Evidence-based GUIDELINE: Premature ovarian insufficiency 2024

DRAFT FOR STAKEHOLDER REVIEW

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The European Society of Human Reproduction and Embryology (hereinafter referred to as 'ESHRE') developed the current clinical practice guideline, to provide clinical recommendations to improve the quality of healthcare delivery within the European field of human reproduction and embryology. This guideline represents the views of ESHRE, which were achieved after careful consideration of the scientific evidence available at the time of preparation. In the absence of scientific evidence on certain aspects, a consensus between the relevant ESHRE stakeholders has been obtained.

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- ESHRE
- Our partner organisations which co-funded the guideline: American Society for Reproductive Medicine (ASRM), International Menopause Society (IMS), and The Australian National Health and Medical Research Council (NHMRC) through the funded Centre for Research Excellence in Women's Health in Reproductive Life (CRE WHiRL)
- Our collaborating and engaged societies and consumer groups.

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Introduction

Clinical need

This guideline provides an update of the ESHRE Guideline of the Management of women with premature ovarian insufficiency, published in December 2015 (Webber *et al.*, 2016). While regular revision and updating of guidelines is part of the methodology and essential to ensure up-to-date clinical guidance, the need for this update is underscored by several external key factors. Firstly, studies, such as that conducted by Gameiro et al. (2019), have identified a concerning trend of low uptake of the original guideline (Gameiro *et al.*, 2019). Additionally, an audit conducted at a prominent UK teaching hospital, as reported by Richardson et al. (2018), revealed inconsistent adherence to recommended investigation and treatment protocols, with care variation observed across different clinical specialties (Richardson *et al.*, 2018). These findings highlight a critical gap between guideline recommendations and their implementation in clinical practice, which may significantly impact the quality of care and outcomes for women with POI.

The current update of the 2015 guideline as well as the planned implementation and translation resources for this guideline will be imperative to support high quality and evidence-based care for women with POI.

Guideline scope

This guideline offers best practice advice on the care of women with premature/primary ovarian insufficiency (POI), both primary and secondary. The first chapters of this guideline will elaborate on the nomenclature and definition of POI.

Furthermore, this clinical guideline provides recommendations on the initial assessment and management of women with POI. The initial assessment includes diagnosis, assessment of causation, and basic assessment. The management includes hormonal treatment. Since POI has consequences for health apart from gynaecological issues, these are also described. Consequences of POI and treatment options are included in the following domains: fertility and contraception, musculoskeletal health, cardiovascular issues, psychosexual function, psychological function, and neurological function. Other topics discussed are puberty induction, life expectancy, and implications for relatives of women with POI.

This guideline is limited to POI and does not apply to women with low ovarian reserve. Reference to early menopause is included where evidence is available but was not the focus of the key questions.

While the care for women with Turner Syndrome, as a subgroup of POI, is covered, the reader is referred to other guidelines specifically addressing Tuner Syndrome for more in depth clinical guidance (Gravholt, 2024).

Guideline development

While the previous version of the guideline on the Management of women with premature ovarian insufficiency (Webber *et al.*, 2016) was developed by ESHRE only, the current version was developed by ESHRE in partnership with the Centre For Research Excellence In Women's Health In Reproductive Life (CRE-WHiRL), the American Society For Reproductive Medicine (ASRM) and the International Menopause Society (IMS). The four partners were represented in the guideline development group. An ESHRE research specialist supported the guideline development. The members of the guideline

development group, representing experts in the various topics covered in the guideline, are listed in Annex 1.

The guideline was developed according to the published methodology (Vermeulen *et al.*, 2020). More details on the methodology are included in Annex 4.

Target users of the guideline

The guideline covers the care provided by health care providers who have direct contact with, and make decisions concerning the care of, women with POI. ESHRE guidelines are mainly focussed on gynaecologists. However, women with POI suffer health problems that require multi-disciplinary care and are not limited to the field of gynaecology. Therefore, this guideline is also targeted at health care providers of other disciplines (e.g. general practitioners, endocrinologists, oncologists, geneticists, paediatricians, internists). During the review phase and in development of tools for implementation, specific attention will be given to these health care providers.

This guideline is of relevance to health care providers and women with POI globally. For the benefit of patient education and shared decision making, a patient version of this guideline will be developed. Translation and resource development will be led by CRE WHiRL and modelled on the example of the international PCOS guideline (https://www.monash.edu/medicine/mchri/pcos/guideline).

Patient population

The current guideline focusses on women with POI, both primary and secondary. The patient population comprises women younger than 40 years (which includes Turner Syndrome patients) and women older than 40 years, but with disease onset before age 40. Reference to women with early menopause (menopause occurring between the ages of 40 and 45) is included where the evidence is available but was not a focus of the key questions or search strategy.

In this guideline, in line with published research, the terminology and discussion focus on women. The guideline group recognises that there are individuals living with POI who are transgender or who do not identify with the terms used in the literature. For the purpose of this guideline, we use the term "women with POI". The terminology, however, is not intended to isolate, exclude, or diminish any individual's experience nor to discriminate against any group.

Terminology

Apart from the term POI, which is discussed in depth in section I.1. POI Nomenclature, several other terms have been variably used throughout the literature, sometimes with regional preferences. For the sake of clarity, the Guideline group opted for consistent use of a single term throughout the guideline Table I).

Table I Terminology used in this document

Term used in this document	Definition	Other terms used in literature/other sources
Non-iatrogenic POI	POI not caused by a medical intervention (i.e. iatrogenic POI)	Spontaneous POI, natural POI
Natural pregnancy	Pregnancy occurring through intercourse (to differentiate from pregnancy after ART)	Spontaneous pregnancy, un-assisted pregnancy

Usual age menopause / age at usual menopause	Menopause at age 45 to 55 years	Normal menopause, natural menopause (age at natural menopause is still used for epidemiological studies)
Hot flushes		Hot flashes
Hormone therapy	As an overarching term, including HRT and the COC	Menopausal hormone therapy
Risk reducing bilateral salpingo-oophorectomy (RRBSO)	BSO performed for reducing risk of breast/ovarian cancer (e.g. in women with a BRCA ½ mutation)	Prophylactic BSO
Sequential		Cyclical

Previous versions

This guideline provides an update of the ESHRE Guideline of the Management of women with premature ovarian insufficiency, published in December 2015 (Webber *et al.*, 2016).

List of all recommendations

Nr	Recommendation	Evidence level	Strength[1]
	PART A: Introduction to POI		
	Key Question: What should this condition be called?		
1	The guideline group recommends that the term "premature ovarian insufficiency" is used to describe this condition in research and clinical practice.		GPP
	Key Question: How should POI be defined?		
2	Premature ovarian insufficiency is a condition defined by loss of ovarian activity before the age of 40 years. POI is characterised by amenorrhea or oligomenorrhea with elevated gonadotropins and low estradiol. In this guideline, cessation of ovarian function in women aged between 40 and less than 45 (age 40-44 years) will be termed early menopause. Even if this group is outside the scope of the current guideline, the evidence and recommendations may still be relevant to women with early menopause.		GDG STATEMENT
	Key Question: What is the prevalence of POI in the general population?		
3	The reported prevalence of non-iatrogenic POI varies from approximately 1% in older studies to 3,5% in recent publications. Population characteristics such as ethnicity may affect the prevalence of non-iatrogenic POI.		GDG STATEMENT
	PICO Question: What are the risk factors for POI?		
4	The guideline group recommends that in view of the long-term health consequences of POI, efforts should be made to reduce the risk of POI. Modifiable factors may include: - gynaecological surgical practice - lifestyle such as smoking cessation - modified treatment regimens for malignant and chronic diseases.		GPP
5	The guideline group recommends that women with risk factors for POI are counselled regarding the potential for prevention of POI, such as stopping smoking, and fertility preservation.		GPP
	PART B: Diagnosis of POI		
	PICO Question: What are the symptoms of POI?		
6	The guideline group recommends that HCPs enquire about symptoms of estrogen deficiency in women presenting with oligomenorrhea or amenorrhea.		GPP
7	The guideline group recommends HCPs consider and exclude the diagnosis of POI in women aged less than 40 years who have amenorrhea/oligomenorrhea or estrogen-deficiency symptoms .		GPP
	PICO Question: What investigations should be performed for diagnosis of POI?		
8	HCPs should diagnose POI based on the presence of amenorrhea or oligomenorrhea and biochemical confirmation.	⊕⊕◯◯	STRONG
9	Although proper diagnostic accuracy in POI is lacking, the guideline group recommends the following diagnostic criteria: amenorrhea or oligomenorrhea for at least 4 months, and an elevated FSH level > 25 IU/l. FSH assessment should be repeated after > 4 weeks if there is diagnostic uncertainty.		GPP
	PICO Question: What is the role of AMH to predict/ diagnose POI?		

10	AMH testing could be considered in the diagnosis of POI where there is diagnostic uncertainty. However, it has not been shown to have benefit over existing FSH-based diagnostic testing.	⊕◯◯◯	CONDITIONAL
11	The guideline group recommends that AMH tests are interpreted within the clinical context. Further research is required to determine diagnostic thresholds for POI.		GPP
	PICO Question: What are the known causes of non-iatrogenic POI and how should they be investigated?		
12	The guideline group recommends that HCPs should 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 determined		GPP
13	The guideline group recommends that HCPs treating women with medical or surgical intervention that may cause POI should discuss the risk of POI as part of the consent process.		GPP
14	Chromosomal analysis and Fragile X premutation testing is recommended for all women with non-iatrogenic POI	⊕⊕◯◯	STRONG
15	Where available and after comprehensive genetic counselling, additional genetic testing (e.g. NGS) can be offered to identify other potential genes that may cause POI.	⊕⊕◯◯	CONDITIONAL
16	The guideline group recommends that the age of a woman with POI should not be used to restrict access to genetic testing.		GPP
17	Screening for 21OH-Abs should be performed in women with POI of unknown cause.	⊕◯◯◯	STRONG
18	Screening for anti-ovarian autoantibodies should not be used to diagnose autoimmune POI.	⊕◯◯◯	STRONG
19	Thyroid function should be assessed by measuring TSH at diagnosis. TSH measurement should be repeated every 5 years or when symptoms arise.	⊕◯◯◯	STRONG
20	The guideline group recommends that HCPs do not 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.		GPP
	PICO Question: How often should tests for autoantibodies be repeated?		
21	Women with POI and positive 21OH-Ab should be referred to an endocrinologist for testing of adrenal function.	⊕◯◯◯	STRONG
22	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.	⊕◯◯◯	STRONG
23	Women with POI with abnormal TSH levels should be referred to an endocrinologist for evaluation and treatment for thyroid hormone disorders.	⊕◯◯◯	STRONG
	Care for women with POI at diagnosis		
24	The guideline group recommends that HCPs convey the diagnosis of POI in a compassionate and sensitive manner, provide personalised evidence-based information about the condition and ensure enough time for the women to ask questions.		GPP
25	The guideline group recommends shared decision making and support for continuity of care in managing POI.		GPP
26	The guideline group recommends referral of women with POI to appropriate support groups and mental health care.		GPP
	PICO Question: What are the implications for relatives of women with POI?		
27	The guideline group recommends that relatives of women with the Fragile X premutation or other identified genetic causes of POI should be offered genetic counselling and testing.		¨GPP

28	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	⊕⊕◯◯	STRONG
29	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		GPP
30	The guideline group recommends that female relatives (such as sisters or daughters) of women with non-iatrogenic POI should be informed of the signs and symptoms of POI and should promptly seek medical advice if this occurs.		GPP
31	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.		GPP
	PART C: Sequelae of POI		
	PICO Question: What are the consequences of POI for life expectancy?		
32	Women with POI should be informed that POI without hormone therapy is associated with reduced life expectancy, largely due to cardiovascular disease.	⊕⊕◯◯	STRONG
33	Women with POI should be offered hormone therapy at least until the usual age of menopause as primary prevention to reduce risk of overall morbidity and mortality.	⊕◯◯◯	STRONG
34	The guideline group recommends that, in addition to hormone therapy, women with POI are advised to reduce cardiovascular risk by avoidance of smoking, healthy diet, regular exercise, and maintaining a healthy weight range		GPP
	PICO Question: What are the consequences of POI for fertility?		
35	Women with non-surgical POI should be informed that ovarian activity may occur. This is associated with a chance of natural conception.	⊕◯◯◯	STRONG
36	Women with non-surgical POI should be advised to use contraception if they wish to avoid pregnancy.	⊕◯◯◯	STRONG
	PICO Question: What fertility interventions are effective?		
37	Women with POI should be informed that there are no interventions that have been reliably shown to increase ovarian activity and natural conception rates.	⊕⊕⊕◯	STRONG
38	Women with POI should be informed that oocyte donation is an established option to achieve pregnancy after a diagnosis of POI	⊕⊕◯◯	STRONG
39	Women with non-iatrogenic POI considering oocyte donation from sisters should be informed that this includes shared genetic risk and carries a higher risk of ovarian stimulation cycle cancellation.	⊕⊕◯◯	STRONG
	PICO Question: What therapies are effective for fertility preservation and /or prevention of POI?		
40	The guideline group recommends that fertility preservation is discussed with women at risk of POI. In women with established POI, the opportunity for fertility preservation has passed.		GPP
	PICO Question: What are the obstetric risks associated with POI?		
41	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.	⊕⊕⊕◯	STRONG
42	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 with their obstetric team.	⊕⊕◯◯	STRONG

43	Pregnancies after radiation to the uterus are at high risk of obstetric complications and should be managed in an appropriate obstetric unit.	⊕⊕◯◯	STRONG
44	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.	⊕⊕◯◯	STRONG
45	A cardiologist should be involved in care of pregnant women who have received anthracyclines and/or cardiac irradiation.	⊕◯◯◯	STRONG
	PICO Question: How should fitness for pregnancy be assessed in women with POI?		
46	Women presenting for oocyte donation who are suspected of having POI should be fully investigated prior to oocyte donation, including thyroid and adrenal function as well as genetic testing.	⊕⊕◯◯	STRONG
47	Women previously exposed to anthracyclines, high dose cyclophosphamide or mediastinal irradiation should have an echocardiogram prior to pregnancy, and referral to a cardiologist if indicated.	⊕◯◯◯	STRONG
48	Thorough cardiac screening and appropriate counselling by maternal–foetal medicine specialists and cardiologists with expertise in managing women with Turner Syndrome is recommended prior to planning a pregnancy, especially if oocyte or embryo donation is considered	⊕⊕◯◯	STRONG
49	Women with POI should have their cardiometabolic and thyroid function assessed prior to pregnancy.	⊕◯◯◯	STRONG
50	Pregnancy in some women can be of such high risk that clinicians may consider oocyte donation pregnancy to be life threatening and therefore inappropriate.	⊕◯◯◯	STRONG
	PICO Question: What are the consequences of POI for skeletal health?		
51	Women with POI and HCPs should be aware that POI is associated with abnormal bone microarchitecture and reduced bone mineral density (BMD)	⊕⊕◯◯	STRONG
52	It is suggested that HCPs inform women that POI may be associated with an increased risk of fracture later in life, although this has not been adequately demonstrated	⊕◯◯◯	CONDITIONAL
	PICO Question: What are the treatment options for bone protection and improvement?		
53	The guideline group recommends that HCPs advise women with POI regarding bone health.		GPP
54	The guideline group recommends that osteoporosis risk factors should be identified in women with POI.		GPP
55	The guideline group recommends that women with POI should be advised to maintain a healthy lifestyle, involving weight-bearing exercise, avoidance of smoking, and maintenance of normal body weight to optimize bone health.		GPP
56	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 value in women with low BMD.	⊕⊕◯◯	CONDITIONAL
57	Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.	⊕⊕◯◯	STRONG
58	A daily dose of HT containing at least 2 mg oral estradiol or 100 µg transdermal estradiol or equivalent is suggested to optimise bone density.	⊕◯◯◯	CONDITIONAL
59	Delayed initiation and non-adherence of estrogen replacement should be avoided.	⊕◯◯◯	STRONG
60	The combined oral contraceptive pill may be appropriate for some women. A continuous or extended regimen is recommended.	⊕⊕◯◯	CONDITIONAL

