteristics, use of exogenous hormones and Parkinson disease in women from the E3N study. *Brain : a journal of neurology* 2023;146: 2535-2546.
- Peycheva D, Sullivan A, Hardy R, Bryson A, Conti G, Ploubidis G. Risk factors for natural menopause before the age of 45: evidence from two British population-based birth cohort studies. *BMC women's health* 2022;22: 438.
- Pires ES, Khole VV. A block in the road to fertility: autoantibodies to heat-shock protein 90-beta in human ovarian autoimmunity. *Fertility and sterility* 2009;92: 1395-1409.
- Podfigurna-Stopa A, Czyzyk A, Grymowicz M, Smolarczyk R, Katulski K, Czajkowski K, Meczekalski B. Premature ovarian insufficiency: the context of long-term effects. *Journal of endocrinological investigation* 2016;39: 983-990.
- Podfigurna A, Maciejewska-Jeske M, Nadolna M, Mikolajska-Ptas P, Szeliga A, Bilinski P, Napierala P, Meczekalski B. Impact of Hormonal Replacement Therapy on Bone Mineral Density in Premature Ovarian Insufficiency Patients. *Journal of clinical medicine* 2020;9.
- Poggio F, Del Mastro L, Bruzzone M, Ceppi M, Razeti MG, Fregatti P, Ruelle T, Pronzato P, Massarotti C, Franzoi MA *et al.* Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis. *Breast cancer research and treatment* 2022;191: 269-275.
- Pokoradi AJ, Iversen L, Hannaford PC. Factors associated with age of onset and type of menopause in a cohort of UK women. *American journal of obstetrics and gynecology* 2011;205: 34 e31-13.
- Popat VB, Calis KA, Kalantaridou SN, Vanderhoof VH, Koziol D, Troendle JF, Reynolds JC, Nelson LM. Bone mineral density in young women with primary ovarian insufficiency: results of a three-year randomized controlled trial of physiological transdermal estradiol and testosterone replacement. *The Journal of clinical endocrinology and metabolism* 2014;99: 3418-3426.
- Poppe K, Velkeniers B, Glinoeer D. The role of thyroid autoimmunity in fertility and pregnancy. *Nat Clin Pract Endocrinol Metab* 2008;4: 394-405.



- Poteet B, Ali N, Bellcross C, Sherman SL, Espinel W, Hipp H, Allen EG. The diagnostic experience of women with fragile X-associated primary ovarian insufficiency (FXPOI). *Journal of assisted reproduction and genetics* 2023;40: 179-190.
- Prince C, Sharp GC, Howe LD, Fraser A, Richmond RC. The relationships between women's reproductive factors: a Mendelian randomisation analysis. *BMC medicine* 2022;20: 103.
- Pyri F, Abedi P, Maraghi E, Jefreh MG. The Effect of Mindfulness on Quality of Life among Women with Premature Ovarian Insufficiency: A Randomized Clinical Trial. *J Midlife Health* 2021;12: 116-121.
- Rafique M, AlObaid S, Al-Jaroudi D. 47, XXX syndrome with infertility, premature ovarian insufficiency, and streak ovaries. *Clinical case reports* 2019;7: 1238-1241.
- Reato G, Morlin L, Chen S, Furmaniak J, Smith BR, Masiero S, Albergoni MP, Cervato S, Zanchetta R, Betterle C. Premature ovarian failure in patients with autoimmune Addison's disease: clinical, genetic, and immunological evaluation. *The Journal of clinical endocrinology and metabolism* 2011;96: E1255-1261.
- Rebar RW, Connolly HV. Clinical features of young women with hypergonadotropic amenorrhea. *Fertility and sterility* 1990;53: 804-810.
- Riemma G, Schiattarella A, La Verde M, Zarobbi G, Garzon S, Cucinella G, Calagna G, Labriola D, De Franciscis P. Efficacy of Low-Dose Paroxetine for the Treatment of Hot Flashes in Surgical and Physiological Postmenopausal Women: Systematic Review and Meta-Analysis of Randomized Trials. *Medicina (Kaunas, Lithuania)* 2019;55.
- Rios-Espinosa A, Cruz-Luna M, Garmendia-Gallardo C, Hernández-Castañón MY, Hernández-Hernández VY, Sánchez-Tinoco PM, Bajonero-Domínguez A, Vergara Lope-Núñez JA, Álvarez-Pérez MA, González-Quiroz JL *et al.* Citalopram improves vasomotor syndrome and urogenital syndrome of menopause in Mexican women: a randomized clinical trial. *Archives of gynecology and obstetrics* 2022;306: 2035-2045.
- Rivera CM, Grossardt BR, Rhodes DJ, Brown RD, Jr., Roger VL, Melton LJ, 3rd, Rocca WA. Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause* 2009a;16: 15-23.
- Rivera CM, Grossardt BR, Rhodes DJ, Rocca WA. Increased mortality for neurological and mental diseases following early bilateral oophorectomy. *Neuroepidemiology* 2009b;33: 32-40.
- Rocca WA, Faubion SS. Estrogen and dementia. *Maturitas* 2022;165: 120-121.
- Rocca WA, Gazzuola Rocca L, Smith CY, Grossardt BR, Faubion SS, Shuster LT, Kirkland JL, Stewart EA, Miller VM. Bilateral Oophorectomy and Accelerated Aging: Cause or Effect? *J Gerontol A Biol Sci Med Sci* 2017;72: 1213-1217.
- Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ, 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *The Lancet Oncology* 2006;7: 821-828.
- Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, estrogen, and dementia: a 2014 update. *Molecular and cellular endocrinology* 2014;389: 7-12.
- Rocca WA, Grossardt BR, Shuster LT, Stewart EA. Hysterectomy, oophorectomy, estrogen, and the risk of dementia. *Neuro-degenerative diseases* 2012;10: 175-178.
- Rocca WA, Lohse CM, Smith CY, Fields JA, Machulda MM, Mielke MM. Association of Premenopausal Bilateral Oophorectomy With Cognitive Performance and Risk of Mild Cognitive Impairment. *JAMA network open* 2021a;4: e2131448.
- Rocca WA, Mielke MM, Gazzuola Rocca L, Stewart EA. Premature or early bilateral oophorectomy: a 2021 update. *Climacteric : the journal of the International Menopause Society* 2021b;24: 466-473.
- Rocca WA, Smith CY, Gazzuola Rocca L, Savica R, Mielke MM. Association of Premenopausal Bilateral Oophorectomy With Parkinsonism and Parkinson Disease. *JAMA network open* 2022;5: e2238663.
- Rodari G, Federici S, Todisco T, Ubertaini G, Cattoni A, Pagano M, Giacchetti F, Profka E, Citterio V, Messetti D *et al.* Towards an individualized management of pubertal induction in girls with hypogonadism: insight into the best replacement outcomes from a large multicentre registry. *European journal of endocrinology / European Federation of Endocrine Societies* 2023;188: 467-476.
- Rogol AD. Sex chromosome aneuploidies and fertility: 47,XXY, 47,XYY, 47,XXX and 45,X/47,XXX. *Endocrine connections* 2023;12.
- Roland N, Neumann A, Hoisnard L, Duranteau L, Froelich S, Zureik M, Weill A. Use of progestogens and the risk of intracranial meningioma: national case-control study. *BMJ (Clinical research ed)* 2024;384: e078078.
- Roman Lay AA, do Nascimento CF, Horta BL, Dias Porto Chiavegatto Filho A. Reproductive factors and age at natural menopause: A systematic review and meta-analysis. *Maturitas* 2020;131: 57-64.



- Rosario R, Anderson RA. Novel approaches to fertility restoration in women with premature ovarian insufficiency. *Climacteric : the journal of the International Menopause Society* 2021;24: 491-497.
- Ross JL, Quigley CA, Cao D, Feuillan P, Kowal K, Chipman JJ, Cutler GB, Jr. Growth hormone plus childhood low-dose estrogen in Turner's syndrome. *The New England journal of medicine* 2011;364: 1230-1242.
- Rossetti R, Ferrari I, Bonomi M, Persani L. Genetics of primary ovarian insufficiency. *Clin Genet* 2017;91: 183-198.
- Ruiz-Rios M, Maldonado-Martin S. Physical activity on cardiorespiratory fitness and cardiovascular risk in premenopausal and postmenopausal women: a systematic review of randomized controlled trials. *Menopause* 2022;29: 1222-1229.
- Ruth KS, Day FR, Hussain J, Martinez-Marchal A, Aiken CE, Azad A, Thompson DJ, Knoblochova L, Abe H, Tarry-Adkins JL *et al.* Genetic insights into biological mechanisms governing human ovarian ageing. *Nature* 2021;596: 393-397.
- Ruth KS, Perry JR, Henley WE, Melzer D, Weedon MN, Murray A. Events in Early Life are Associated with Female Reproductive Ageing: A UK Biobank Study. *Scientific reports* 2016;6: 24710.
- Ryan J, Scali J, Carrière I, Amieva H, Rouaud O, Berr C, Ritchie K, Ancelin ML. Impact of a premature menopause on cognitive function in later life. *BJOG : an international journal of obstetrics and gynaecology* 2014;121: 1729-1739.
- Ryu KJ, Park H, Jeong Y, Nam S, Jeong HG, Kim T. Age at Menopause and Suicidal Ideation in Menopausal Women: A Study of Korea National Health and Nutrition Examination Survey Data. *J Korean Med Sci* 2022;37: e330.
- Saari V, Holopainen E, Mäkitie O, Laakso S. Pubertal development and premature ovarian insufficiency in patients with APECED. *European journal of endocrinology / European Federation of Endocrine Societies* 2020;183: 513-520.
- Sadeghijoola N, Afshari P, Jofreh MG, Haghighizadeh MH, Abedi P. Comparing the effects of face-to-face versus phone counseling based on cognitive-behavioral therapy for vasomotor symptoms in postmenopausal women: a randomized controlled trial. *Postepy psychiatrii neurologii* 2022;31: 114-120.
- Sadrzadeh S, Painter RC, van Kasteren YM, Braat DD, Lambalk CB. Premature ovarian insufficiency and perinatal parameters: A retrospective case-control study. *Maturitas* 2017;96: 72-76.
- Saeai N, Peeyanjarassri K, Liabsuetrakul T, Buhachat R, Myriokefalitaki E. Hormone replacement therapy after surgery for epithelial ovarian cancer. *The Cochrane database of systematic reviews* 2020;1: Cd012559.
- Safiyeh FD, Mojgan M, Parviz S, Sakineh MA, Behnaz SO. The effect of selenium and vitamin E supplementation on anti-Mullerian hormone and antral follicle count in infertile women with occult premature ovarian insufficiency: A randomized controlled clinical trial. *Complementary therapies in medicine* 2021;56: 102533.
- Samad N, Nguyen HH, Hashimura H, Pasco J, Kotowicz M, Strauss BJ, Ebeling PR, Milat F, Vincent AJ. Abnormal Trabecular Bone Score, Lower Bone Mineral Density and Lean Mass in Young Women With Premature Ovarian Insufficiency Are Prevented by Oestrogen Replacement. *Frontiers in endocrinology* 2022;13: 860853.
- Santos Silva IM, Paula Pinto M, Gonçalves D. Educational Programs and Sexual Counselling for Postmenopausal Sexual Dysfunction: A Systematic Review and Meta-Analysis. *J Sex Med* 2022;19: 54-63.
- Sauer MV. Spontaneous pregnancy in women awaiting oocyte donation. *The Journal of reproductive medicine* 1995;40: 630-632.
- Sauer MV, Paulson RJ, Ary BA, Lobo RA. Three hundred cycles of oocyte donation at the University of Southern California: assessing the effect of age and infertility diagnosis on pregnancy and implantation rates. *Journal of assisted reproduction and genetics* 1994;11: 92-96.
- Scalco R, Trarbach E, Albuquerque EVA, Homma TK, Inoue-Lima TH, Nishi MY, Mendonca BB, Jorge AAL. ESR1 polymorphism (rs2234693) influences femoral bone mass in patients with Turner syndrome. *Endocrine connections* 2019;8: 1513-1519.
- Schneider C, Jick SS, Meier CR. Risk of gynecological cancers in users of estradiol/dydrogesterone or other HRT preparations. *Climacteric : the journal of the International Menopause Society* 2009;12: 514-524.
- Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *International journal of epidemiology* 2014;43: 1542-1562.