61	Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies to women desiring pregnancy.	⊕⊕◯◯	STRONG
	PICO QUESTION: How should skeletal health be monitored in women with POI?		
62	It is important to consider bone health at diagnosis of POI, and during ongoing care. Osteoporosis risk factors should be identified and addressed.	⊕◯◯◯	STRONG
63	Where available, measurement of BMD at initial diagnosis of POI is recommended for all women.	⊕⊕◯◯	STRONG
64	In case of a diagnosis of osteoporosis or low bone mass in women with POI, BMD measurement should be repeated within 5 years. A decrease in BMD should prompt review of estrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate.	⊕◯◯◯	STRONG
65	If BMD is normal and adequate systemic estrogen replacement is commenced, the value of repeated DXA scan within 5 years is low.	⊕◯◯◯	STRONG
66	Assessment of bone turnover markers can be considered as it may be useful in monitoring response and adherence to therapy.	⊕◯◯◯	CONDITIONAL
	PICO Question: what are the consequences of POI for muscle health?		
67	Women with POI and HCPs should be aware that POI is associated with lower muscle mass, strength, and performance.	⊕⊕◯◯	STRONG
68	The guideline group recommends that HCPs be aware that POI may be associated with an increased risk of sarcopenia.		GPP
	PICO Question: What are the treatment options for muscle protection and improvement?		
69	The guideline group recommends that HCPs consider informing women with POI about muscle health.		GPP
70	HCPs should identify modifiable risk factors for muscle health in women with POI. Maintaining a healthy lifestyle, involving adequate nutrition, regular exercise, avoidance of smoking, and maintenance of normal body weight is likely to benefit muscle health	⊕◯◯◯	STRONG
71	Dietary supplementation of calcium and vitamin D may be required in women with inadequate vitamin D status and/or calcium intake and may benefit muscle health.	⊕⊕◯◯	CONDITIONAL
72	Resistance training can be considered as it increases muscle mass, strength and performance in other populations and is likely to be of benefit in POI.	⊕◯◯◯	CONDITIONAL
73	The effect of HT on muscle parameters in women with POI is uncertain but treatment may be of benefit and can be offered.	⊕◯◯◯	CONDITIONAL
74	The effect of other therapies, including testosterone, on muscle health in women with POI is uncertain and they should not be offered.	⊕◯◯◯	STRONG
	PICO Question: how should muscle health be monitored in women with POI?		
75	The guideline group recommends that HCPs consider assessment for sarcopenia at POI diagnosis.		GPP
	PICO Question: What are the consequences of POI for the cardiovascular system?		
76	HCPs should be aware that women with POI are at increased risk of cardiovascular disease, including coronary artery disease, heart failure and stroke.	⊕⊕◯◯	STRONG
77	The guideline group recommends that women with POI should be advised of cardiovascular risk factors that they can modify through behavioural change (e.g. by avoidance of smoking, heart healthy diet, regular exercise, and maintenance of normal body weight).		GPP

78	All women diagnosed with Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease, especially prior to and during pregnancy.	⊕⊕◯◯	STRONG
	PICO Question: Is estrogen replacement cardio-protective?		
79	Despite a lack of data from randomised controlled trials, hormone therapy with early initiation is recommended in women with POI to control future risk of cardiovascular disease. HT should be continued at least until the usual age of menopause.	⊕⊕◯◯	STRONG
	PICO Question: Should cardiovascular risk factors be monitored?		
80	The guideline group recommends that cardiovascular risk should be assessed in women diagnosed with POI.		GPP
81	The guideline group recommends that all women with POI should have annual monitoring of blood pressure, weight and smoking status, and where available blood tests for lipid profile and diabetes screening. Other tests for assessing cardiovascular risk can be performed upon indication.		GPP
	PICO Question: What are the consequences of POI on psychological wellbeing and quality of life?		
82	HCPs should be aware that a diagnosis of POI can have a significant impact on psychological wellbeing and quality of life	⊕◯◯◯	STRONG
83	The guideline group recommends offering assessment of psychological health and quality of life to all women with POI.		GPP
	PICO Question: What are the management options for reduced quality of life associated with POI?		
84	Personalised care, including psychological support, should be accessible to women with POI	⊕◯◯◯	STRONG
	PICO Question: What are the consequences of POI for sexuality?		
85	HCPs should be aware that a diagnosis of POI can have a significant impact on sexual wellbeing and function	⊕⊕◯◯	STRONG
86	The guideline group recommends that HCPs routinely enquire about sexual wellbeing and sexual function in women with POI.		GPP
	PICO Question: What are the management options for the effects of POI on sexuality?		
87	The guideline group recommends personalised management using the biopsychosocial model for the effects of POI on sexuality .		GPP
88	Where available, transdermal testosterone therapy at physiological premenopausal levels can be considered as it may improve HSDD and sexual function.	⊕⊕◯◯	CONDITIONAL
89	HCPs should be aware that although short term treatment with transdermal testosterone at physiological premenopausal levels is safe, longer term safety data are lacking	⊕⊕◯◯	STRONG
90	HCPs should be aware that HT prescribed to women with POI for other indications may improve sexual function, although the effect is generally small.	⊕◯◯◯	STRONG
	PICO Question: What treatments are available for genital-urinary symptoms in POI?		
91	HCPs should offer local estrogen therapy (LET) to improve genital, sexual and urinary GSM symptoms.	⊕◯◯◯	STRONG
92	Women with POI may be offered local estrogen therapy (LET) if GSM is not fully relieved by using systemic HT.	⊕◯◯◯	CONDITIONAL
93	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.	⊕◯◯◯	CONDITIONAL
94	The guideline group recommends that laser or thermal energy is not currently considered standard care for GSM due to the lack of clear benefit in RCTs		GPP

	PICO Question: What are the consequences of POI on cognition/neurological function?		
95	HCPs should be aware that earlier age of menopause is associated with an increased risk of dementia.	⊕◯◯◯	STRONG
96	The guideline group recommends that HCPs implement appropriate preventive actions for the consequences of POI on neurological function		GPP
97	The possible detrimental effect on cognition and the increased risk of dementia, parkinsonism, and other neurologic diseases should be discussed when planning a bilateral oophorectomy under the age of 45 years, especially for women at average risk of ovarian cancer.	⊕◯◯◯	STRONG
	PICO Question: What are the management options for the effect of POI on cognition/neurological function?		
98	Hormone replacement therapy to reduce the possible risk of cognitive impairment and the risk of dementia, parkinsonism and other neurologic diseases is recommended in women with POI at least until the usual age of menopause.	⊕⊕◯◯	STRONG
99	Hormone replacement therapy may be recommended for neurological function even in the absence of menopausal symptoms, as HRT is for cardiovascular and bone health.	⊕⊕◯◯	CONDITIONAL
100	The guideline group recommends that women with POI should be advised to maintain a healthy lifestyle, involving exercise, healthy diet, avoidance of smoking, and maintenance of normal body weight to reduce possible risks for cognitive impairment.		GPP
	Hormone therapy in POI – Principles and indications		
101	Women with POI should be advised that hormone therapy is recommended for the preservation of bone, cardiovascular and brain health.	⊕⊕◯◯	STRONG
102	Women with POI should be advised that hormone therapy is recommended for the treatment of symptoms due to low estrogen.	⊕⊕◯◯	STRONG
103	HT should be continued until at least the usual age of menopause	⊕⊕◯◯	STRONG
	PICO Question: What are the risks of hormone therapy?		
104	It is suggested that women with POI be informed that hormone therapy does not appear to increase the risk of breast cancer before the usual age of menopause compared to women without POI in the same age group.	⊕⊕◯◯	CONDITIONAL
105	Women with POI should be informed that hormone therapy is generally contra-indicated in breast cancer survivors.	⊕⊕⊕◯	STRONG
106	Women with BRCA1/2 mutations without a personal history of breast cancer should be advised that hormone therapy is an option after risk reducing bilateral salpingo-oophorectomy.	⊕⊕◯◯	STRONG
107	Women with POI should be advised that progestogen should be given in combination with estrogen therapy to protect the endometrium in all women with an intact uterus.	⊕⊕◯◯	STRONG
108	It is suggested that the dose of progestogen is increased when higher doses of estrogen therapy are used.	⊕◯◯◯	CONDITIONAL
109	The guideline group recommends that HCPs treat women with a history of endometriosis after surgical menopause with combined estrogen-progestogen at least until the usual age of menopause		GPP
110	Migraine should not be seen as a contraindication to hormone therapy use by women with POI.	⊕⊕◯◯	STRONG
111	HCPS should consider changing dose, route of administration or regimen if migraine worsens during hormone therapy.	⊕⊕◯◯	STRONG
112	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
	PICO Question: What are the options for hormone therapy?		

113	The guideline group recommends that women are advised that compounded "bio-identical" preparations of estrogen and progesterone are not recommended due to lack of data on efficacy and safety unless no alternative regimens are available.		GPP
114	Women with POI should be advised that estradiol has advantages over ethinylestradiol and conjugated equine estrogens when used for hormone therapy.	⊕⊕⊕◯	STRONG
115	The guideline group recommends shared decision making when prescribing each component of hormone therapy with consideration of patient preference, contraceptive needs, and presence of co-morbidities.		GPP
116	Women with POI should be advised that adherence to hormone therapy is important to minimise long term health risks and therefore long term follow up is needed	⊕⊕◯◯	STRONG
	Monitoring hormone therapy		
117	Women with POI should be advised to have a clinical review at least annually, addressing individualised risk review (specifically cardiovascular and bone health) and adherence to therapy.	⊕⊕◯◯	STRONG
	PICO Question: What is the role of testosterone therapy in POI?		
118	Testosterone treatment should be considered in women with POI to manage hypoactive sexual desire disorder (HSDD) when other biopsychosocial aetiologies are excluded.	⊕⊕◯◯	STRONG
119	The guideline group recommends that women with POI are informed that there is limited data for androgen treatment for indications other than hypoactive sexual desire disorder (HSDD), and that long-term health effects are unknown.		GPP
	PICO Question: What are the specific considerations for hormone therapy in iatrogenic POI ?		
120	The guideline group recommends a personalised approach to risks and benefits of HT in women with iatrogenic POI after gynaecological/breast cancer		GPP
121	Hormone therapy does not increase the risk of recurrence of squamous cell carcinoma of the cervix and is recommended for women with iatrogenic POI due to treatment of squamous cell carcinoma.	⊕⊕⊕◯	STRONG
122	Hormone therapy may be associated with a low risk of recurrence of cervical adenocarcinoma and a personalised approach considering individualised hormone therapy risk and benefits is recommended.	⊕⊕◯◯	STRONG
123	HCPs could consider use of hormone therapy in women with early-stage low-risk endometrioid adenocarcinoma, as there is a low risk of cancer recurrence with hormone therapy use	⊕⊕◯◯	CONDITIONAL
124	HCPs could consider hormone therapy in women with iatrogenic POI due to epithelial ovarian cancer.	⊕⊕⊕◯	CONDITIONAL
125	The effect of hormone therapy on the risk of recurrence of non-epithelial ovarian cancer is unclear and it is suggested that HCPs use an individualised approach to prescribing hormone therapy including consideration of tumour hormone receptor status.	⊕◯◯◯	CONDITIONAL
126	Hormone therapy 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.	⊕⊕⊕◯	STRONG
127	Women should be informed of the risks of iatrogenic POI and risks and benefits of hormone therapy before risk reducing bilateral salpingo-oophorectomy	⊕◯◯◯	STRONG
128	It is recommended that individualised hormone therapy or pubertal induction be commenced in girls/women with POI following hematopoietic stem cell transplantation.	⊕⊕◯◯	STRONG
	PICO Question: What non-hormonal therapies are available for POI?		

129	Non-hormonal pharmacologic and non-pharmacologic therapies effective in peri-/postmenopausal women are likely to be helpful in women with POI although POI specific data is lacking	⊕◯◯◯	CONDITIONAL
	PICO Question: What complementary treatments are effective for managing the sequelae of POI?		
130	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		GPP
131	Complementary treatments do not prevent the long-term sequalae of POI and should therefore not be used to replace hormone therapy	⊕◯◯◯	STRONG
132	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.	⊕◯◯◯	STRONG
133	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 hormone therapy.	⊕◯◯◯	STRONG
134	Women who are considering using nutrient supplements for improving reproductive parameters in POI should be informed that the evidence is very limited with only one intervention (Vitamin E and selenium) studied in randomised controlled trials.	⊕◯◯◯	STRONG
135	Women who are considering using other nutrient supplements and herbal medicines should be informed that there is insufficient evidence to support its use.	⊕◯◯◯	STRONG
	PICO Question: What are the lifestyle management options for POI?		
136	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
137	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.		GPP
	PICO Question: How should puberty be induced?		
138	Puberty should be induced or progressed with 17β-estradiol, starting with low dose at the age of 11 with a gradual increase over 2 to 3 years.	⊕⊕◯◯	STRONG
139	In cases of late diagnosis and for those girls in whom growth is not a concern, a modified regimen of estradiol can be considered.	⊕◯◯◯	CONDITIONAL
140	Evidence for the optimum mode of administration (oral or transdermal) is inconclusive. Transdermal estradiol may result in more physiological estrogen levels and may therefore be preferred.	⊕◯◯◯	CONDITIONAL
141	The oral contraceptive pill should not be used for puberty induction.	⊕◯◯◯	STRONG
142	The guideline group recommends starting cyclical progestogens after about 2 years of estrogen therapy or when breakthrough bleeding occurs.		GPP

[1]GDG, guideline development group; GPP, good practice point

PART A: Introduction to POI

I. PREMATURE OVARIAN INSUFFICIENCY (POI)

This chapter summarises the nomenclature for POI and formulates guidance on what this condition should be called in clinical practice and future research. Furthermore, the definition and prevalence of POI are discussed.

I.1. POI Nomenclature

KEY QUESTION: WHAT SHOULD THIS CONDITION BE CALLED?

The condition addressed in this guideline was first described as Primary Ovarian Insufficiency by Fuller Albright in 1942 (Albright *et al.*, 1942). Subsequently several terms have been used, with variation between specialities (e.g. gynaecology, endocrinology) and between countries (e.g. USA, UK).

The use of standard terminology is important to clarify information given to women, improve communication between health professionals, facilitate data collection and audit, and aid future research.

The ESHRE Guideline: management of women with premature ovarian insufficiency published in 2015/2016 recommended that the term "premature ovarian insufficiency" should be used to describe the condition in research and clinical practice (Webber *et al.*, 2016). This followed a workshop convened by ESHRE Special Interest Group for Reproductive Endocrinology (Utrecht, December 2013) for the guideline development group, patient representatives, and the broader membership. It was felt that in Europe the terms "primary" and "secondary" were widely used to classify amenorrhoea in relation to menarche, and thus "primary ovarian insufficiency" would lead to confusion, as it was not synonymous with primary amenorrhoea. Consensus was easily reached to recommend the term "insufficiency" instead of "failure" as this more accurately describes the fluctuating nature of the condition and does not carry the negative connotation of "failure".

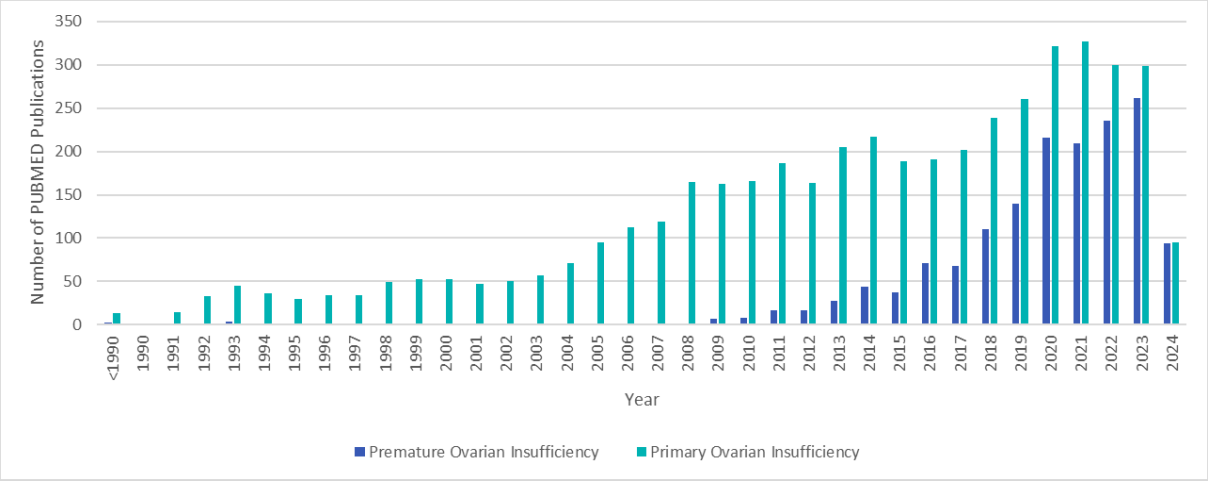
The uptake of the term "premature ovarian insufficiency" and the use of other terms can be assessed through a search of PUBMED, updated from Cooper and colleagues and the previous guideline (Cooper *et al.*, 2011, Webber *et al.*, 2016) (Table II). The results indicate that since the publication of the ESHRE Guideline: management of women with premature ovarian insufficiency, the term "premature ovarian insufficiency" has been increasingly used over the last decade, even if "Primary Ovarian Insufficiency" is still the most prevalent term in current research publications (Figure 1).

A second source of information is the scoping survey performed as part of this guideline development process. This included 282 consumer and 473 healthcare professional responses, with international representation. 'Premature ovarian failure' was the term used by most consumer (40%) and health care professional (71%) respondents. 'Primary ovarian insufficiency' was used by approximately 15% of both consumer and healthcare professionals, predominately in North America. 'Premature ovarian failure' was the term used by 26% of consumer and 13% of healthcare professionals respectively (unpublished data).

TABLE II NUMBER OF PAPERS RETRIEVED IN PUBMED FOR THE DIFFERENT TERMS USED FOR POI, IN TOTAL AND SINCE THE ESHRE RECOMMENDATION WAS PUBLISHED (MAY 2016)

	Number of papers retrieved in PUBMED	Number of papers retrieved in PUBMED, since May 2016
Primary Ovarian Insufficiency	3837	1647
Premature Ovarian Failure	2856	852
Gonadal dysgenesis	4268	598
Premature menopause	1779	553
Early menopause	1218	454
Hypergonadotropic hypogonadism	688	249
Premature Ovarian Insufficiency	1156	1011
Ovarian dysgenesis	276	52
Primary ovarian failure	220	50
Hypergonadotropic amenorrhea	62	4
Climacterium praecox	5	0
Menopause praecox	1	0

FIGURE 1 NUMBER OF PUBMED CITATIONS USING THE TERM "PREMATURE OVARIAN INSUFFICIENCY" AND "PRIMARY OVARIAN INSUFFICIENCY" PER YEAR (SOURCE PUBMED, ACCESSED 05/04/2024).



Recommendation

The guideline group recommends that the term "premature ovarian insufficiency" is used to describe this condition in research and clinical practice.	**GPP**

Justification

In developing an international guideline, the terminology used must be unambiguous and consistent, in order to ensure clarity. The guideline group encourages consistency in the terminology used in published studies and clinical practice.

The issue of terminology was discussed within the guideline development group and the advantages and disadvantages of the different terms used in the literature and clinical practice were weighed. The Guideline Development Group acknowledges the preferences in terminology from individual authors,

but also regional preferences, such as the preference in the USA to refer to 'primary ovarian insufficiency'.

To ensure the terminology does not hinder implementation, the Guideline Development Group has used the abbreviation "POI" throughout this guideline.

I.2. Definition of POI

KEY QUESTION: HOW SHOULD POI BE DEFINED?

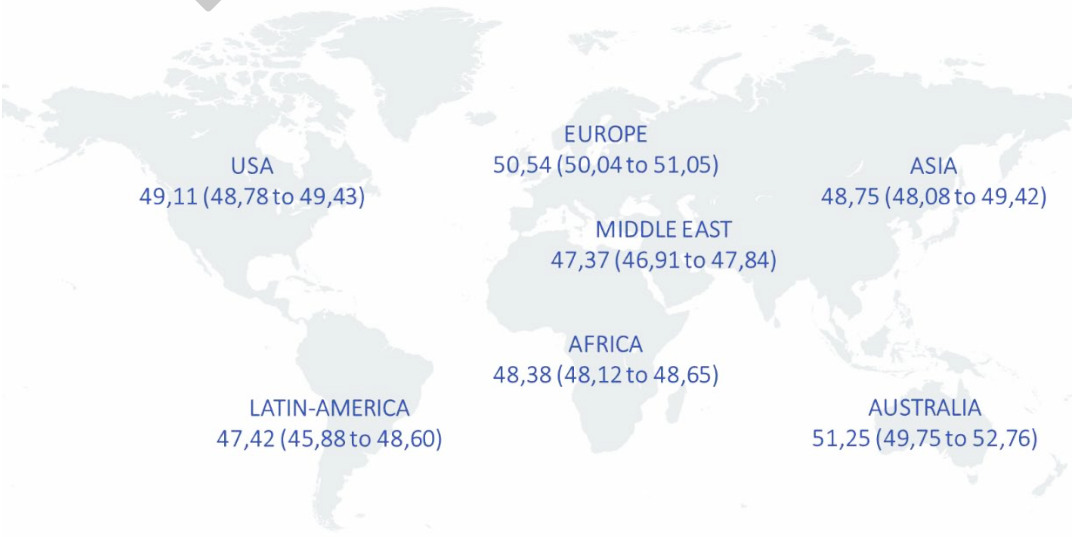
A definition of POI is important to differentiate women with menopause at usual age from women with POI, as these women have unique needs and management options. Women with POI may not only suffer from vasomotor symptoms and symptoms associated with estrogen deficiency, but they can also experience infertility and psychological problems with a significant impact on their quality of life and later health outcomes (see IV. POI and life expectancy).

POI is a clinical condition characterised by loss of ovarian function indicated by amenorrhoea, or oligomenorrhoea, for more than 4-6 months together with biochemical confirmation of ovarian insufficiency before the age of 40. It is a state of female hypergonadotropic hypogonadism. It can manifest as primary amenorrhea, with onset before menarche, or secondary amenorrhea.

The age of 40 years is set by convention but is supported by clinical observations.

The usual age of menopause is a first relevant point of relevance. A systematic review and meta-analysis analysed 46 studies across 24 countries (Schoenaker *et al.*, 2014). They calculated the overall mean age of menopause is 48.78 years (95% CI 48.33 to 49.22). However, there was substantial heterogeneity between studies, with mean age ranging from 46 to 52 years. There was a geographical variation in the usual age of menopause across regions, see Figure 2. In addition to the regional variation, the authors also highlighted general trends of increasing age of menopause (Schoenaker *et al.*, 2014). This trend was confirmed by an analysis in the USA that reported that over the last 6 decades, the usual age of menopause increased by 1.5 years (from 48.4 years in 1959-1962 to 49.9 years in 2015-2018)(Appiah *et al.*, 2021). Similar data were reported from a population study in Norway. In this study, the mean age of menopause increased from 50.31 years (95% CI 50.25 to 50.37 years) among women born during 1936–1939 to 52.73 years (95% CI 52.64 to 52.82 years) among women born during 1960–1964 (Gottschalk *et al.*, 2020).

FIGURE 2 USUAL AGE OF MENOPAUSE PER REGION, BASED ON DATA FROM (SCHOENAKER *ET AL.*, 2014).



From a statistical point of view, the age limit of 40 is approximately two standard deviations (SD) below the usual age of menopause (50 ± 4 years). Conventionally, menopause occurring in the 40-44 age group is referred to as 'early menopause'; although, this may include age 45 years in some studies.

POI versus diminished ovarian reserve

Loss of ovarian function in POI can be entangled with low ovarian reserve, although these need to be considered as separate entities in different patients, with different management needs. Low ovarian reserve is a condition in which the ovary loses its normal reproductive potential; it is characterized by regular menses with alterations of ovarian reserve tests.

The term 'ovarian reserve' encompasses both the quantity and quality of primordial follicles. Women with low ovarian reserve often respond poorly to ovarian stimulation resulting in retrieval of fewer oocytes, producing poorer quality embryos and reduced implantation rates and pregnancy rates. Incidence of poor ovarian response over all assisted conception cycles ranges from 5 to 35% (The ESHRE Guideline Group On Ovarian Stimulation *et al.*, 2020).

It is important to distinguish between low ovarian reserve and POI, although they may lie on the same spectrum, because women with POI face challenges much wider than fertility alone and will need appropriate management options.

GDG statement

Premature ovarian insufficiency is a condition defined by loss of ovarian activity before the age of 40 years.

POI is characterised by amenorrhea or oligomenorrhea, with elevated gonadotropins and low estradiol.

In this guideline, cessation of ovarian function in women aged between 40 and less than 45 (age 40-44 years) will be termed early menopause. Even if this group is outside the scope of the current guideline, the evidence and recommendations may still be relevant to women with early menopause.

I.3. Prevalence of POI

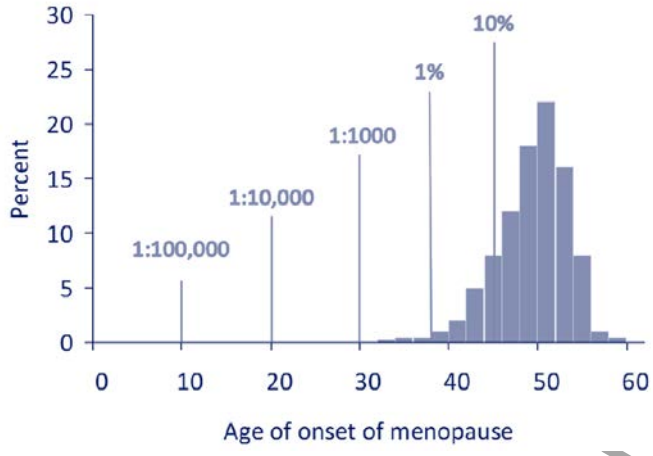
KEY QUESTION: WHAT IS THE PREVALENCE OF POI IN THE GENERAL POPULATION?

Epidemiological data

Earlier studies indicated that the prevalence of non-iatrogenic menopause before the age of 40 was approximately 1% (Krailo and Pike, 1983, Coulam *et al.*, 1986, Cramer and Xu, 1996, Luborsky *et al.*, 2003). Coulam and colleagues established that the rate of non-iatrogenic menopause is ten times higher in the 40 to 44 age group; conventionally this is called "early menopause", as compared to the 30 to 39 age group (Coulam *et al.*, 1986) (Figure 3). However, more recent data suggest a higher prevalence. In a large meta-analysis, the prevalence of non-iatrogenic menopause in women below 40 years old was 3.7% (95% CI 3.1 to 4.3) (Golezar *et al.*, 2019). The authors also calculated the prevalence of menopause in other age groups, and reported a prevalence of 12.2% (95% CI 10.5 to 14.0) in those between 40 and 45 years old, 78.1% (95% CI 75.9 to 80.3) in women between 45 and 55 years old (Usual age menopause), and 7.2% (95% CI 4.5 to 10) in women above 55 years old (late menopause) (Golezar *et al.*, 2019) (see Figure 4). The meta-analysis. further reported that the prevalence of POI was greater in medium (4.9%),

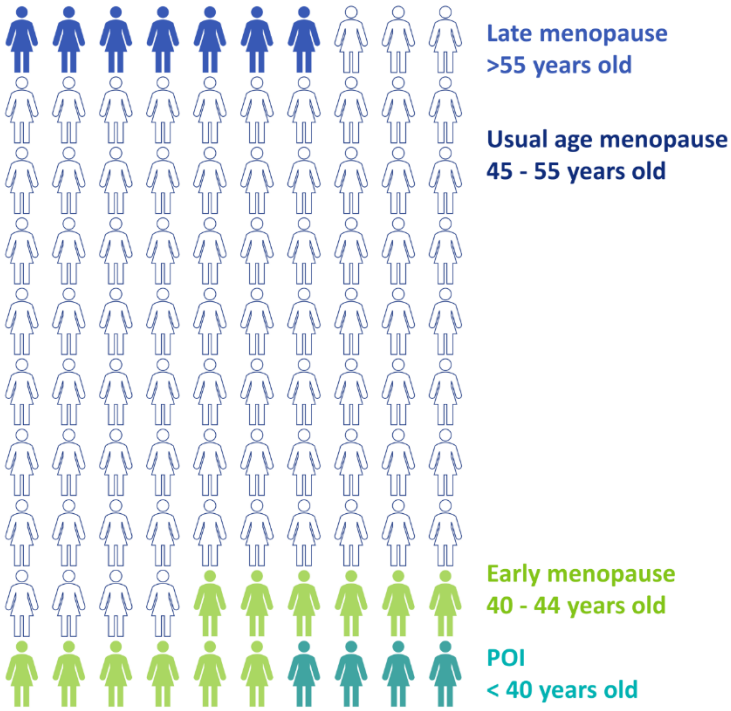
and low (23.8%) human development index (HDI) countries as opposed to high (3.6%) HDI countries (Golezar *et al.*, 2019).

FIGURE 3 DISTRIBUTION OF AGE OF MENOPAUSE.



A similar global overall prevalence of POI of 3.5% was reported in a more recent systematic review and meta-analysis (Li *et al.*, 2023a). The prevalence of POI differed between regions globally, as well as between developing and developed countries. In addition, the trend of prevalence of POI over the past 20 years appears to be on the rise (Li *et al.*, 2023a).

FIGURE 4 DISTRIBUTION OF AGE OF MENOPAUSE AND PREVALENCE OF NON-IATROGENIC POI (BASED ON (GOLEZAR *ET AL.*, 2019)).



Iatrogenic POI

Historically, bilateral oophorectomy has been practised at the time of hysterectomy for benign gynaecological disease. Hysterectomy rates of about 20% by age 55 were estimated in a UK cohort in the early 1990s (Vessey *et al.*, 1992, Kramer and Reiter, 1997, Hill *et al.*, 2010, Pokoradi *et al.*, 2011). A large study on unilateral and bilateral oophorectomy trends in Minnesota (USA) concluded that there has been a notable decrease in the incidence of premenopausal oophorectomies over the 69-year study period (1950 – 2018). These findings suggest a shift in clinical practice towards more conservative approaches in managing ovarian health, particularly in women without a high genetic risk or ovarian indication for surgery (Erickson *et al.*, 2022). Still, bilateral oophorectomy is the most common cause of POI in Western countries (Rocca *et al.*, 2023).

Of current concern is the rising incidence of iatrogenic POI in young cancer survivors, consequent on the increasing success of cancer therapy. A systematic review of 36 studies from 1990 to 2017 (sample size ranging from 15 to 3749) reported the prevalence of POI in female childhood or adolescent cancer survivors aged 0 to 24 years as 2.1% to 82.2% (Gargus *et al.*, 2018, Giri and Vincent, 2020). A meta-analysis of 68 studies included 26 585 patients with breast cancer and reported an overall prevalence of chemotherapy-induced amenorrhea of 63.3% (16 927 patients) (Wang *et al.*, 2022). The prevalence of chemotherapy-induced amenorrhea was lower in women below 40 years at the time of treatment and women with hormone receptor negative tumours. Incidence was further impacted by chemotherapy regimen. In women below 40, the incidence of chemotherapy-induced amenorrhea was 35.53%.

Iatrogenic POI may also arise from the increasing use of cytotoxic agents in treatment of serious non-malignant disease such as cyclophosphamide for systemic lupus erythematosus (Huong *et al.*, 2002, Katsifis and Tzioufas, 2004), stem cell transplant for haemoglobinopathies (Rahal *et al.*, 2018) or surgery for ovarian endometriosis (Coccia *et al.*, 2011).

All causes of POI, including associated diseases, are summarised in section II.3 Investigating the cause for POI

GDG statement

The reported prevalence of non-iatrogenic POI varies from approximately 1% in older studies to 3,5% in recent publications Population characteristics such as ethnicity may affect the prevalence of non-iatrogenic POI.

I.4. Risk factors for POI.

Identifying risk factors for POI is crucial as it may allow for preventive measures both on a patient-level and on a public health level, facilitate early detection and diagnosis, and allow for decisions about fertility preservation. It is widely agreed that early diagnosis is important to prevent some consequences of POI.

PICO Question: What are the risk factors for POI?

Risk factors for POI or early menopause include many but not all factors that influence age of natural menopause. Additionally, there is reported disparity regarding factors affecting early menopause versus POI risk which may reflect methodological rather than physiological differences. Risk factors for POI include both non-modifiable and modifiable. A recent position statement concluded that the following were predictors of POI: genetic abnormalities; family history of premature or early menopause; being a

child of multiple pregnancy, early menarche, nulliparity/low parity, cigarette smoking (dose–response effect), and being underweight (Mishra *et al.*, 2019). Specific factors are discussed in more detail below.

Genetic

Specific chromosomal abnormalities and genetic variants are associated with an increased risk of POI. In a registry study of 5011 women diagnosed with POI, 15.9% had at least one diagnostic code for a genetic disorder or congenital malformation. Documented congenital malformations among women ultimately diagnosed with POI included malformations of the ovary, fallopian tubes, and broad ligaments, skin and mammary gland anomalies, malformations of the nervous system, eye, ear, face, and neck, lip and cleft palate, and malformations of the digestive, urinary, and musculoskeletal systems (Silven *et al.*, 2023).

Specific chromosomal abnormalities and genetic variants are associated with an increased risk of POI. Genetic causes of POI, prevalence and genetic testing is discussed in section II.3.a POI and genetic causes .

Family history and demographic factors

Multiple studies have identified family history as a strong predictor of the age of menopause. Indeed, hereditability estimates suggest that approximately 50% of interindividual variation in age of menopause can be explained by genetic effects, with higher values associated with twin studies (Giri and Vincent, 2020). The odds of early menopause (OR 6.1; 95% CI 3.9 to 9.4) was increased with a family history of early menopause affecting mother, sister, aunt, or grandmother in a USA case-control study after adjusting for smoking, education, BMI, and parity (Cramer *et al.*, 1995). Higher risks were observed with multiple family members affected or a family history of an affected sister; greatest risk observed in association with an affected twin sister (Cramer *et al.*, 1995, Morris *et al.*, 2011, Silvén *et al.*, 2022). More recently, a US study using data linkage, reported that the risk of POI was increased 18-fold in first degree relatives, 4-fold in second degree relatives and 2.7-fold in third degree relatives of women with POI compared with controls (Verrilli *et al.*, 2023). Among a cohort of 955 Chinese women with POI, 12.25% of patients reported a family history of either POI or early menopause (Jiao *et al.*, 2017). In another cohort of 553 Han Chinese women, a family history of a relative with menstrual abnormalities was strongly associated with a future diagnosis of POI (OR 28.12; 95% CI 8.84 to 89.46) (Wang *et al.*, 2015).