- Shan D, Zou L, Liu X, Shen Y, Cai Y, Zhang J. Efficacy and safety of gabapentin and pregabalin in patients with vasomotor symptoms: a systematic review and meta-analysis. *American journal of obstetrics and gynecology* 2020;222: 564-579.e512.
- Shea AK, Buwembo A, Mayhew A, Sohel N, Griffith LE, Raina P. The association between primary ovarian insufficiency and osteoporosis in the Canadian Longitudinal Study on Aging. *Menopause* 2021;28: 693-698.
- Shea AK, Wolfman W. The role of hormone therapy in the management of severe postpartum depression in patients with Turner syndrome. *Menopause* 2017;24: 1309-1312.
- Shen J, Qu D, Gao Y, Sun F, Xie J, Sun X, Wang D, Ma X, Cui Y, Liu J, Diao F. Genetic etiologic analysis in 74 Chinese Han women with idiopathic premature ovarian insufficiency by combined molecular genetic testing. *Journal of assisted reproduction and genetics* 2021;38: 965-978.
- Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR *et al.* Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *The New England journal of medicine* 2000;343: 682-688.
- Shim S, Streich-Tilles T, Gutmark-Little I, Yao M, Shafer J, Breech L, Casnellie L, Backeljauw P. Abnormal Uterine Bleeding during Pubertal Induction with Transdermal Estrogen in Individuals with Turner Syndrome. *Journal of pediatric and adolescent gynecology* 2023;36: 358-362.
- Shim SH, Lee SJ, Kim SN. Effects of hormone replacement therapy on the rate of recurrence in endometrial cancer survivors: a meta-analysis. *European journal of cancer (Oxford, England : 1990)* 2014;50: 1628-1637.
- Shorey S, Ang L, Lau Y. Efficacy of mind-body therapies and exercise-based interventions on menopausal-related outcomes among Asian perimenopause women: A systematic review, meta-analysis, and synthesis without a meta-analysis. *Journal of advanced nursing* 2020;76: 1098-1110.
- Silva CA, Yamakami LY, Aikawa NE, Araujo DB, Carvalho JF, Bonfa E. Autoimmune primary ovarian insufficiency. *Autoimmunity reviews* 2014;13: 427-430.
- Silvén H, Savukoski SM, Pesonen P, Pukkala E, Gissler M, Suvanto E, Niinimäki M. Incidence and familial risk of premature ovarian insufficiency in the Finnish female population. *Human reproduction (Oxford, England)* 2022;37: 1030-1036.
- Silven H, Savukoski SM, Pesonen P, Pukkala E, Ojaniemi M, Gissler M, Suvanto E, Niinimäki M. Association of genetic disorders and congenital malformations with premature ovarian insufficiency: a nationwide register-based study. *Human reproduction (Oxford, England)* 2023;38: 1224-1230.
- Simon J, Braunstein G, Nachtigall L, Utian W, Katz M, Miller S, Waldbaum A, Bouchard C, Derzko C, Buch A *et al.* Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *The Journal of clinical endocrinology and metabolism* 2005;90: 5226-5233.
- Simon JA, Davis SR, Althof SE, Chedraui P, Clayton AH, Kingsberg SA, Nappi RE, Parish SJ, Wolfman W. Sexual well-being after menopause: An International Menopause Society White Paper. *Climacteric : the journal of the International Menopause Society* 2018a;21: 415-427.
- Simon JA, Gaines T, LaGuardia KD. Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. *Menopause* 2016;23: 1214-1221.
- Simon JA, Goldstein I, Kim NN, Davis SR, Kellogg-Spadt S, Lowenstein L, Pinkerton JV, Stuenkel CA, Traish AM, Archer DF *et al.* The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Menopause* 2018b;25: 837-847.
- Singh P, Arora S, Lal S, Strand TA, Makharia GK. Celiac Disease in Women With Infertility: A Meta-Analysis. *J Clin Gastroenterol* 2016;50: 33-39.
- Singhal SR, Shullai WK. Comparative study of gabapentin and isoflavone in menopausal vasomotor symptoms. *J Midlife Health* 2016;7: 132-139.
- Sjöberg L, Pitkaniemi J, Harjutsalo V, Haapala L, Tiitinen A, Tuomilehto J, Kaaja R. Menopause in women with type 1 diabetes. *Menopause* 2011;18: 158-163.
- Smith JA, Vitale S, Reed GF, Grieshaber SA, Goodman LA, Vanderhoof VH, Calis KA, Nelson LM. Dry eye signs and symptoms in women with premature ovarian failure. *Archives of ophthalmology* 2004;122: 151-156.
- Snajderova M, Mardesic T, Lebl J, Gerzova H, Teslik L, Zapletalova J, Czech National Study Group for HRT0iP, Adolescent E, Gynaecology. The uterine length in women with Turner syndrome reflects the postmenarcheal daily estrogen dose. *Hormone research* 2003;60: 198-204.