Ethnicity

Usual age of menopause presents with a geographical variation as described previously, with the lower age in African, Asian, Latin American, and Middle Eastern countries (Schoenaker *et al.*, 2014)(see I.3. Prevalence of POI). As with usual age of menopause, the prevalence and thus potential risk of POI varies with ethnicity. The Study of Women's Health Across the Nation (SWAN) identified lower prevalence of POI in Asian women compared with Hispanic, African American or Caucasian. This may reflect both genetic and non-genetic factors (Luborsky *et al.*, 2003).

Early life factors

Large cohort studies suggest a link between early life factors and the age of onset of natural menopause, but data specific to POI is lacking. A 2022 analysis investigated pooled data from two large prospective British birth cohort studies, the 1958 National Child Development Study (NCDS) and the 1970 British Cohort Study (BCS70), which followed a total of 17 614 women from birth through middle age. The study found multiple factors influencing the age of natural menopause across the lifespan and beginning during prenatal life. For example, women whose mothers smoked during pregnancy had 24% higher odds for early menopause as compared to women whose mothers did not smoke (OR 1.24; 95% CI 1.03 to 1.49) (Peycheva *et al.*, 2022). A UK biobank study identified that being part of a multiple birth

is associated with an increased risk of early menopause after adjustment for confounders (OR 1.55; 95% CI 1.13 to 2.13) (Ruth *et al.*, 2016). Twin registry data indicated a higher prevalence of POI and early menopause in twins compared with the general population (Gosden *et al.*, 2007). One small study (n=151) observed an increased prevalence of POI in those born at gestation<37 weeks compared with controls (OR 4.66; 95% CI 1.3 to 16.7) (Sadrzadeh *et al.*, 2017). Association between low birth weight and earlier age at natural menopause is inconclusive (Sadrzadeh *et al.*, 2017).

Neonatal and early childhood factors which have been associated with an earlier age of menopause include shorter duration of breastfeeding (<1 month, OR 1.30; 95% CI 1.05 to 1.60) (Peycheva *et al.*, 2022). Longer duration of breastfeeding was associated with a lower risk of early menopause in the Nurses Health Study II cohort study (Langton *et al.*, 2020). Lower early childhood socioeconomic position has also been associated with an early age of menopause (Peycheva *et al.*, 2022). Finally, higher childhood cognitive ability in early childhood, as measured by reading comprehension and mathematics test scores, is associated with a reduced risk for early menopause (OR 0.64; 95% CI 0.57 to 0.71).

Adverse parenting or childhood experiences is associated with an earlier age of menopause; however, data specific to POI is lacking (Giri and Vincent, 2020).

Reproductive factors

A 2020 meta-analysis observed that parous women had a later age at natural menopause (Roman Lay *et al.*, 2020). Consistent with this, data from the Nurses Health Study II indicated a lower risk of early menopause with one or more pregnancies (Langton *et al.*, 2020). A retrospective Norwegian population study of 310147 women reported lower age of menopause with lower parity (Gottschalk *et al.*, 2022). Data from the UK Biobank revealed that later age at first birth was associated with later age of menopause (Prince *et al.*, 2022). The INTERLACE study (n=51450) identified a 2.26-fold and 1.32-fold increased risk of POI and early menopause respectively, with nulliparity. Risk was further increased with the combination of nulliparity and early menarche (Mishra *et al.*, 2017).

Data are conflicting regarding a possible association between POI or early menopause and earlier age at menarche. A 2020 meta-analysis also concluded that later age of menarche was associated with later age at natural menopause; however, a direct linear relationship was difficult to establish due to multiple potential confounders (Roman Lay *et al.*, 2020). In contrast to older or smaller studies (van Noord *et al.*, 1997, Otero *et al.*, 2010, Wang *et al.*, 2015, Whitcomb *et al.*, 2018a), The InterLACE study (n=51450) reported an association between POI or early menopause and earlier age at menarche (defined as age ≤ 11 years) compared to menarche at age 12-13 years, with risk ratios of 1.8 and 1.32 respectively (Mishra *et al.*, 2017).

Shorter menstrual cycle length<25 days was associated with a 70% higher risk of early menopause compared with cycle lengths of 26 to 31 days in the Nurses health Study II (Whitcomb *et al.*, 2018a). A meta-analysis including 17 observational studies, reported that previous/ever use of the combined oral contraceptive pill (COC) was associated with later age at natural menopause (Roman Lay *et al.*, 2020).

Finally, a case-control study of 553 women with POI and 400 controls reported an increased risk of POI associated with a history of pelvic surgery (OR 5.53; 95% CI 2.15 to 14.23) (Wang *et al.*, 2015).

Body Mass Index

Data from a 2015 meta-analysis indicated that lower body mass index (BMI) <18.5 was associated with an earlier age at natural menopause compared with women with normal BMI (HR 1.08; 95% CI 1.03 to 1.14) (Tao *et al.*, 2015). Consistent with this, findings from the Nurses Health II study and InterLACE study indicate a 30% and two-fold increase respectively in the risk of early menopause with low BMI (Szegda *et al.*, 2017, Zhu *et al.*, 2018b). Data specific to POI is lacking. However, obesity was associated with a

reduced risk of POI (HR 0.43; 95% CI 0.22 to 0.86) in a cohort of cancer survivors (Chemaitilly *et al.*, 2017).

Socio-economic status

Based on 11 studies, a 2014 meta-analysis reported that onset of menopause was later in women with middle (higher school certificate/diploma) and higher (university or higher degree) education levels, compared to in women with lower education (no formal qualifications); corresponding to one-third and two-thirds of a year respectively. Occupation had an effect comparable to education (Schoenaker *et al.*, 2014). More recently, a Finnish study indicated that women with POI had lower socio-economic status and levels of education compared with the general population (Silvén *et al.*, 2022), while a 2022 pooled analysis of the British NCDS and BCS70 studies found an increased odds for early menopause in women without paid employment (OR 1.43; 95% CI 1.13 to 1.81) (Peycheva *et al.*, 2022). Indian women living in rural areas were more likely to experience POI compared to those in urban areas. In addition, POI was associated with poorer wealth quintiles compared with richer (Jungari and Chauhan, 2017). Confounding/ contributing factors could be early life experiences and lifestyle elements such as smoking, BMI, early life factors, and nutrition.

Smoking

Multiple studies have linked smoking to an earlier age of natural menopause (Schoenaker, 2014 #3; Zhu, 2018 #62;Oboni, 2016 #63;Ruth, 2021 #64}(Kato *et al.*, 1998), but not all (van Noord *et al.*, 1997). Tobacco smoke disrupts folliculogenesis and development, increases apoptosis and DNA damage, and disrupts oocyte-granulosa cell communication (Giri and Vincent, 2020, Cui and Wang, 2024). Based on 15 studies, smoking was found to be associated with an earlier mean age of menopause by almost a year (Schoenaker *et al.*, 2014). Another prospective cohort study of 5113 postmenopausal women found that smokers in this study had a mean age of menopause of 45.6 years (SD 6.04 years) as compared to 46.9 years (SD 5.7 years) in non-smokers (Pokoradi *et al.*, 2011). The same was observed in the Massachusetts Women's Health Study and in the National Survey of Health and Development (McKinlay *et al.*, 1985, Hardy *et al.*, 2000), as well as in an analysis of pooled data from the British NCDS and BCS70 studies (OR 1.69, 95% CI 1.28-2.23) (Peycheva *et al.*, 2022). In a study of 244 menopausal Jordanian women, smoking was the major risk factor for early menopausal age (OR 2.46; 95% CI 1.08 to 5.59; $p<0.05$) (Bustami *et al.*, 2021). This association was found in both current and former smokers, and a dose-response relationship was observed. Higher intensity, longer duration, higher cumulative dose, earlier age starting smoking, and shorter time since quitting smoking have all been significantly associated with higher risk of early menopause (Whitcomb *et al.*, 2018b, Zhu *et al.*, 2018a). Passive smoking was not significantly associated with POI or early menopause (Gold *et al.*, 2013).

Alcohol

Alcohol consumption seems to be inversely associated with age at natural menopause. Data from a large prospective study suggest a weak association of moderate alcohol intake (10.0–14.9 g/day) with lower risk of early menopause (<45 years old), but high consumption was not related to lower risk of early menopause (Freeman *et al.*, 2021). A 2016 meta-analysis reported that low and moderate alcohol consumption (more than one drink per week (RR 0.60; 95% CI 0.49 to 0.75) and three or fewer drinks per week (RR 0.75; 95% CI 0.60 to 0.94) were associated with later menopause onset, compared to non-drinkers. The relative risk for earlier menopause onset was 0.95 (95% CI 0.91 to 0.98) when comparing women who reported drinking alcohol versus women who did not (Taneri *et al.*, 2016). Finally, a 2022 analysis of pooled data from two large British cohort studies found that alcohol intake 2-3 times per month was inversely associated with age of menopause (OR 0.76; 95% CI 0.57 to 1.00) (Peycheva *et al.*, 2022). While it has been suggested that the benefits observed with light to moderate alcohol use are due to alterations in sex steroid hormone levels (Gill, 2000), others have argued that these results may

be confounded by inappropriate control groups (e.g. individuals who abstain from alcohol due to former heavy use or underlying long term health problems) (Peycheva *et al.*, 2022).

Infectious causes

POI has been reported following various infections, including mumps, HIV, herpes zoster, cytomegalovirus, tuberculosis, malaria, varicella, and shigella (Goswami and Conway, 2005, Kokcu, 2010). However, only mumps oophoritis has been considered a cause of POI, explaining 3 to 7% of women with POI (BROOKS, 1913, Morrison *et al.*, 1975). Among a cohort of Han Chinese women, a history of mumps conferred an increased odds of POI (OR 3.26; 95% CI 2.38 to 4.47) (Wang *et al.*, 2015).

A systematic review of six studies on the prevalence of early menopause and POI among women living with HIV reported an increased prevalence of both early menopause and POI among women living with HIV (up to 26%, compared to as low as 2.3% among controls in studies including control women) (Van Ommen *et al.*, 2021). However, given that only one study included biochemical confirmation of menopause, and several studies did not include control groups, the authors suggested that these studies might overestimate the prevalence of POI by including women with prolonged amenorrhea. In contrast, a 2022 study of 3059 US women living with or at risk of HIV reported a prevalence of POI and early menopause similar to that reported globally (Bullington *et al.*, 2022).

Coexisting medical conditions

A recent population-based study of women with PCOS (n=7049) and women without PCOS (n=70490) reported that the risk for POI was significantly higher in women with PCOS than controls (adjusted HR 8.31; 95% CI 7.05 to 9.81), with an even higher risk in women with PCOS who did not receive metformin treatment (adjusted HR 9.93; 95% CI 8.28 to 11.90), and was significantly reduced for women with PCOS who received metformin treatment (adjusted HR 5.66; 95% CI 4.36 to 7.35) (Pan *et al.*, 2017). Galactosemia is an inherited metabolic disorder that affects about 1 in 50000 live births in the United States. In a recent cohort study of 102 post-pubertal girls and women with 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 *et al.*, 2018).

Autoimmune disease, especially Addison's disease, has also been associated with an increased risk of POI (see section II.3.b POI and autoimmune causes. The risk of POI associated with medical treatments and iatrogenic causes of POI are discussed in section II.3 Iatrogenic POI.

Chemical exposures

Exposure to endocrine disruptors also appears to impact the usual age of menopause. Examples of endocrine disrupting chemicals (EDCs) include i) heavy metals such as cadmium, thallium, and arsenic, ii) persistent organic pollutants (POPs), a class of carbon-based organic chemicals including pesticides and industrial chemicals which have long environmental half-lives, and iii) plasticizers, a class of additives incorporated into plastics which includes phthalates, perfluoroalkyl and polyfluoroalkyl substances (PFASs), and bisphenol A (BPA). Studies in rodent and mouse models support a detrimental effect of endocrine disruptors on ovarian follicle recruitment and growth, sex steroid hormone levels, oocyte quality and markers of ovarian reserve (Zhu *et al.*, 2024)

In a series of case-control studies comparing a group of Chinese women with POI (defined as age <40, oligomenorrhoea or amenorrhea for at least 4 months, and an elevated FSH level > 25 IU/L on two occasions > 4 weeks apart) to control women, serum and/or urinary levels of multiple EDCs were associated with significantly increased odds for POI (ORs ranging from 1.34 to 3.15). These exposures included heavy metals (thallium, cadmium, and arsenic), pesticides (including pyrethroids, DDT and DDT metabolites), plasticizers including PFAS, and POPs including PCBs and polycyclic aromatic

hydrocarbons (PAHs) (Pan *et al.*, 2019Ye, 2020 #2438, Cao *et al.*, 2020, Pan *et al.*, 2020, Pan *et al.*, 2021, Ma *et al.*, 2022). Findings are mixed regarding the association between BPA exposure and POI risk (Li *et al.*, 2018, Li *et al.*, 2021a). Another case-control study of a group of Chinese women found that high plasma PFAS levels were positively associated with POI (OR 2.81-6.63 for various PFAS chemicals) (Zhang *et al.*, 2018). Finally, a 2024 systematic review and meta-analysis of 10 studies investigating the effect of environmental pollutants on female fertility found an increased pooled odds ratio for POI (OR 2.33; 95% CI 1.97 to 2.68). Pooled exposures in this study included heavy metals (thallium, copper, selenium), plasticizers (PFASs and BPA), and POPs (PCBs, DDT, and pyrethroids) (Zhu *et al.*, 2024).

In the United States, a cross-sectional survey of National Health and Nutrition Examination Survey (NHANES) data, which included 31,575 women gathered between 1999-2008, found that women with high serum or urinary concentrations of certain organochloride pesticides, phthalates, or polychlorinated biphenyls (PCBs, a class of POPs which are widely distributed in the environment) had mean ages of menopause 1.9 to 3.8 years earlier than women with lower levels of these chemicals. (Agency for Toxic Substances and Disease Registry (ATSDR). 2000, Grindler *et al.*, 2015). The SWAN study reported a 63% higher risk of earlier menopause, equivalent to 2 years earlier median time to menopause, associated with high concentrations of perfluorinated compounds (a class of POPs) (Ding *et al.*, 2020). More studies are required to evaluate the effects of EDC exposures on reproductive health and to clarify potential dose-response effects.

Vaccines

While the mean number of reported POI events increased after the first human papillomavirus (HPV) vaccine launch in 2006 with (22.2 POI cases/year up from 1.4 POI cases/year pre-launch) (Tatang *et al.*, 2022), a 2023 meta-analysis, which included four studies and a total of 1 253 758 female children and adolescents, found no increased risk for POI after quadrivalent HPV vaccination (RR 0.47; 95% CI 0.14 to 1.5), as well as no increased risk with quadrivalent HPV vaccines relative to bivalent (RR 0.93; 95% CI 0.33 to 2.64) and 9-valent (RR 0.93; 95% CI 0.33 to 2.64) vaccines (Torella *et al.*, 2023).

A review of women with POI reported to the Vaccine Adverse Event Reporting System (VAERS) [a United States vaccine surveillance system] using the ACOG definition for POI, found 19 reports of POI over a span of 27 years (1990 – 2017). Of these 19 reports, only three met ACOG diagnostic criteria for POI and did not have another underlying cause identified. The authors concluded that, while POI is rarely reported to VAERS and most reports contained limited diagnostic information, results did not suggest a safety concern (Patricia Wodi *et al.*, 2023). Cohort studies have also found no association between POI and other vaccines, including the tetanus, diphtheria, and pertussis (Tdap), inactivated influenza, and meningococcal vaccines (Naleway *et al.*, 2018).

Circulating factors as POI biomarkers

Various circulating factors have been shown to be altered in women with POI in small studies, including vitamin E (Ma *et al.*, 2021), trace elements (Verma *et al.*, 2018), co-enzyme Q10 (Ma *et al.*, 2023), certain gut microbiota (Wu *et al.*, 2021), CD4+ T-cells (Kobayashi *et al.*, 2019), neutrophil to lymphocyte ratios (Yldrm *et al.*, 2015, Ağaçayak *et al.*, 2016), inducible nitric oxide synthase (Tokmak *et al.*, 2015), insulin-like peptide 3 (Zhu *et al.*, 2021), and IFN-γ (Xiong *et al.*, 2020). However, whether these circulating factors are relevant to the pathogenesis of POI, or can serve as novel biomarkers, has not been established.