- Staller K, Townsend MK, Khalili H, Mehta R, Grodstein F, Whitehead WE, Matthews CA, Kuo B, Chan AT. Menopausal Hormone Therapy Is Associated With Increased Risk of Fecal Incontinence in Women After Menopause. *Gastroenterology* 2017;152: 1915-1921.e1911.
- Steenbeek MP, Harmsen MG, Hoogerbrugge N, de Jong MA, Maas A, Prins JB, Bulten J, Teerenstra S, van Bommel MHD, van Doorn HC *et al.* Association of Salpingectomy With Delayed Oophorectomy Versus Salpingo-oophorectomy With Quality of Life in BRCA1/2 Pathogenic Variant Carriers: A Nonrandomized Controlled Trial. *JAMA oncology* 2021;7: 1203-1212.
- Storgaard M, Loft A, Bergh C, Wennerholm UB, Söderström-Anttila V, Romundstad LB, Aittomaki K, Oldereid N, Forman J, Pinborg A. Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis. *BJOG : an international journal of obstetrics and gynaecology* 2017;124: 561-572.
- Stuenkel CA. Menopause, hormone therapy and diabetes. *Climacteric : the journal of the International Menopause Society* 2017;20: 11-21.
- Sturgeon KM, Dean LT, Heroux M, Kane J, Bauer T, Palmer E, Long J, Lynch S, Jacobs L, Sarwer DB *et al.* Commercially available lifestyle modification program: randomized controlled trial addressing heart and bone health in BRCA1/2+ breast cancer survivors after risk-reducing salpingo-oophorectomy. *Journal of cancer survivorship : research and practice* 2017;11: 246-255.
- Stute P, Neulen J, Wildt L. The impact of micronized progesterone on the endometrium: a systematic review. *Climacteric : the journal of the International Menopause Society* 2016;19: 316-328.
- Stuursma A, Lanjouw L, Idema DL, de Bock GH, Mourits MJE. Surgical Menopause and Bilateral Oophorectomy: Effect of Estrogen-Progesterone and Testosterone Replacement Therapy on Psychological Well-being and Sexual Functioning; A Systematic Literature Review. *J Sex Med* 2022.
- Su H, Li H, Yang X, Wang C, Zhao Y. Assessment of menopausal symptoms and quality of life in women with premature ovarian failure after hematopoietic stem-cell transplantation for hematologic diseases. *Menopause* 2020;28: 65-69.
- Su H, Li H, Zhang H, Yang X, Wang C. Menopausal symptoms and quality of life in female survivors treated with hematopoietic stem cell transplantation. *Frontiers in psychiatry* 2023;14: 1050959.
- Sultana F, Davis SR, Bell RJ, Taylor S, Islam RM. Association between testosterone and cognitive performance in postmenopausal women: a systematic review of observational studies. *Climacteric : the journal of the International Menopause Society* 2023a;26: 5-14.
- Sultana F, Davis SR, Islam RM. Effect of dehydroepiandrosterone therapy on cognitive performance among postmenopausal women: a systematic review of randomized clinical trial data. *Menopause* 2023b;30: 1167-1173.
- Sundblad V, Bussmann L, Chiauzzi VA, Pancholi V, Charreau EH. Alpha-enolase: a novel autoantigen in patients with premature ovarian failure. *Clinical endocrinology* 2006;65: 745-751.
- Sung L, Bustillo M, Mukherjee T, Booth G, Karstaedt A, Copperman AB. Sisters of women with premature ovarian failure may not be ideal ovum donors. *Fertility and sterility* 1997;67: 912-916.
- Suriano KA, McHale M, McLaren CE, Li KT, Re A, DiSaia PJ. Estrogen replacement therapy in endometrial cancer patients: a matched control study. *Obstetrics and gynecology* 2001;97: 555-560.
- Sybert VP. Phenotypic effects of mosaicism for a 47,XXX cell line in Turner syndrome. *J Med Genet* 2002;39: 217-220.
- Sybert VP, McCauley E. Turner's syndrome. *The New England journal of medicine* 2004;351: 1227-1238.
- Szegda KL, Whitcomb BW, Purdue-Smithe AC, Boutot ME, Manson JE, Hankinson SE, Rosner BA, Bertone-Johnson ER. Adult adiposity and risk of early menopause. *Human reproduction (Oxford, England)* 2017;32: 2522-2531.
- Taeabi M, Abdollahian S, Ozgoli G, Ebadi A, Kariman N. Strategies to improve menopausal quality of life: A systematic review. *Journal of education and health promotion* 2018;7: 93.
- Takamizawa S, Shibahara H, Shibayama T, Suzuki M. Detection of antizona pellucida antibodies in the sera from premature ovarian failure patients by a highly specific test. *Fertility and sterility* 2007;88: 925-932.
- Tamimi RM, Hankinson SE, Chen WY, Rosner B, Colditz GA. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. *Archives of internal medicine* 2006;166: 1483-1489.
- Tan R, Pu D, Cao J, Ge H, Chang X, Ye G, Wu J. Prevalence of Stress Urinary Incontinence in Women with Premature Ovarian Insufficiency. *Journal of women's health (2002)* 2018;27: 1508-1512.
- Taneri PE, Kieft-de Jong JC, Bramer WM, Daan NM, Franco OH, Muka T. Association of alcohol consumption with the onset of natural menopause: a systematic review and meta-analysis. *Human reproduction update* 2016;22: 516-528.



Tang R, Yu Q. The significance of FMR1 CGG repeats in Chinese women with premature ovarian insufficiency and diminished ovarian reserve. *Reproductive biology and endocrinology : RB&E* 2020;18: 82.

Tang VW, Faiman C. Premature ovarian failure: a search for circulating factors against gonadotropin receptors. *American journal of obstetrics and gynecology* 1983;146: 816-821.

Tanska K, Gietka-Czernel M, Glinicki P, Kozakowski J. Thyroid autoimmunity and its negative impact on female fertility and maternal pregnancy outcomes. *Frontiers in endocrinology* 2022;13: 1049665.

Tao X, Jiang A, Yin L, Li Y, Tao F, Hu H. Body mass index and age at natural menopause: a meta-analysis. *Menopause* 2015;22: 469-474.

Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. A review of trisomy X (47,XXX). *Orphanet journal of rare diseases* 2010;5: 8.

Tartagni M, Cicinelli E, De Pergola G, De Salvia MA, Lavopa C, Loverro G. Effects of pretreatment with estrogens on ovarian stimulation with gonadotropins in women with premature ovarian failure: a randomized, placebo-controlled trial. *Fertility and sterility* 2007;87: 858-861.

Tata LJ, Card TR, Logan RF, Hubbard RB, Smith CJ, West J. Fertility and pregnancy-related events in women with celiac disease: a population-based cohort study. *Gastroenterology* 2005;128: 849-855.

Taylor AE, Adams JM, Mulder JE, Martin KA, Sluss PM, Crowley WF, Jr. A randomized, controlled trial of estradiol replacement therapy in women with hypergonadotropic amenorrhea. *The Journal of clinical endocrinology and metabolism* 1996;81: 3615-3621.

Taylor HS, Tal A, Pal L, Li F, Black DM, Brinton EA, Budoff MJ, Cedars MI, Du W, Hodis HN *et al.* Effects of Oral vs Transdermal Estrogen Therapy on Sexual Function in Early Postmenopause: Ancillary Study of the Kronos Early Estrogen Prevention Study (KEEPS). *JAMA internal medicine* 2017;177: 1471-1479.

Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. *Lancet* 1996;348: 1402-1406.

Terra L, Beekman MJ, Engelhardt EG, Heemskerk-Gerritsen BAM, van Beurden M, Roeters van Lennep JE, van Doorn HC, de Hullu JA, Van Dorst EBL, Mom CH *et al.* Sexual functioning more than 15 years after premenopausal risk-reducing salpingo-oophorectomy. *American journal of obstetrics and gynecology* 2023;228: 440.e441-440.e420.

The Writing Group for the PEPI. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. *Jama* 1996;276: 1389-1396.

Thomas HN, Brotto LA, de Abril Cameron F, Yabes J, Thurston RC. A virtual, group-based mindfulness intervention for midlife and older women with low libido lowers sexual distress in a randomized controlled pilot study. *J Sex Med* 2023;20: 1060-1068.

Thong EP, Codner E, Laven JSE, Teede H. Diabetes: a metabolic and reproductive disorder in women. *The lancet Diabetes & endocrinology* 2020;8: 134-149.

Torella M, Marrapodi MM, Ronsini C, Ruffolo AF, Braga A, Frigerio M, Amabile E, Vastarella MG, Rossi F, Riemma G. Risk of Premature Ovarian Insufficiency after Human Papilloma Virus Vaccination: A PRISMA Systematic Review and Meta-Analysis of Current Evidence. *Vaccines* 2023;11.

Torres-Santiago L, Mericq V, Taboada M, Unanue N, Klein KO, Singh R, Hossain J, Santen RJ, Ross JL, Mauras N. Metabolic effects of oral versus transdermal 17beta-estradiol (E2): a randomized clinical trial in girls with Turner syndrome. *The Journal of clinical endocrinology and metabolism* 2013;98: 2716-2724.

Tosh D, Rao KL, Rani HS, Deenadayal DA, Murty US, Grover P. Association between fragile X premutation and premature ovarian failure: a case-control study and meta-analysis. *Archives of gynecology and obstetrics* 2014.

Tsuburai T, Nakamura T, Yoshikata H, Miyagi E, Sakakibara H. Eldecacitol increases bone mass in patients with Turner syndrome who have insufficient bone mass acquisition after estrogen replacement therapy. *Endocrine journal* 2018;65: 629-638.

Tucker PE, Cohen PA, Bulsara MK, Jeffares S, Saunders C. The impact of bilateral salpingo-oophorectomy on sexuality and quality of life in women with breast cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2021;29: 369-375.