Recommendations

The guideline group recommends that in view of the long-term health consequences of POI, efforts should be made to reduce the risk of POI. Modifiable factors may include: **- gynaecological surgical practice** **- lifestyle such as smoking cessation** **- modified treatment regimens for malignant and chronic diseases.**	**GPP**

The guideline group recommends that women with risk factors for POI are counselled regarding potential for prevention of POI, such as stopping smoking, and fertility preservation.	**GPP**

Justification

POI and early menopause are associated with both modifiable and non-modifiable risk factors including family history, early life, reproductive, socio-economic, co-existing illness, lifestyle, and environmental factors. Identification of risk factors for POI, especially about family history, is important to identify those at risk of POI thereby facilitating potential POI prevention strategies and fertility preservation.

Research recommendation.

Further research is required to (i) identify and clarify risk factors for POI, in addition to those related to early menopause, especially the role of socio-economic factors, lifestyle and environmental chemicals; and (ii) identify and quantify strategies that may mitigate modifiable risk factors.

PART B: Diagnosis of POI

II. Symptoms, diagnosis, and initial assessment

This chapter explores the symptoms of POI, the diagnostic criteria as well as investigations to establish the causation of POI.

II.1. Symptoms

PICO Question: What are the symptoms of POI?

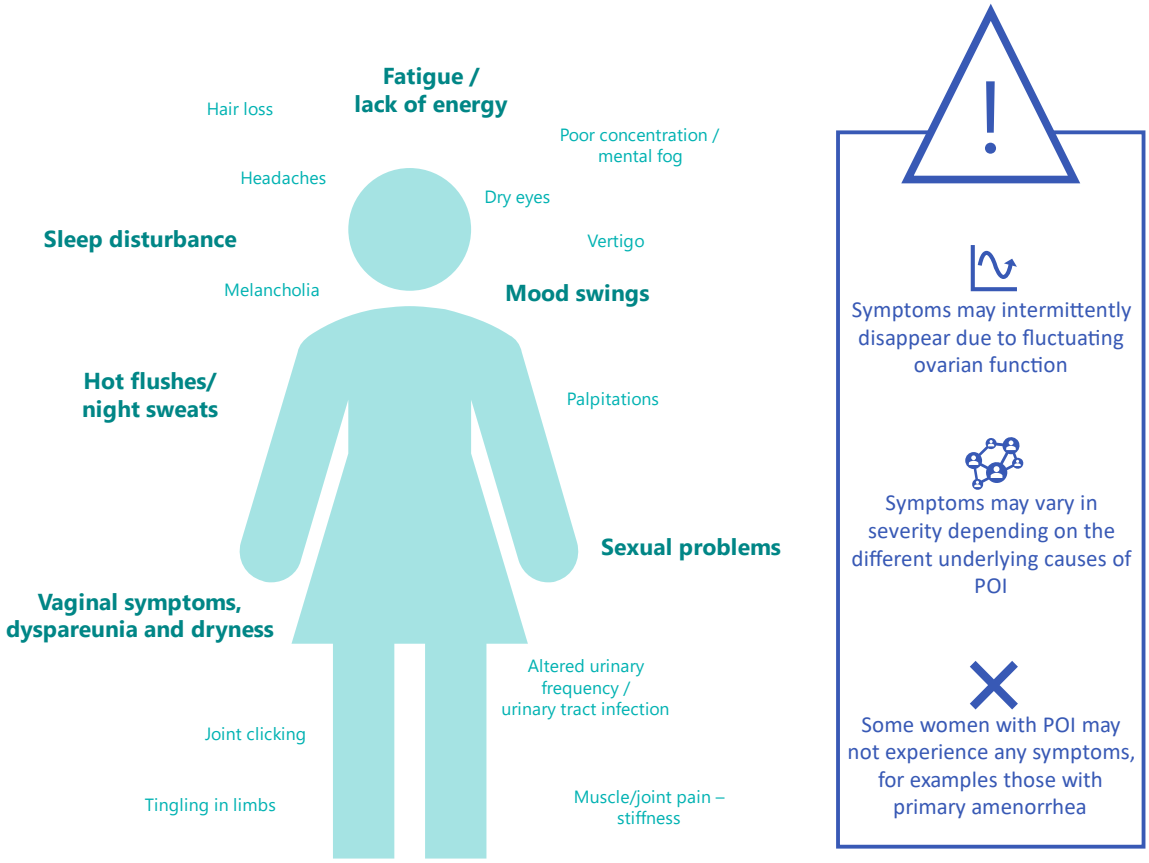
The clinical presentation of POI is quite variable. In a cohort of 955 women with overt POI, 86% presented with secondary amenorrhea and 14% with primary amenorrhea (Jiao *et al.*, 2017). More than 50% of women developed amenorrhea within 1 year after irregularity occurred (69.18%, 568/821) (Jiao *et al.*, 2017), although amenorrhea is not required for a diagnosis of POI. Menstrual cycle irregularities may be followed by symptoms related to estrogen deficiency, such as hot flushes and night sweats (Conway, 2000) and vaginal symptoms such as dyspareunia and dryness (Davis 2011). Other symptoms include sleep disturbance, mood changes, poor concentration, stiffness, dry eyes (Smith *et al.*, 2004), altered urinary frequency, low libido, and lack of energy (Conway, 2000). In a cross-sectional study of 293 Chinese women with POI, the most prevalent symptoms were mood swings (73.4%), insomnia (58.7%), sexual problems (58.7%), and fatigue (57.3%). Other symptoms – with varying severity - reported by the women with POI include hot flushes/sweating (49.5 %), melancholia (44.4%), headaches (37.5%), vertigo (36.3%), muscle/joint pain (36.2%), palpitations (32.1), formication[1] (20.1%), urinary tract infection (19.1%) and paraesthesia (17.7%) (Huang *et al.*, 2021). In another study of 160 women with POI, women reported a number of menopausal symptoms, including mood swings and mental fog (>75% reporting); hair loss, dry eyes, cold intolerance, and joint clicking (>50% reporting); tingling in limbs(Allshouse *et al.*, 2015). These symptoms can represent a significant source of distress for patients (Davis and Jane, 2011).

POI-related symptoms may be transient or intermittent and can vary in severity, reflecting the fluctuations in ovarian activity that occur after the onset of non-iatrogenic POI (Welt, 2008, Knauff *et al.*, 2009). Some women with POI may not experience any symptoms. Young women with primary amenorrhea due to POI are less likely to experience symptoms related to estrogen deficiency at presentation. In a cohort of women with primary and secondary amenorrhea, symptoms of intermittent estrogen deficiency were reported in 85.6% of those with secondary amenorrhea, while only 22.2% of women with primary amenorrhea reported symptoms ($p<0.001$) (Rebar and Connolly, 1990). These findings suggest that the onset of these symptoms is due to estrogen withdrawal rather than estrogen deficiency. In contrast, women experiencing surgical menopause usually have severe and persistent symptoms. Women may also experience sudden severe symptoms upon cessation of the contraceptive pill. Symptoms have also been reported to vary according to the type of POI (iatrogenic or non-iatrogenic) and the underlying cause (Deeks *et al.*, 2011, Gibson-Helm *et al.*, 2014).

More information on the impact of POI on psychosocial wellbeing and sexuality is available in in section VIII.1. Impact of POI on psychological wellbeing and IX.1. Impact of POI on sexuality, respectively.

[1] Formication is an acutely distressing sensation of ants or other insects crawling on the skin (cfr APA Dictionary of Psychology).

514 **FIGURE 5. SYMPTOMS OF POI (SYMPTOMS IN BOLD ARE MOST COMMON/IMPORTANT)**



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517 *Recommendations*

The guideline group recommends that HCPs enquire about symptoms of estrogen deficiency in women presenting with amenorrhea or oligomenorrhea.	**GPP**

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The guideline group recommends HCPs consider and exclude the diagnosis of POI in women aged less than 40 years who have amenorrhea, oligomenorrhea or estrogen-deficiency symptoms.	**GPP**

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II.2. Diagnosis

The diagnosis of POI is confirmed in women < 40 years by a combination of a 4-to-6-month period of disordered menses (including amenorrhea or irregular menses) and measurement of elevated follicle stimulating hormone (FSH). The value of FSH, and other tests used to make the diagnosis of POI, are explored in this chapter.

The second part of the diagnostic work-up is to establish a cause for POI. Establishing causation may have implications for the management options for symptoms associated with POI, and/or associated conditions. Finally, autoantibody tests used in POI are further explored, including what clinicians should do in case of a positive antibody test result, and when to repeat the test in case of a negative result.

PICO Question: What investigations should be performed for diagnosis of POI?

POI is characterised by menstrual disturbance, raised gonadotropins, and low estradiol. However, standardized diagnostic criteria have not been established by any professional organization. The 2015 National Institute for Health and Care Excellence (NICE) guidelines recommend making a diagnosis of POI in women under 40 based on a combination of menopausal symptoms (including amenorrhea or infrequent periods, with consideration of whether the woman has a uterus) and elevated serum FSH twice, at least 4-6 weeks apart (NICE, 2015, NICE, 2019). Women presenting with amenorrhea should be directly questioned about symptoms, as they may not volunteer these, or indeed be aware that their symptoms are related to menstrual disturbance. Other aetiologies of amenorrhea (e.g. pregnancy, polycystic ovary syndrome (PCOS), thyroid dysfunction, hyperprolactinemia) should be ruled out before assigning a diagnosis of POI. FSH levels are used as the gold standard in establishing a diagnosis of POI but there is insufficient high-quality evidence to propose definitive cut-off levels. Indeed, ovarian function decline can be intermittent and erratic, and POI can still be characterized by periods of low FSH concentrations and vaginal bleeding (De Vos *et al.*, 2010). As such, FSH thresholds to diagnose POI vary in the literature, with suggested cut-off levels ranging from >15 (Gordon *et al.*, 2017) to >40 (2014) or >50 (Ishizuka, 2021). Nelson *et al* proposed using criteria as defined by the reporting laboratory (FSH level in the menopausal range) (Nelson, 2009).

Histological evaluation of ovarian biopsies from women with primary amenorrhea found no follicles when FSH levels were above 33 mIU/ml, while in women with secondary amenorrhea no follicles were found when the FSH was >40 mIU/ml (Goldenberg *et al.*, 1973). However, some women with POI express FSH levels lower than these values, particularly women with autoantibodies. La Marca found that women with POI due to steroidogenic cell autoimmunity had significantly lower FSH levels (n=26; median 37 mIU/ml; range 26-64 mIU/ml) compared with idiopathic POI (median 99 mIU/ml; range 61-166 mIU/ml; p=0.001) (La Marca *et al.*, 2009). As such, the previous guideline group proposed a cut off level of FSH > 25 IU/l to diagnose POI, as this is above the physiological range for FSH even at the pre-ovulatory peak and even in women with autoimmune POI (Webber *et al.*, 2016). No new evidence exists to alter this proposed cutoff. While estradiol alone should not be used to make the diagnosis of POI, estradiol levels of less than 50 pg/mL (183.6 pmol/L) indicate hypoestrogenism (ACOG, 2014).

If the clinical presentation and initial biochemical testing (high FSH/low estradiol) are consistent, then the diagnosis of POI should be made. A second test may be required if the first set of results are inconclusive, and the index of clinical suspicion is high. Given the sometimes-fluctuant nature of the condition, menses may return, and FSH/estradiol levels normalise, thus a second test may paradoxically confuse the situation.

Recommendations

HCPs should diagnose POI based on the presence of amenorrhea or oligomenorrhea and biochemical confirmation.	⊕⊕◯◯	**STRONG**

Although proper diagnostic accuracy in POI is lacking, the guideline group recommends the following diagnostic criteria: amenorrhea or oligomenorrhea for at least 4 months, and an elevated FSH level >25 IU/l. **FSH assessment should be repeated after >4 weeks if there is diagnostic uncertainty.**	**GPP**

Justification

POI is characterised by oligo/amenorrhoea, raised gonadotropins, and low estradiol. In the absence of new data, the previous diagnostic criteria were accepted by the Guideline development group. An elevated FSH> 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 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.

Research Recommendation

Further research is required to establish the optimal FSH criteria for the diagnosis of POI or a sensitive and specific alternative biomarker that is readily available.

Measurement of AMH in women with POI

PICO Question: What is the role of AMH to predict/ diagnose POI?

AMH now has an established role as a clinically useful predictor of the ovarian response to stimulation in IVF (The ESHRE Guideline Group On Ovarian Stimulation *et al.*, 2020). This reflects its known main source of production, which is predominantly the population of small antral follicles in the ovary. It is produced by ovarian follicles when they start to grow, i.e. from the primary stage onwards but their relatively small size and thus small number of granulosa cells compared to the much larger small antral follicles means that the latter is the predominant source of AMH in circulation. This is important in the context of its potential use in POI as it means that AMH will be detectable within the serum of women with a very small number of antral follicles, even when the population of primordial and early growing follicles is extremely depleted. Diagnostic accuracy will also be impacted by the fluctuant ovarian function that is characteristic of POI, but particularly in the initial years (see section V. POI, fertility and pregnancy), all confounding the simplistic assumption that AMH will be undetectable or nearly so in women with POI.

The value of AMH in both prediction and diagnosis of both usual age menopause and POI has recently been subject of a systematic review (Nelson *et al.*, 2023) which evaluated 11 publications that investigated the use of AMH in the context of POI. This excludes women treated for cancer, also the subject of a recent specific systematic review (Anderson *et al.*, 2022a). Another more general review of the use of AMH also included POI as a specific diagnosis of evaluation (Iwase *et al.*, 2024). In summary,

these studies confirm that AMH levels are markedly reduced in women with POI, and it does, therefore, have diagnostic value. This is particularly the case to distinguish POI from the common alternative diagnosis of PCOS in a woman with amenorrhea, where AMH levels are high, and in women with hypothalamic amenorrhea, where AMH levels are normal or only mildly reduced. While longitudinal studies are lacking, cross-sectional studies do suggest an increase in the likelihood of very low or undetectable AMH levels in women with developing POI. While these studies are subject to enrichment bias, there may be clinical value in women with a known risk factor for POI, such as those with Turner syndrome. Studies assessing the formal diagnostic accuracy of AMH for the diagnosis of POI have, however, shown very good sensitivity and specificity. The largest such study, including 410 women with clinical presentations including early and established POI, found that a diagnostic threshold of less than 0.25 ng per mL (1.78 pmol/L) gave an optimum combination for the diagnosis of POI with sensitivity 92.5% and specificity 90%. However, there is no evidence for an advantage over current FSH-based diagnostic testing. Further studies are required to confirm and refine the potential value, particularly identifying more clearly populations of women with some aetiologies of POI who have relatively maintained AMH levels. This particularly appears to be associated with women with developing autoimmune POI where the pathological stage of follicle loss occurs relatively late in folliculogenesis, but this remains to be established in adequately sized and designed studies.

In the context of POI after cancer treatment, the possibility of post-treatment recovery of ovarian function in many women resulted in their exclusion from characterization and diagnostic recommendations in the Stages of Reproductive Aging in Women analysis (Harlow *et al.*, 2012). However, the diagnostic accuracy of AMH for the diagnosis of POI after chemotherapy for breast cancer has been demonstrated to have very high sensitivity and specificity when assessed approximately 2 years after completion of treatment (in the absence of confounding endocrine treatment) (Anderson *et al.*, 2017b). Early assessment after completion of treatment also shows good accuracy, but particularly in women over the age of 40 (Anderson *et al.*, 2022c) and thus is of less clear value in the population of women to whom the term POI pertains. While it seems likely that AMH will have similar value for the diagnosis of POI after treatment of other cancers, this has not been formally tested.