Tuke MA, Ruth KS, Wood AR, Beaumont RN, Tyrrell J, Jones SE, Yaghootkar H, Turner CLS, Donohoe ME, Brooke AM *et al.* Mosaic Turner syndrome shows reduced penetrance in an adult population study. *Genetics in medicine : official journal of the American College of Medical Genetics* 2019;21: 877-886.



- Uldbjerg CS, Wilson LF, Koch T, Christensen J, Dehlendorff C, Priskorn L, Abildgaard J, Simonsen MK, Lim YH, Jørgensen JT *et al.* Oophorectomy and rate of dementia: a prospective cohort study. *Menopause* 2022;29: 514-522.
- Valloton MB, Forbes AP. Antibodies to cytoplasm of ova. *Lancet* 1966;2: 264-265.
- van Barele M, Buis CCM, Brood-van Zanten MMA, van Doorn HLC, Gaarenstroom KN, Heemskerck-Gerritsen BAM, Hooning MJ, de Hullu J, Mourits MJ, Burger CW. The effect of hormone therapy on breast density following risk-reducing salpingo-oophorectomy in women with an increased risk for breast and ovarian cancer. *Menopause* 2021;28: 1307-1312.
- van Driel C, de Bock GH, Schroevers MJ, Mourits MJ. Mindfulness-based stress reduction for menopausal symptoms after risk-reducing salpingo-oophorectomy (PURSUE study): a randomised controlled trial. *BJOG : an international journal of obstetrics and gynaecology* 2019a;126: 402-411.
- van Driel CM, Stuursma A, Schroevers MJ, Mourits MJ, de Bock GH. Mindfulness, cognitive behavioural and behaviour-based therapy for natural and treatment-induced menopausal symptoms: a systematic review and meta-analysis. *BJOG : an international journal of obstetrics and gynaecology* 2019b;126: 330-339.
- van Kasteren YM, Hundscheid RD, Smits AP, Cremers FP, van Zonneveld P, Braat DD. Familial idiopathic premature ovarian failure: an overrated and underestimated genetic disease? *Human reproduction (Oxford, England)* 1999;14: 2455-2459.
- van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. *Human reproduction update* 1999;5: 483-492.
- van Noord PA, Dubas JS, Dorland M, Boersma H, te Velde E. Age at natural menopause in a population-based screening cohort: the role of menarche, fecundity, and lifestyle factors. *Fertility and sterility* 1997;68: 95-102.
- Van Ommen CE, King EM, Murray MCM. Age at menopause in women living with HIV: a systematic review. *Menopause* 2021;28: 1428-1436.
- Vargiu V, Amar ID, Rosati A, Dinoi G, Turco LC, Capozzi VA, Scambia G, Villa P. Hormone replacement therapy and cervical cancer: a systematic review of the literature. *Climacteric : the journal of the International Menopause Society* 2021;24: 120-127.
- Verbeek JGE, Atema V, Mewes JC, van Leeuwen M, Oldenburg HSA, van Beurden M, Hunter MS, van Harten WH, Aaronson NK, Retèl VP. Cost-utility, cost-effectiveness, and budget impact of Internet-based cognitive behavioral therapy for breast cancer survivors with treatment-induced menopausal symptoms. *Breast cancer research and treatment* 2019;178: 573-585.
- Vermeulen RFM, Beurden MV, Kieffer JM, Bleiker EMA, Valdimarsdottir HB, Massuger L, Mourits MJE, Gaarenstroom KN, van Dorst EBL, van der Putten H, Aaronson NK. Hormone replacement therapy after risk-reducing salpingo-oophorectomy minimises endocrine and sexual problems: A prospective study. *European journal of cancer (Oxford, England : 1990)* 2017;84: 159-167.
- Verrilli L, Johnstone E, Welt C, Allen-Brady K. Primary ovarian insufficiency has strong familiarity: results of a multigenerational genealogical study. *Fertility and sterility* 2023;119: 128-134.
- Vinogradova Y, Coupland C, Hippisley-Cox J. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ (Clinical research ed)* 2015;350: h2135.
- Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. *BMJ (Clinical research ed)* 2020;371: m3873.
- Viuff MH, Berglund A, Juul S, Andersen NH, Stochholm K, Gravholt CH. Sex Hormone Replacement Therapy in Turner Syndrome: Impact on Morbidity and Mortality. *The Journal of clinical endocrinology and metabolism* 2020;105.
- Vogt EC, Bratland E, Berland S, Berentsen R, Lund A, Björnsdottir S, Husebye E, Oksnes M. Improving diagnostic precision in primary ovarian insufficiency using comprehensive genetic and autoantibody testing. *Human reproduction (Oxford, England)* 2024;39: 177-189.
- Vogt EC, Breivik L, Røyrvik EC, Grytaas M, Husebye ES, Øksnes M. Primary Ovarian Insufficiency in Women With Addison's Disease. *The Journal of clinical endocrinology and metabolism* 2021;106: e2656-e2663.
- Vogt EC, Real FG, Husebye ES, Björnsdottir S, Benediktsdottir B, Bertelsen RJ, Demoly P, Franklin KA, de Aja Gallastegui LS, González FJC *et al.* Premature menopause and autoimmune primary ovarian insufficiency in two international multi-center cohorts. *Endocrine connections* 2022;11.
- Vrselja A, Latifi A, Baber RJ, Stuckey BGA, Walker MG, Stearns V, Hickey M, Davis SR. Q-122 as a novel, non-hormonal, oral treatment for vasomotor symptoms in women taking tamoxifen or an



aromatase inhibitor after breast cancer: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2022;400: 1704-1711.

Walker MD, Zylberberg HM, Green PHR, Katz MS. Endocrine complications of celiac disease: a case report and review of the literature. *Endocrine research* 2019;44: 27-45.

Wang H, Chen H, Qin Y, Shi Z, Zhao X, Xu J, Ma B, Chen ZJ. Risks associated with premature ovarian failure in Han Chinese women. *Reproductive biomedicine online* 2015;30: 401-407.

Wasserman H, Backeljauw PF, Khoury JC, Kalkwarf HJ, Gordon CM. Bone fragility in Turner syndrome: Fracture prevalence and risk factors determined by a national patient survey. *Clinical endocrinology* 2018;89: 46-55.

Wasserman MC, Rubin RS. Urologic view in the management of genitourinary syndrome of menopause. *Climacteric : the journal of the International Menopause Society* 2023;26: 329-335.

Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, Cifkova R, de Muinck Keizer-Schrama S, Hogervorst E, Janse F *et al*. ESHRE Guideline: management of women with premature ovarian insufficiency. *Human reproduction (Oxford, England)* 2016;31: 926-937.

Weghofer A, Barad D, Li J, Gleicher N. Aneuploidy rates in embryos from women with prematurely declining ovarian function: a pilot study. *Fertility and sterility* 2007;88: 90-94.

Wei D, Chen Y, Wu C, Wu Q, Yao L, Wang Q, Wang XQ, Yang KH. Effect and safety of paroxetine for vasomotor symptoms: systematic review and meta-analysis. *BJOG : an international journal of obstetrics and gynaecology* 2016;123: 1735-1743.

Weiderpass E, Adami HO, Baron JA, Magnusson C, Bergström R, Lindgren A, Correia N, Persson I. Risk of endometrial cancer following estrogen replacement with and without progestins. *Journal of the National Cancer Institute* 1999;91: 1131-1137.

Welt CK. Primary ovarian insufficiency: a more accurate term for premature ovarian failure. *Clinical endocrinology* 2008;68: 499-509.

Wheatcroft NJ, Toogood AA, Li TC, Cooke ID, Weetman AP. Detection of antibodies to ovarian antigens in women with premature ovarian failure. *Clin Exp Immunol* 1994;96: 122-128.

Whitcomb BW, Purdue-Smithe A, Hankinson SE, Manson JE, Rosner BA, Bertone-Johnson ER. Menstrual Cycle Characteristics in Adolescence and Early Adulthood Are Associated With Risk of Early Natural Menopause. *The Journal of clinical endocrinology and metabolism* 2018a;103: 3909-3918.

Whitcomb BW, Purdue-Smithe AC, Szegda KL, Boutot ME, Hankinson SE, Manson JE, Rosner B, Willett WC, Eliassen AH, Bertone-Johnson ER. Cigarette Smoking and Risk of Early Natural Menopause. *American journal of epidemiology* 2018b;187: 696-704.

Winqvist O, Gebre-Medhin G, Gustafsson J, Ritzén EM, Lundkvist O, Karlsson FA, Kämpe O. Identification of the main gonadal autoantigens in patients with adrenal insufficiency and associated ovarian failure. *The Journal of clinical endocrinology and metabolism* 1995;80: 1717-1723.

Wu X, Cai H, Kallianpur A, Li H, Yang G, Gao J, Xiang YB, Ji BT, Yu T, Zheng W, Shu XO. Impact of Premature Ovarian Failure on Mortality and Morbidity among Chinese Women. *PloS one* 2014;9: e89597.

Xi D, Chen B, Tao H, Xu Y, Chen G. The risk of depressive and anxiety symptoms in women with premature ovarian insufficiency: a systematic review and meta-analysis. *Archives of women's mental health* 2023;26: 1-10.

Xing Z, Alman AC, Kirby RS. Premature Menopause and All-Cause Mortality and Life Span Among Women Older Than 40 Years in the NHANES I Epidemiologic Follow-Up Study: Propensity Score Matching Analysis. *Journal of women's health (2002)* 2023;32: 950-959.

Xu Z, Chung HF, Dobson AJ, Wilson LF, Hickey M, Mishra GD. Menopause, hysterectomy, menopausal hormone therapy and cause-specific mortality: cohort study of UK Biobank participants. *Human reproduction (Oxford, England)* 2022;37: 2175-2185.

Yang X, Touraine P, Desai S, Humphreys G, Jiang H, Yatsenko A, Rajkovic A. Gene variants identified by whole-exome sequencing in 33 French women with premature ovarian insufficiency. *Journal of assisted reproduction and genetics* 2019;36: 39-45.

Yang X, Wang C, He X, Wei J, Wang Y, Li X, Xu LP. Hormone therapy for premature ovarian insufficiency patients with malignant hematologic diseases. *Climacteric : the journal of the International Menopause Society* 2017;20: 268-273.

Yarde F, van der Schouw YT, de Valk HW, Franx A, Eijkemans MJ, Spiering W, Broekmans FJ. Age at menopause in women with type 1 diabetes mellitus: the OVADIA study. *Human reproduction (Oxford, England)* 2015;30: 441-446.