Recommendations

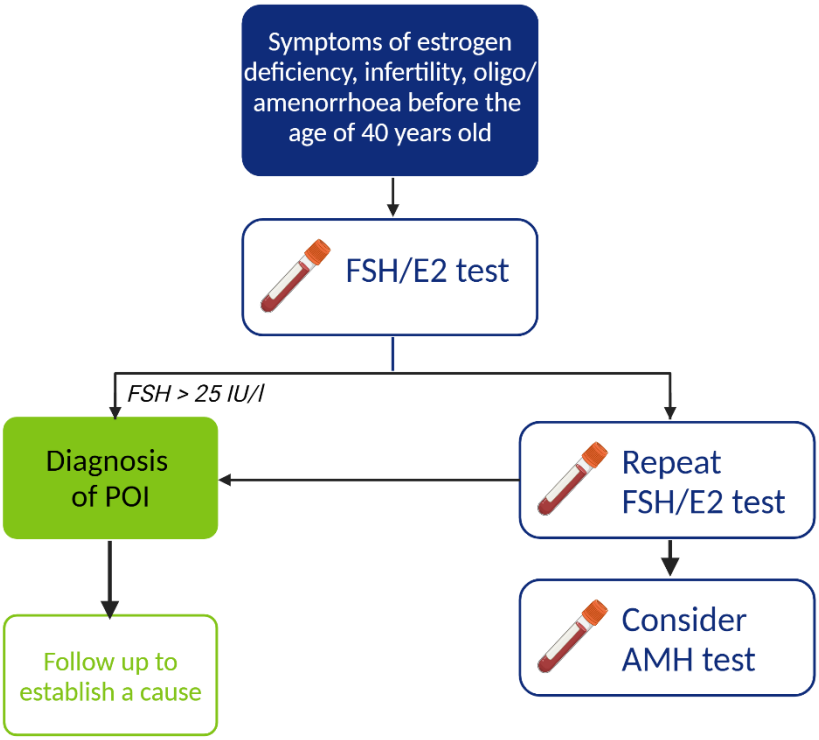
AMH testing could be considered in the diagnosis of POI where there is diagnostic uncertainty. However, it has not been shown to have benefit over existing FSH-based diagnostic testing.	⊕◯◯◯ **CONDITIONAL**

The guideline group recommends that AMH tests are interpreted within the clinical context. Further research is required to determine diagnostic thresholds for POI.	**GPP**

Justification

As AMH is a direct product of the small growing follicles of the ovary, it has theoretical value as a diagnostic test in POI. However, the evidence at present does not support its value over the existing, FSH-based, approach. 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. 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. Availability of the test, particularly in primary care, remains limited.

633 **Figure 6 Algorithm for the diagnosis of POI (Created with BioRender.com)**



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II.3 The causes of POI

POI is a complex, multifactorial condition and its aetiology remains poorly understood in many cases (Rahman and Panay, 2021). A combination of different factors (see I.4. Risk factors for POI), may ultimately precipitate the disorder (Panay *et al.*, 2020).

In broad terms, POI can be iatrogenic or spontaneous (Nash and Davies, 2024). The proportion of women with different causes of POI has not been established overall, as it varies by patient population and clinical setting. (Nash and Davies, 2024)

In a proportion of women with non-iatrogenic POI, a genetic cause, such as chromosomal defects, Fragile X syndrome, or autosomal gene defects, or a genetic predisposition can be identified. Other women with POI could be linked to autoimmune conditions. Testing for genetic causes and autoimmune causes after a diagnosis of POI is discussed in this chapter. Other causes and risk factors, such as infection, mumps oophoritis, toxins, galactosemia, (Panay *et al.*, 2020, Rahman and Panay, 2021, Nash and Davies, 2024) are usually not tested in clinical practice, due to low prevalence, and lack of evidence of causation, and limited relevance for clinical management of POI, and hence are not discussed in detail.

It has been estimated that the aetiology of non-iatrogenic POI is unknown in 70–90% of diagnosed women (Nelson, 2009) and for these women, the term idiopathic POI is appropriate. However, improved genetic testing is likely to reduce the proportion of women designated as having 'idiopathic' POI (see also Figure 7 Summary of testing to establish a cause for POI).

Recommendation

The guideline group recommends that HCPs should 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 determined	**GPP**

Iatrogenic POI

In a subgroup analysis of a systematic review and meta-analysis, an iatrogenic etiology was determined in 11.2% of women with POI, followed by autoimmunity (10.5%) (Li *et al.*, 2023a).

Iatrogenic POI includes POI after i) chemotherapy; ii) pelvic field radiotherapy; iii) linked to ovarian pathology or pelvic surgery, e.g. endometriosis surgery, ovarian torsion, or surgery to remove large ovarian cysts; and iv) bilateral oophorectomy (Nash and Davies, 2024).

Chemotherapy, pelvic field radiotherapy and surgery for treatment of common cancers in younger women will often cause ovarian damage, potentially inducing permanent menopause (Szabo *et al.*, 2019, Hickey *et al.*, 2024). These common cancers include breast, gynaecological, haematological, and some low colorectal cancers.

Chemotherapy-induced amenorrhea (often used as a surrogate marker of POI)is a common complication observed in premenopausal women with breast cancer, and the incidence of chemotherapy-induced amenorrhea ranges from 15% to 94% (5) in women with breast cancer after receiving chemotherapy. Whether or not chemotherapy for breast cancer will result in POI is affected by several factors. The meta-analysis by Wang reported that women treated before the age of 40 were less likely to develop POI (pooled OR 0.136; 95% CI 0.104 to 0.177; p <0.001). In terms of chemotherapy treatments, the risk of POI was increased with the addition of taxanes to anthracycline-based treatments

(OR 0.699; 95% CI 0.608 to 0.803; p <0.001 for anthracycline versus anthracycline-taxane), and with the addition of tamoxifen treatment (OR 0.568; 95% CI 0.461 to 0.701; p < 0.001)(Wang *et al.*, 2022).

Gynaecological cancers (estimated 1·8 million diagnosis in women per year) are commonly treated with bilateral oophorectomy, pelvic radiation and/or gonadotoxic chemotherapy, which all potentially induce POI or early menopause (Brennan *et al.*, 2021).

Colorectal cancer diagnosis is increasing in younger women, particularly rectal and anal cancer, which are commonly treated with pelvic irradiation that will induce POI (Sung *et al.*, 2021, Hickey *et al.*, 2024).

Leukaemia and lymphomas comprise about 4% of all cancers in women younger than 50 years and are commonly treated with a stem-cell transplant (Sung *et al.*, 2021). Gonadotoxic chemotherapy before stem-cell transplantation will induce menopause in the majority of premenopausal women, depending on their age and nature of the conditioning regimen (Lee *et al.*, 2023b).

A history of pelvic surgery was found associated with an increased risk of POI in a case-control study of 553 women with POI and 400 controls (OR 5.53; 95% CI 2.15 to 14.23) (Wang *et al.*, 2015). Both ovarian surgery for endometrioma and endometriosis as a disease seem to influence age of menopause, and the risk of POI(Coccia *et al.*, 2011, Raffi *et al.*, 2012, Somigliana *et al.*, 2012).

Finally, bilateral oophorectomy before the age of 40 will result in POI. Often, bilateral salpingo-oophorectomy is performed by age 35–40 years in women at elevated risk of ovarian cancer due to pathogenic gene variants such as BRCA1 or BRCA2, in line with international guidelines (Daly *et al.*, 2021).

Recommendation

The guideline group recommends that HCPs treating women with medical or surgical intervention that may cause POI should discuss the risk of POI as part of the consent process.	**GPP**

Genetic background of POI

The risk of POI is increased in female relatives of women with POI (RR 4.6; 95% CI 3.3 to 6.5) (Silvén *et al.*, 2022) (see also I.4. Risk factors for POI), and approximately 15-30% of women with POI have family members who are also affected, pointing to an underlying genetic component (Bachelot, et al., 2009, Panay, et al., 2020, van Kasteren, et al., 1999, Vegetti, et al., 1998). Twin studies have indicated a high concordance of POI among monozygotic twins (Gosden, et al., 2007, Huhtaniemi, et al., 2018, Ruth, et al., 2016). Genetic factors also explain a large proportion of the variability of the age of natural menopause, ranging from 45 to 85% depending on the studies (McGrath, et al., 2021, Murabito, et al., 2005).

Genetic causes of POI are not restricted to X chromosome anomalies, variants linked to POI have been identified across many of the chromosomes. The mode of transmission of POI is either recessive (and the parents are not affected), dominant (and the mother can be affected), or X-linked, depending on the gene involved. Some genetic causes are shared between female and male infertility (notably in the case of the involvement of meiosis/DNA repair genes) and in such families, men with azoospermia can be found as well as women with POI. Numerical and structural abnormalities on the X chromosome as well as dysfunction in several genes that regulate ovarian development and function are strongly associated with POI. Next-generation sequencing (NGS) of all coding genes (exome or genome studies) has made it easier to reveal new pathogenic variants in genes already identified or newly related to POI thus increasing the frequency of a positive genetic diagnosis for women with POI which would otherwise

be designated as "idiopathic" POI. International standards have been developed to ensure rigorous assessment of whether an identified genetic variant is truly causal for POI (Richards *et al.*, 2015).

The possible genetic cause of POI supports the collection of information on the patient and her family about fertility and other associated pathologies (developmental disorder, neurologic signs, mental retardation, sensorial symptoms, cardiovascular symptoms, endocrine or metabolic associated disorder, tumours, etc.) as well as drawing up a family tree.

PICO Question: What are the known genetic causes of POI and how should they be investigated?

Chromosomal anomalies

Large cohort studies and meta-analyses have found the frequency of chromosomal anomalies in women with POI to be approximately 10-13%, of which the majority are X chromosomal anomalies (X aneuploidy or X structural abnormalities) (Chen, et al., 2023, Jiao, et al., 2012, Lakhal, et al., 2010). A large Finnish population-based study including 5011 women with POI, found an odds ratio (OR) for Turner syndrome of 275 (95% CI 68.1 to 1110). For other sex chromosome abnormalities, the OR was 12.7 (95% CI 4.1 to 39.1)(Silven *et al.*, 2023). Abnormal karyotypes are more commonly diagnosed in women with primary amenorrhea (21%) than in those presenting with secondary amenorrhea (11%) (Jiao, et al., 2012, Kalantari, et al., 2013). As chromosomal anomalies may result in more extreme phenotypes, including syndromic features, the incidence is higher at younger age of POI diagnosis (Gruber, et al., 2020, Jiao, et al., 2017).

Normal germ cells carry two X chromosomes, of which one is initially inactivated during the early stages of oocyte formation in the foetal ovary. However, the presence of two transcriptionally active X chromosomes are essential for normal germ cell maturation and the second X chromosome is temporary reactivated at later stages of germ cell differentiation (Arnold, et al., 2016, Khan and Theunissen, 2023). Furthermore, approximately 20% of the genes on the inactivated X chromosomes escape inactivation and continue to be expressed in somatic cells, maintaining the dosage specific gene products, essential to the female phenotype (Loda, et al., 2022, Tukiainen, et al., 2017)(Fukami, 2023).

Chromosomal Aneuploidy

Turner syndrome (TS) is caused by the complete or partial loss of one X chromosome, i.e. 45,X karyotype, and occurs in approximately 25-50 per 100 000 live female births (Rossetti, et al., 2017, Sybert and McCauley, 2004)(Gravholt, 2024). Haploinsufficiency, when one copy of the X chromosome is missing, leads to lack of required dosages of particular X-linked gene products causing accelerated loss of primordial oocytes during female foetal development, resulting in streak gonads at birth (Castronovo *et al.*, 2014, Ibarra-Ramírez *et al.*, 2023). Clinically, women with TS with complete 45,X karyotype are characterized by primary amenorrhea and POI. Other characteristic phenotypic features of TS include short stature, lymphedema, webbed neck, shield chest, wide-spaced nipples, cubitus valgus as well as cardiac anomalies (coarctation or aortic anomalies) (Gravholt, et al., 2017, Sybert and McCauley, 2004). Mosaicism with 45,X/46,XX karyotypes are found in 15-25% of women with TS (Gravholt, et al., 2023). Other TS karyotypes include more complex forms of mosaicism such as 45,X/47,XXX, mosaicism with 3 or more different cell lines (e.g. 45,X/46,XX/47,XXX), or mosaicism with structural variants of the X chromosome (Gravholt, et al., 2023). In women with mosaic TS, the severity of symptoms may vary, and menarche and pregnancy can occur (Castronovo, et al., 2014, Tuke, et al., 2019).

Other numerical chromosome abnormalities are also associated with POI, including Triple X syndrome (TXS), with the presence of an extra X chromosome resulting in a 47,XXX karyotype (Davis, et al., 2020, Franić-Ivanišević, et al., 2016, Rafique, et al., 2019). TXS affects approximately 1 in 1000-2000 live female births (Davis, et al., 2020). However, it is estimated that only 10% of women with TXS receive a diagnosis and that many receive a delayed diagnosis (Berglund, et al., 2019, Tartaglia, et al., 2010). Although many women are asymptomatic, a wide variety of clinical and psychological conditions are associated with TXS; the most common characteristics include tall stature, hypotonia in infancy, epicanthal folds, clinodactyly, and constipation (Davis, et al., 2020, Sybert, 2002, Tartaglia, et al., 2010). Low AMH concentrations in TXS women, indicating diminished ovarian reserves, have been demonstrated in two case-control studies (Davis, et al., 2020). Several case reports have illustrated that women with TXS are at increased risk of early menopause and POI; however, available data on frequency TXS in POI are limited (Rafique, et al., 2019, Rogol, 2023). A case-control study of 269 women with POI found a 5-fold increase of TXS compared to 46,XX women (Baronchelli *et al.*, 2011). A similar frequency was noted in a Chinese cohort of 531 women with POI (~0.6%) (Jiao, et al., 2012).

Y chromosome material may be present in some women, and confers an increased risk of gonadal tumours (10-30%) (Gravholt, et al., 2000, Matsumoto, et al., 2020, Michala, et al., 2008, Steinmacher, et al., 2021). Gonadoblastoma and dysgerminoma are the most common types of tumours found in these patients (Matsumoto *et al.*, 2020). In a study of 102 women with disorders of sex development (DSD) and karyotypic Y chromosome or Y-derived sequences present, the total incidence of gonadoblastomas was 17.6% (Liu, et al., 2014). In TS women with 45,X/46,XX mosaicism, Y chromosomal material was present in 10% to 12% (Gravholt, 2024). Several small studies have found a high incidence of gonadoblastomas in TS patients with Y chromosome material present, detected in 36.4% (4 of 11) and 18% (6 of 34) (Dendrinos *et al.*, 2015, Matsumoto *et al.*, 2020, Steinmacher *et al.*, 2021). It is therefore important that women with TS have had an accurate karyotype, including investigation for low level Y chromosome mosaicism (Gravholt, et al., 2017).

Structural X chromosome anomalies

Structural defects of the long Xq arm, especially deletions, duplications, inversions, isochromosomes and translocations affecting the critical regions Xq13-21 and Xq23-27 are associated with reduced ovarian function (Rossetti, et al., 2017). A number of studies have established a relationship between structural X chromosomal disorders and POI, with a frequency ranging from 4% to 12% (Ceylaner, et al., 2010, Chen, et al., 2023, Di-Battista, et al., 2020, Jiao, et al., 2012, Lakhal, et al., 2010, Toniolo, 2006). POI is observed in approximately 50% of translocations affecting the X chromosome, more often when breakpoints fall in one of the two POI critical regions, while breakpoints outside these regions rarely result in ovarian impairment (Di-Battista, et al., 2020).

Several mechanisms have been suggested to explain the association with structural defects in the POI critical regions, including gene disruption and/or down regulation of genes necessary for normal ovarian function in these regions, as well as implications on positioning effects resulting in meiosis error. Moreover, many POI candidate genes on the X chromosome have been identified by analyzing the X-autosome translocation breakpoints, pointing to these areas as important for ovarian function (Bestetti, et al., 2021, Di-Battista, et al., 2020, Tšuiko, et al., 2016).

Fragile X premutation

Premutation of the Fragile X mental-retardation 1 (*FMR1*) gene (55-200 trinucleotide repeats) is the most common single genetic disorder linked with POI (Cronister, et al., 1991, Schwartz, et al., 1994)(Tassone *et al.*, 2023). *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 (Chen, et al., 2023, Conway, et al., 1998, Fink, et al., 2018, Murray, et al., 2014, Wittenberger, et al., 2007). In a large UK cohort population study including more than 2000 women with POI or early menopause, the prevalence of *FMR1* premutation

was 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 (Murray, et al., 2014). This association between *FMR1* premutation and POI was not found in a meta-analysis of 4 studies on POI in an Asian population (Tosh, et al., 2014). The *FMR1* premutation frequency is also lower among Chinese women 0.49 to 1.6% (Guo, et al., 2014, Tang and Yu, 2020).

Women who carry the premutation of the *FMR1* gene have a 20% increased risk of developing Fragile X-associated POI (FXPOI) (Hunter JE., et al., 2019, Sherman, 2000, Wittenberger, et al., 2007). The exact molecular mechanism by which the *FMR1* premutation leads to ovarian failure and POI has not yet been fully elucidated but when CGG trinucleotide repeats of the *FMR1* gene are duplicated to 55-200 repeats the premutation becomes unstable and results in inadequate production of the *FMR1* protein which is likely to be important for normal follicle function (Lu, et al., 2012, Rosario, et al., 2022, Rossetti, et al., 2017). The age at development of POI in women with *FMR1* premutations is variable. Background modifier genes and environmental factors as well as the number of CGG repeats are related to the severity of FXPOI (Allen, et al., 2007, Spath, et al., 2011, Tejada, et al., 2008, Trevino, et al., 2021). In a recent meta-analysis involving 3394 women with idiopathic POI and 8461 controls, *FMR1* premutation was significantly associated with increased risks of POI (OR 8.13; 95% CI 4.35 to 15.19; p<0.00001) but also diminished ovarian reserve (characterised by subfertility, normal or slightly elevated FSH levels, low anti-mullerian hormone (AMH), low antral follicle count) (OR 14.87; 95% CI 5.20 to 42.52; p<0.00001) (Huang, et al., 2019). Other studies have demonstrated a bell-shaped relationship with CGG repeat numbers of 80 to 100 CGG triplets, yielding the highest risk for FXPOI compared to repeat lengths of 59 to 79 or >100 (Allen, et al., 2007, Hipp, et al., 2016, Tassone, et al., 2023). No correlation is found between the *FMR1* CGG high normal intermediate repeat length (45-54 trinucleotide repeats) and FXPOI (Huang, et al., 2019, Ruth, et al., 2016). The risk of developing FXPOI is also not increased in women with the full mutation (>200 trinucleotide repeats) (Bennett, et al., 2010).

Clinically, *FMR1* premutation carriers may exhibit a wide range of symptoms and phenotypes including neuropsychological conditions (Coffey, et al., 2008, Tassone, et al., 2023). *FMR1* premutation increases the risk of Fragile X-associated tremor/ataxia syndrome (FXTAS), a neurological condition characterized by late-onset, progressive cerebellar ataxia and intention tremor followed by cognitive impairment. The penetrance of FXTAS among adult *FMR1* premutation carriers increases with age, exceeding 50% for men aged 70-90 years. Females are also affected but severity and penetrance are less (16%-20%) (Jacquemont *et al.*, 2007, Hagerman and Hagerman, 2013, Hunter JE. *et al.*, 2019, Schneider *et al.*, 2020). Psychological difficulties have also been associated with *FMR1* premutation. In a population-based cohort of 20 000 patients, *FMR1* genotyping demonstrated increased rates of anxiety conditions in both female and male premutation carriers compared to non-carriers (Movaghar, et al., 2019).

FMR1 premutations can expand to a full mutation (>200 repeats) when transmitted to the next generation, causing Fragile X syndrome (FXS). The Fragile X syndrome is an X-linked inherited condition characterized by mental retardation, primarily affecting male offspring (Tassone, et al., 2023).

Other genetic causes of POI

The advent of next-generation sequencing (NGS) with whole exome (WES) and whole genome (WGS) sequencing has provided the opportunity to simultaneously study a series of genes in large patient cohorts and allowed a leap in the identification of novel genes involved in POI in the last ten years (Huhtaniemi, et al., 2018). Data from international studies with large cohorts and using strict criteria have shown genetic causation with positive gene variants identified in 14 to 30% of women with POI depending on the size of the gene panels used (Patiño *et al.*, 2017, Jolly *et al.*, 2019, Yang *et al.*, 2019, França *et al.*, 2020, Bestetti *et al.*, 2021, Eskenazi *et al.*, 2021, Rossetti *et al.*, 2021, Shen *et al.*, França and Mendonca, 2022, Heddar *et al.*, 2022, Chen *et al.*, 2023, Ke *et al.*, 2023, Luo *et al.*, 2023, Long *et al.*, 2024, Vogt *et al.*, 2024). Higher gene variant positivity, for example up to 75% of women with POI (Rossetti *et*

al., 2021), has been reported in studies employing different methodologies including criteria in determining the causative importance of genes for POI when constructing a gene panel. Familial/consanguineous POI (30.5-36.7% patients (Jolly *et al.*, 2019, Heddar *et al.*, 2022) or syndromic POI (58.3% patients (Heddar *et al.*, 2022) is associated with higher gene variant positivity compared with sporadic POI (gene variants reported in 15-20% in Brazilian (França *et al.*, 2020), Chinese (Shen *et al.*, 2021) and Norwegian (Vogt *et al.*, 2024) cohorts.

Systematic reviews and standardized clinical validity assessment of genes involved in POI have been performed (França and Mendonca, 2022, Volozonoka *et al.*, 2022, Doulgeraki *et al.*, 2023, Van Der Kelen *et al.*, 2023). Pathologic variants in approximately 100 genes associated with POI, indicating a high genetic heterogeneity, have been identified and the list is constantly expanding (Rossetti *et al.*, 2021, Ruth *et al.*, 2021, Yang *et al.*, 2021, França and Mendonca, 2022, Volozonoka *et al.*, 2022, Doulgeraki *et al.*, 2023, Ke *et al.*, 2023, Van Der Kelen *et al.*, 2023). Virtual POI gene panels and genetic variant classifications based on continuously updated expert curated databases exist (e.g.: Genomic England, or PanelApp Australia).

As mentioned, approximately 100 monogenic causes of POI have been reported, where a single genetic variant is sufficient to cause the POI phenotype. Apart from research on monogenic causes, there has been focus on oligogenic inheritance with possible synergistic effects explaining the variance in phenotype seen (Rossetti *et al.*, 2021). A NGS study of 64 women with POI noted at least one POI gene related variant in 48/64 and 2 or more variants in 34/64 patients where type and number of gene variants influenced the severity of the POI clinical phenotype (Rossetti et al 2021). A study of a Chinese POI cohort (n=1030) identified pathogenic/likely pathogenic gene variants in 19% of women with POI overall where 80% were monogenic and 7.3% had multiple variants identified in different genes (Ke *et al.*, 2023). A large cohort study investigating the presence of genetic variants for 105 genes associated with POI in 104 733 women from the UK Biobank (1.14% with menopause before 40 years/POI), reported that pathogenic variants in these genes were commonly found in the heterozygous state in women with menopause within the normal age range (Shekari *et al.*, 2023). These data provide evidence towards the hypothesis that POI may be polygenic in nature in some cases, where women inherit a number of common alleles associated with earlier age of menopause that, when combined with other risk factors, could push them into the extreme end of the phenotypic distribution (Shekari *et al.*, 2023). However, further studies are needed to clarify potential oligogenic/ polygenic contributions to the POI phenotype.

Categories of genes where the associated molecular defects, cellular dysfunction and disrupted pathways illustrate the range of causes of POI. Genes involved in DNA repair (37.4%) or follicular growth (35.4%) were the most common pathways identified in a study of 375 European women with POI (Heddar, et al., 2022). Similar findings were obtained in study of 1030 Chinese women with POI where genes involved in meiosis (48.7%) were most commonly affected (Ke *et al.*, 2023). These categories can be listed:

- Genes involved in DNA and meiosis repair. Mutations cause chromosomal fragility severe enough to impact meiosis with significant impact on fertility and increased susceptibility to tumorigenesis. Screening for and identifying variants in this class of genes should be considered in collaboration with multidisciplinary teams to facilitate presymptomatic co-morbidity screening and prevention.
- Genes involved in metabolism and mitochondrial functions resulting in isolated or syndromic POI such as Perrault syndrome or galactosemia.
- Genes involved in follicle growth, coding for hormone receptors, such as *FSHR*, or oocyte growth factors, such as *GDF9* and *BMP15*.

Other gene families linked to POI include:

- Genes involved in ovarian or early follicle development may be associated with POI, and other organ defects if they play a role in development (for example, *SF1/NR5A1* gene, which is also involved in adrenal development).
- Genes involved in follicular atresia. Very few genes in this family have been identified so far.
- Genes involved in immune function such as *NF-KB*
- Genes involved in RNA metabolism and translation such as *FMR1*.

POI is usually isolated (i.e. sporadic POI), with no associated clinical signs, but can also be syndromic, associated with other more complex pathologies requiring multidisciplinary management. (see Table II Syndromes associated with POI). The specific genes associated with syndromic POI can be screened routinely in expert laboratories where available. A population-based register study in Finland including >5000 women with POI (1988-2017) showed that 15.9% of women had at least one other congenital disorder (Silven, et al., 2023). In the cohort of Heddar *et al*, 44.8% of patients had, or were at risk to develop, associated comorbidities, requiring a comprehensive assessment by a multidisciplinary team. POI pathogenic variants of genes causing syndromic POI were identified in 8.5% of cases (Heddar *et al.*, 2022). Symptoms of syndromic POI may include endocrine symptoms, neurosensorial symptoms, cardiovascular symptoms, inborn errors of metabolisms, ovarioleukodystrophy, and susceptibility to tumours/cancers when meiosis/DNA repair genes are involved (Huhtaniemi, 2018 #2885).

TABLE III SYNDROMES ASSOCIATED WITH POI (LIST BASED ON QIN 2015 AND HUHTANIEMI 2018, NOT EXHAUSTIVE)

Syndrome	OMIM	Gene(s)	Further information
Acromesomelic chondrodysplasia with genital anomalies	#609441	BMPR1B	Particular features: Severe brachydactyly with radial deviation of the fingers, ulnar deviation of the hands, fusion of the carpal/tarsal bones, aplasia of the fibula, bilateral clubfeet with small broad feet and short toes
Ataxia telangiectasia	#208900	*ATM*	Progressive cerebellar degeneration, telangiectasias, immunodeficiency, recurrent infections, insulin-resistant diabetes, premature aging, radiosensitivity, and high risk for epithelial cancers in surviving adults.
Autoimmune polyendocrine syndrome type I (APS-1)	#240300	*AIRE*	Rare autoimmune condition including chronic mucocutaneous candidiasis, hypoparathyroidism, and autoimmune adrenal failure. Some patients also present with POI. It results from mutations in the AIRE gene, with complex transmission: recessive autosomal in some variants, and dominant in others. Also called Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED)
Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES)	#110100	*FOXL.2*	Prevalence: ~1–9/100,000 Transmission: Autosomal dominant Rare congenital palpebral malformation It is in some cases associated with POI; in which case it is known as type-1 BPES.
Bloom syndrome	#210900	*BLM*	Chromosomal breakage leading to early onset of aging, short stature, and elevated rates of most cancers.
Fanconi anemia	#227650 #227645 #614082	*FANCA* *FANCC* *FANCG*	Particular features: Pancytopenia, small stature, microcephaly, ear anomalies, heart defects, kidney malformations, radial aplasia and thumb deformities, intellectual disability, café-au lait spots
Fragile X syndrome	#300624	*FMR1*	Attention deficits, hyperactivity, social deficits, anxiety disorder, deficits in cognitive flexibility.
Galactosemia	#230400	*GALT*	A metabolic disease related to abnormal glucose metabolism. The culprit gene in this form showing recessive autosomal transmission is GALT. The POI is due to accumulation of galactose in the ovaries, leading to oocyte apoptosis. Acute neonatal life-threatening symptoms are observed (e.g., vomiting, poor feeding, lethargy, metabolic acidosis, jaundice,

			abnormal clotting, liver failure) but adults are also affected in milder forms.
GAPO	#230740	*ANTXR1*	Particular features: Growth retardation, alopecia, pseudoanodontia, optic atrophy, high forehead, midface hypoplasia
Hutchinson-Gilford progeria	#176670	*LMNA*	Particular features: Progeria, short stature, low body weight, early loss of hair, lipodystrophy, scleroderma, decreased joint mobility, osteolysis, cardiomyopathy
Nijmegen breakage syndrome	#251260	*NBN*	Particular features: Prenatal growth retardation, progressive mental deterioration, microcephaly, recurrent infections, increased risk for neoplasias such as lymphoma
Perrault syndrome	#233400 #614926 #614129 #615300 #616138 #605608 #612425 #609947 #607435	*HSD17B4* *HARS2* *LARS2* *CLPP* *C10orf2* *CLDN14* *SGO2* *KIAA0391* *ERAL1*	Associated with ovarian dysgenesis and sensorineural hearing loss. Like the hearing loss, the dysgenesis is extremely variable, but systematic. Identifying new candidate genes should shed light on the pathophysiology of the hearing loss and of POI in this syndrome
PMM2-CDG CDG-1 (a previously known as congenital disorder of glycosylation type 1a)	#212065	*PMM2*	Cerebellar dysfunction (ataxia, dysarthria, dysmetria), non-progressive cognitive impairment, stroke-like episodes, peripheral neuropathy with or without muscle wasting, absent puberty in females, small testes in males, retinitis pigmentosa, progressive scoliosis with truncal shortening, joint contractures, and premature aging
Progressive external ophthalmoplegia, PEO	#157640	*POLG*	Particular features: Ptosis, progressive external ophthalmoplegia, sensorineural hearing loss, axonal neuropathy, muscle weakness, ataxia, dysarthria, dysphagia, and late onset Parkinsonism
Proximal symphalangism, SYM1	#185800	*NOG*	Ankylosis of the proximal interphalangeal joints. Particular features: symphalangism, hearing loss
Pseudohypopara thyroidism	#103580	*GNAS*	Particular features: Brachydactyly, short stature, hypocalcemia and hyperphosphatemia, hypothyroidism, obesity
Pseudohypoparathyroidism type 1A (PHP 1A)	#103580	*GNAS*	An endocrine disease characterized by resistance to parathyroid hormone and other hormones such as TSH and GnRH. Particular features: Brachydactyly, short stature, hypocalcemia and hyperphosphatemia, hypothyroidism, obesity
Retinal dystrophy with or without extraocular anomalies	#617175	RCBTB1	Particular features: Retinal dystrophy, goiter, intellectual disability, hypogonadism
Rothmund–Thomson syndrome, RTS	#268400	*RECQL4*	Cutaneous rash, sparse hair, small stature, skeletal and dental abnormalities, cataracts, premature aging, and an increased risk for cancer, especially malignancies originating from bone and skin tissue.
SF1-related XX-DSD	#612964	*NR5A1/SF1*	Particular features: Adrenal insufficiency
Vanishing white matter disease, ovarioleukodystrophy	#603896 #615889	*EIF2B* *AARS2*	Neurological disorder characterized by involvement of the white matter of the central nervous system. When Leukodystrophies associated with premature ovarian failure referred to as ovarioleukodystrophy.
Werner syndrome	#277700	*WRN*	Premature aging of the skin, vasculature, and bone and elevated rates of certain cancers, particularly sarcomas.
Woodhouse-Sakati syndrome	#241080	*C2orf37*	Particular features: Alopecia, deafness, hypogonadism, diabetes, intellectual disability
WT1-related XX-DSD	#194070	*WT1*	Particular features: Nephropathy, diaphragmatic hernia
XRCC4-related disorder	#616541	*XRCC4*	Particular features: Short stature, microcephaly, developmental delay, diabetes mellitus

Rationale for genetic testing

Identifying the genetic cause of POI can be helpful for patients and families by enabling (Heddar *et al.*, 2022):

- potential psychological benefits including providing a cause of POI rather than the term "idiopathic".
- better understanding of prognosis, including fertility, thus facilitating counselling and personalised management.
- appropriate co-morbidity screening with involvement of multidisciplinary teams (e.g. oncogeneticists).
- family screening, including male siblings (Huhtaniemi, et al., 2018), facilitating fertility preservation and co-morbidity screening in members not yet affected.
- development of novel prevention or treatment strategies (Heddar, et al., 2022, Ke, et al., 2023; Yang 2021).

Clinical steps in identifying a genetic cause.

Informed consent and genetic counselling

Information and written consent should be obtained from the patient and all family members tested before genetic testing. The implications of the genetic testing including the implications of NGS analysis, should be explained to the patient before the genetic testing. Genetic counselling may be performed in a multidisciplinary team setting according to the gene altered.

Advancement of precision and personalised medicine have raised several ethical issues regarding genetic testing, especially where novel gene variants are detected. As with other genetic diseases, there are issues regarding pathogenic accuracy, interpretation of variants, and potential variable expression. Not everyone with a pathogenic genetic variant associated with POI develops the disease. This must be considered both in diagnostic and predictive testing, especially regarding screening of healthy relatives. On the other hand, information about the risk of POI can enable these women to make adjustments in their lives in order to deal with potential fertility issues. Awareness of the implications and limitations of genetic testing as well as clinical counselling is essential. Clinicians should have a clear understanding of the patients' phenotype, as well as the medical- and family histories of the women, to ensure appropriate interpretation of variants in close collaboration with geneticists.

Genetic studies

Chromosomal analysis

Karyotyping using G-banded chromosome analysis is the gold standard for detecting numerical anomalies, including mosaicism and Y chromosomal material, as well as larger structural chromosomal abnormalities. Other methods such as chromosomal microarray (CMA) and other new technologies exist and can be useful in detecting smaller copy number variants and mapping breakpoints of structural chromosomal rearrangements. Use of molecular and cytomolecular techniques such as PCR (polymerase chain reaction) and FISH (fluorescence in situ hybridization) can detect chromosome mosaicisms (Soares, et al., 2021). Recent observations have suggested chromosomal abnormalities are underdiagnosed in POI in older women (Berglund, et al., 2019), thus an age cut-off limit for testing for chromosomal abnormalities is not recommended, Women with Y chromosome material present should be counselled about the risk of development of a gonadal tumour and gonadectomy should be advised.