- Yaron Y, Ochshorn Y, Amit A, Yovel I, Kogosowki A, Lessing JB. Patients with Turner's syndrome may have an inherent endometrial abnormality affecting receptivity in oocyte donation. *Fertility and sterility* 1996;65: 1249-1252.
- Ye M, Shou M, Zhang J, Hu B, Liu C, Bi C, Lv T, Luo F, Zhang Z, Liang S *et al.* Efficacy of cognitive therapy and behavior therapy for menopausal symptoms: a systematic review and meta-analysis. *Psychological medicine* 2022;52: 433-445.
- Yeganeh L, Boyle JA, Gibson-Helm M, Teede H, Vincent AJ. Women's perspectives of early menopause: development of a word cloud. *Climacteric : the journal of the International Menopause Society* 2020;23: 417-420.
- Yeh ML, Liao RW, Hsu CC, Chung YC, Lin JG. Exercises improve body composition, cardiovascular risk factors and bone mineral density for menopausal women: A systematic review and meta-analysis of randomized controlled trials. *Applied nursing research : ANR* 2018;40: 90-98.
- Yi A, Qin X, Du Z, Wang T, Liu F. Clinical Observation on the Improvement of Serum Sex Hormone and Ovarian Function in Premature Ovarian Failure Patients with Deficiency-Cold Syndrome by Combining Wenjing Decoction with Tiaobu Chongren Acupuncture and Moxibustion. *Evidence-based complementary and alternative medicine* 2021;2021.
- Yoon SH, Lee JY, Lee C, Lee H, Kim SN. Gabapentin for the treatment of hot flushes in menopause: a meta-analysis. *Menopause* 2020;27: 485-493.
- Yuk JS, Kim BG, Lee BK, Seo J, Kim GS, Min K, Lee HY, Byun YS, Kim BO, Yang SW *et al.* Association of Early Hysterectomy With Risk of Cardiovascular Disease in Korean Women. *JAMA network open* 2023;6: e2317145.
- Zhai T, Diergaarde B, Wilson DO, Kang H, Sood A, Bayliss SH, Yuan JM, Picchi MA, Lan Q, Belinsky SA *et al.* Early natural menopause is associated with poor lung health and increased mortality among female smokers. *American journal of obstetrics and gynecology* 2022;227: 885 e881-885 e812.
- Zhang S, Tan R, Pan R, Xiong J, Tian Y, Wu J, Chen L. Association of Perfluoroalkyl and Polyfluoroalkyl Substances With Premature Ovarian Insufficiency in Chinese Women. *The Journal of clinical endocrinology and metabolism* 2018;103: 2543-2551.
- Zhang S, Zhu D, Mei X, Li Z, Li J, Xie M, Xie HJW, Wang S, Cheng K. Advances in biomaterials and regenerative medicine for primary ovarian insufficiency therapy. *Bioactive materials* 2021;6: 1957-1972.
- Zhang YL, Chen JH, Lu W, Li BL, Zhu QY, Wan XP. Efficacy of Postoperative Hormone Replacement Therapy on Prognosis of Patients with Serous Ovarian Carcinoma. *Chinese medical journal* 2016;129: 1316-1321.
- Zhong HZ, Li MY, Yin XL, Bin CL, Zhou SY, Wei SB. Chinese patent medicines combined with hormone replacement therapy for premature ovarian failure: A Bayesian network meta-analysis. *Frontiers in medicine* 2022;9: 1043390.
- Zhou WS, Mao SJ, Zhang SK, Xu H, Li WL. Effects of aquatic exercises on physical fitness and quality of life in postmenopausal women: an updated systematic review and meta-analysis. *Front Public Health* 2023;11: 1126126.
- Zhu D, Chung HF, Dobson AJ, Pandeya N, Brunner EJ, Kuh D, Greenwood DC, Hardy R, Cade JE, Giles GG *et al.* Type of menopause, age of menopause and variations in the risk of incident cardiovascular disease: pooled analysis of individual data from 10 international studies. *Human reproduction (Oxford, England)* 2020;35: 1933-1943.
- Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, Brunner EJ, Kuh D, Hardy R, Avis NE *et al.* Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *The Lancet Public health* 2019;4: e553-e564.
- Zhu D, Chung HF, Pandeya N, Dobson AJ, Cade JE, Greenwood DC, Crawford SL, Avis NE, Gold EB, Mitchell ES *et al.* Relationships between intensity, duration, cumulative dose, and timing of smoking with age at menopause: A pooled analysis of individual data from 17 observational studies. *PLoS medicine* 2018a;15: e1002704.
- Zhu D, Chung HF, Pandeya N, Dobson AJ, Kuh D, Crawford SL, Gold EB, Avis NE, Giles GG, Bruinsma F *et al.* Body mass index and age at natural menopause: an international pooled analysis of 11 prospective studies. *European journal of epidemiology* 2018b;33: 699-710.
- Zilio Rech CM, Clapauch R, Bouskela E. Sexual Function Under Adequate Estrogen Therapy in Women After Oophorectomy Versus Natural Menopause. *Journal of women's health (2002)* 2019;28: 1124-1132.
- Zilski N, Speiser D, Bartley J, Roehle R, Blohmer JU, Keilholz U, Goerling U. Quality of life after risk-reducing salpingo-oophorectomy in women with a pathogenic BRCA variant. *J Sex Med* 2023;21: 33-39.



Zuckerman-Levin N, Frolova-Bishara T, Militianu D, Levin M, Aharon-Peretz J, Hochberg Z. Androgen replacement therapy in Turner syndrome: a pilot study. *The Journal of clinical endocrinology and metabolism* 2009;94: 4820-4827.

Zugna D, Richiardi L, Akre O, Stephansson O, Ludvigsson JF. A nationwide population-based study to determine whether coeliac disease is associated with infertility. *Gut* 2010;59: 1471-1475.