FMR1 gene testing

The diagnosis of an *FMR1* disorder is established through the use of molecular genetic testing to detect and quantify the CGG trinucleotide repeat expansion in the 5' UTR of *FMR1*. In some cases, Southern

blot analysis may be performed to confirm the results of PCR and to assess methylation status which might affect *FMR1* gene expression. It should be noted that typical multigene panels and NGS are not useful in detecting *FMR1* premutations (Hunter JE., et al., 2019). Genetic counselling for *FMR1* should include education about *FMR1*-related disorders and the possibility and implications for the patients and their families (Poteet, et al., 2023). Genetic screening of family members of women with *FMR1* premutations is recommended, not only for fertility assessment of female relatives but also because of the risk of passing on an unstable mutation to potential offspring resulting in full mutations and FXS. This requires careful counselling before the test is performed.

Specific gene variant testing

If karyotype and *FMR1* gene testing is normal, the study of specific genes should be performed where available in a specialised laboratory according to international best practice. Tailored NGS POI gene panels can be useful in diagnostic testing of women affected, as well as in predictive genetic screening of family members and women at risk of POI.

At present, extended testing using targeted NGS gene panels or virtual in silico panels based on WES/WGS are not available as routine assessments for women with POI in most countries. NGS has however proven to be a powerful tool in unravelling an expanding number of genetic variants associated with POI, thus increasing the possibilities to find underlying causes of POI (França and Mendonca, 2022) especially in large cohorts of POI (Heddar *et al.*, 2022, Ke *et al.*, 2023). A dynamic evaluation of which genes to include in disease specific NGS gene panels is important. Custom gene panels must be consecutively modified and updated, allowing for the addition of novel genes found to be involved in POI or the removal of genes that upon re-evaluation are found not be associated with POI.

These studies should be performed as recommended by both the European Society of Human Genetics (Matthijs *et al.*, 2016) and the American College of Medical Genetics and Genomics (ACMG) (Rehm *et al.*, 2013) and strict ACMG/AMP criteria or similar should be used to interpret variants in a clinical setting (Richards *et al.*, 2015). Analysis of gene copy number variations is not routinely performed due to the absence or very low positivity observed.

At present, there is a NGS approach for the diagnosis of rare endocrine disorders of sex development and maturation including POI across several European countries (www.endo-ern.eu) (Persani *et al.*, 2022). Additional genetic testing is available in France and a French position statement on the diagnosis and management of POI (except Turner syndrome) recommends gene panel or WGS analysis in all undiagnosed POI (Christin-Maitre *et al.*, 2021). It is likely that the availability of additional genetic testing will continue to increase globally with a resulting decrease in the costs.

Recommendations

Chromosomal analysis and Fragile X premutation testing are recommended for all women with non-iatrogenic POI.	⊕⊕◯◯	**STRONG**
Where available and after comprehensive genetic counselling, additional genetic testing (e.g. NGS) can be offered to identify other potential genes that may cause POI.	⊕⊕◯◯	**CONDITIONAL**
The guideline group recommends that the age of a woman with POI should not be used to restrict access to genetic testing.		**GPP**

Justification

Chromosomal anomalies are common among women with POI, affecting 10-13% of patients. These chromosomal anomalies include X chromosome aneuploids and mosaicisms as well as structural X chromosomal defects. Based on the significant prevalence of chromosomal anomalies in women with POI and the implications thereof, chromosomal analysis is recommended. A specific age cut-off limit for testing for chromosomal abnormalities is not recommended. Based on its prevalence and potentially severe implications, Fragile X testing is indicated in all women diagnosed with POI. Genetic counselling for *FMR1* should include education about *FMR1*-related disorders and the possibility and implications for the patients and their families (Poteet, et al., 2023).Additional genetic testing (e.g. NGS) may be offered, based on the potential of such 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. Large cohorts of women with POI have been studied and shown diagnostic positivity in up to 30% using NGS (Heddar *et al.*, 2022, Ke *et al.*, 2023). However, there are prerequisites for genetic studies of POI in clinical practice. Only genes that are fully characterized and proven to cause POI should be used for clinical diagnostics. The availability of NGS tests in specialised laboratories and the associated costs are currently barriers to widespread use.

Research recommendations.

Ongoing research both in animal models and humans is required to identify additional genes involved in POI and to allow uncovering of molecular defects in non-coding regions of known genes, copy number variations and structural variations.

Exploration of how genetic variants combine with environmental factors to determine the clinical phenotype is also needed. This will markedly enhance the positivity of genetic testing, availability of genetic testing and development of novel management strategies.

Improvements in genetic sequencing techniques and interpretive approaches may provide a more precise determination of the mechanisms underlying ovarian dysfunction, facilitate screening, diagnosis, and cost-effectiveness.

Autoimmune causes of POI

PICO QUESTION: WHAT ARE THE KNOWN AUTOIMMUNE CAUSES OF NON-IATROGENIC POI AND HOW SHOULD THEY BE INVESTIGATED?

The ovaries have been shown to be a target of autoimmune attacks manifested by endocrine and reproductive dysfunction in POI. The uncertainty with regards to reported frequencies of autoimmune causes of POI (3–30%), probably reflects heterogenic study populations as well as use of variable diagnostic methods (Silva *et al.*, 2014, Kirshenbaum and Orvieto, 2019).

Ovarian biopsies of subgroups of women with POI have demonstrated autoimmune oophoritis with mononuclear infiltrates of the theca cells in growing follicles, initially sparing the primordial, primary and preantral follicles (Irvine *et al.*, 1968, Bakalov *et al.*, 2005, Welt *et al.*, 2005). Immunohistochemical studies have revealed that the immune infiltrates contain both B- and T cells as well as polyclonal plasma cells, suggesting a complex immune system interplay (Sedmak *et al.*, 1987, Suh, 1992, Warren *et al.*, 2014, Jacob and Koc, 2015).

Clinically women with autoimmune oophoritis present with higher serum inhibin B and AMH levels compared to women with other causes of POI, reflecting the presence of functional intact granulosa cells within the quiescent follicles (Tsigkou *et al.*, 2008, La Marca *et al.*, 2009, Falorni *et al.*, 2012). On ultrasound, the ovaries can be of normal size or enlarged and follicles may have a cystic appearance

due to gonadotropin stimulation (Bannatyne *et al.*, 1990, Welt *et al.*, 2005, Nelson, 2009). Autoimmune POI is rarely a dichotomous event and several years of fluctuating ovarian function may precede complete ovarian failure (Nelson, 2009).

Markers of autoimmune oophoritis

Diagnostic biopsies of the ovaries are not recommended as a routine investigation partly because of the general inaccessibility of the ovaries but also because studies have shown good correlation between histologically confirmed autoimmune oophoritis and autoantibodies (Khastgir *et al.*, 1994, Hoek *et al.*, 1997, Bakalov *et al.*, 2005).

To establish an autoimmune pathogenesis, it is common practice to evaluate the presence of disease-specific autoantibody markers. Historically methods of indirect immunofluorescence have been used to detect autoantibodies against ovarian antigens, including anti-ovarian autoantibodies (AOA) and Steroid-cell autoantibodies (SCA) (Vallotton and Forbes, 1966, Blizzard *et al.*, 1967 Sotsiou, 1980 #1761, Chen *et al.*, 1996, Hoek *et al.*, 1997, Falorni *et al.*, 2002, Dal Pra *et al.*, 2003, Bakalov *et al.*, 2005, La Marca *et al.*, 2010, Gao *et al.*, 2017). Multiple specific ovarian autoantigens have been identified as targets for AOAs, including the oocyte, gonadotropin receptors, β-subunit of FSH, zona pellucida, corpus luteum, heat shock proteins, alpha-enolase, beta-actin and NACHT leucine-rich-repeat protein 5 (NALP5) (Tang and Faiman, 1983, Moncayo *et al.*, 1989, Forges *et al.*, 2004, Ryan and Jones, 2004, Kelkar *et al.*, 2005, Sundblad *et al.*, 2006, Takamizawa *et al.*, 2007, Pires and Khole, 2009, Otsuka *et al.*, 2011). Despite biopsy-confirmed autoimmune oophoritis being coherent with AOA in 100% of cases, the diagnostic significance of AOAs is questionable as 2/3 of all women with POI are positive. In addition, AOAs have been demonstrated in up to 1/3 of women with infertility of unknown cause (Coulam and Ryan, 1985, Wheatcroft *et al.*, 1994, Luborsky *et al.*, 1999).

Although SCAs are more specific than AOA, the diagnostic accuracy is low because of lack of standardization of methods and use of antigens from various steroid hormone producing tissues (testes, ovaries, placenta, or adrenal cortex) (Novosad *et al.*, 2003).

Use of specific immunoprecipitation methods such as Radio-Ligand Binding Assay (RIA) and Enzyme-linked immunosorbent assay (ELISA) have identified ovarian target antigens against several steroidogenic enzymes: 21-hydroxylase (21OH-Ab), cytochrome P450 side-chain cleavage enzyme (P450SCC), 17α-hydroxylase (17α-OH) and 3β-hydroxysteroid dehydrogenase (3βHSD) (Winqvist *et al.*, 1995, Chen *et al.*, 1996, Arif *et al.*, 1999, Falorni *et al.*, 2002, Dal Pra *et al.*, 2003, La Marca *et al.*, 2009, Reato *et al.*, 2011, Brozzetti *et al.*, 2015). Approximately 3-5% of women with POI are positive for 21OH-Ab, a frequency significantly higher than the expected in the general population (<0.6%) (Betterle *et al.*, 2005, Del Pilar Larosa *et al.*, 2018, Vogt *et al.*, 2022, Vogt *et al.*, 2024). Antibodies against 21OH-Ab appear to be the marker with the highest diagnostic accuracy for autoimmune POI and is also the only one commercially available.

Associated autoimmune disease.

Autoimmune disorders are more frequent in women with POI than in the general population, and non-iatrogenic POI is more frequent in women with certain autoimmune disorders. It is uncertain whether this association is due to an overlapping autoimmune process involving common antigens or if it is caused by a general immune dysregulation triggered by the complex interaction between hormones and the immune system impacted by estrogen withdrawal in POI.

The clinically most important association is with autoimmune adrenal insufficiency (Addison's disease) and autoimmune polyendocrine syndrome (APS-1) (La Marca *et al.*, 2010, Kirshenbaum and Orvieto, 2019, Panay *et al.*, 2020). Between 6-20% of women with autoimmune adrenal insufficiency have POI, while approximately 2-3% of women with POI develop adrenal autoimmunity. The diagnosis of POI most often precedes but can also manifest after adrenal insufficiency (1/3 of cases) (Bakalov *et al.*, 2005, Reato

et al., 2011, Webber *et al.*, 2016, Kirshenbaum and Orvieto, 2019, Vogt *et al.*, 2021). This association might be a consequence of a common embryological adrenogonadal primordium and autoantibodies cross-reacting against antigens of steroid producing cells in both the adrenals and ovaries. The correlation with POI is strongest in the context of autoimmune APS-1, an autosomal recessive disease caused by mutation in the autoimmune regulator (AIRE) gene involved in negative selection of T cells in the thymus (Anderson *et al.*, 2002, Husebye *et al.*, 2018). APS-1 predominantly manifests as adrenal insufficiency, mucocutaneous candidiasis, hypoparathyroidism and 50–60% of these women develop POI (Saari *et al.*, 2020, Garelli *et al.*, 2021). Most women with autoimmune adrenal insufficiency will already have disease-associated 21OH-Ab and these can therefore not be used to diagnose autoimmune POI. Instead, autoantibodies against P450SCC can be used for screening (Vogt *et al.*, 2021).

Autoimmune thyroid hormone disorders are common in women with POI affecting approximately 20% compared to 5-10% in the general female population (Coulam, 1983, Silva *et al.*, 2014, Kirshenbaum and Orvieto, 2019, Grossmann *et al.*, 2020 , Hsieh and Ho, 2021, Chaker *et al.*, 2022). Thyroid function and the gonadal axis are tightly intertwined through the hypothalamic-pituitary axes and the presence of thyroid hormone receptors in the ovaries, but the pathogenic mechanisms of how autoimmune thyroid disease can impair the ovarian reserve are still unclear (Poppe *et al.*, 2008, Khizroeva *et al.*, 2019). Thyroid peroxidase autoantibodies (TPO Abs) have been detected in ovarian follicles but have not been linked with immunological damage of ovarian tissue (Persani *et al.*, 2009) (Monteleone *et al.*, 2011, Osuka *et al.*, 2018). A recent meta-analysis confirmed a higher frequency of TPO-Ab positivity in women with POI (OR 2.26; 95% CI 1.31 to 3.92; p=0.004) (Li *et al.*, 2022, Tańska *et al.*, 2023). However, TPO abs are common in disease-free women, detectable in 15-20%, with increasing incidence with ageing (Hollowell *et al.*, 2002). TPO abs should therefore not be analysed for screening purposes in women with POI. As autoimmune thyroid hormone disorders are common in women with POI and some symptoms and clinical manifestations are similar, it is reasonable to screen newly diagnosed women with POI with TSH measurement.

Type 1 diabetes mellitus has historically been associated with delayed menarche and menopause at a younger age (Dorman *et al.*, 2001, Brand *et al.*, 2015). Other reports have failed to find significant age difference at menopause in women with type 1 diabetes mellitus compared with healthy controls, (Sjöberg *et al.*, 2011, Kim *et al.*, 2014, Yarde *et al.*, 2015), probably reflecting better general health and glucose control in newer study populations (Stuenkel, 2017). Currently no significant data indicate the need for routine screening for concomitant type 1 diabetes mellitus in patients with POI (Thong *et al.*, 2020).

Coeliac disease has been associated with a shorter reproductive period, early menopause, and infertility in women (Kotze, 2004). The mechanisms causing reproductive dysfunction in coeliac disease have been inadequately investigated to date. Very few studies have evaluated hormonal status and they have failed to show altered values of gonadotropins and sex hormones in women with coeliac disease (Cakmak *et al.*, 2018, Comba *et al.*, 2020). According to several meta-analyses and large population-based reports there appears to be an increased risk of undiagnosed coeliac disease among women with infertility (Tata *et al.*, 2005, Zugna *et al.*, 2010, Lasa *et al.*, 2014, Singh *et al.*, 2016). Available data suggests no increased prevalence of infertility in women with diagnosed coeliac disease, implying that treatment of coeliac disease may restore reproductive function, however prospective longitudinal studies are needed to confirm this. Existing data do not imply a direct association with POI (Walker *et al.*, 2019).

POI may also be associated with other organ specific or systemic autoimmune disorders, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, immune thrombocytopenic purpura, autoimmune haemolytic anaemia, pernicious anaemia, vitiligo, alopecia areata, inflammatory bowel diseases, primary biliary cirrhosis, glomerulonephritis, multiple sclerosis, and myasthenia gravis (Coulam,

1983, Silva *et al.*, 2014, Kirshenbaum and Orvieto, 2019, Grossmann *et al.*, 2020). Testing for these conditions is however only indicated if symptoms of disease are present.

Recommendations

Screening for 21OH-Abs should be performed in women with POI of unknown cause.	⊕◯◯◯	**STRONG**
Screening for anti-ovarian autoantibodies should not be used to diagnose autoimmune POI.	⊕◯◯◯	**STRONG**
Thyroid function should be assessed by measuring TSH at diagnosis. TSH measurement should be repeated every 5 years or when symptoms arise.	⊕◯◯◯	**STRONG**
The guideline group recommends that HCPs do not perform 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.		**GPP**

Justification

An autoimmune aetiology of POI should be considered in the presence of associated autoimmune disorders, the existence of POI associated autoantibodies or histologically verified lymphocytic oophoritis. Antibodies against 21OH-Ab are currently the marker with the highest diagnostic accuracy for autoimmune POI and should be analysed in women with idiopathic POI. Although currently there is no specific treatment option for autoimmune POI, identification of women with autoimmune POI is clinically relevant for diagnosing subclinical or latent autoimmune adrenal insufficiency.

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). Therefore, screening for TSH should be performed in women with POI.

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

POI may precede the diagnosis of autoimmune adrenal insufficiency (Vogt *et al.*, 2021). About 1 in 5 women with positive 21 OH autoantibodies develop overt autoimmune adrenal insufficiency within 10 years (Naletto *et al.*, 2019). Women with POI and positive 21 OH autoantibodies should be referred to an endocrinologist. Basal determination of morning cortisol and adrenocorticotropic hormone (ACTH) levels should be used as routine screening tools. Additionally, plasma renin activity and ACTH stimulation test at five yearly intervals should be considered if adrenal insufficiency is suspected (Husebye *et al.*, 2021).

There are no longitudinal studies available providing information on the natural history of autoimmunity in women with POI that have negative autoantibodies at initial screening. In women with POI and negative autoantibody tests and absence of clinical signs and symptoms of endocrine disease, follow-up should be applied as for the general population of women. There is no consensus for repeated analysis for autoantibody tests if the initial tests are negative.

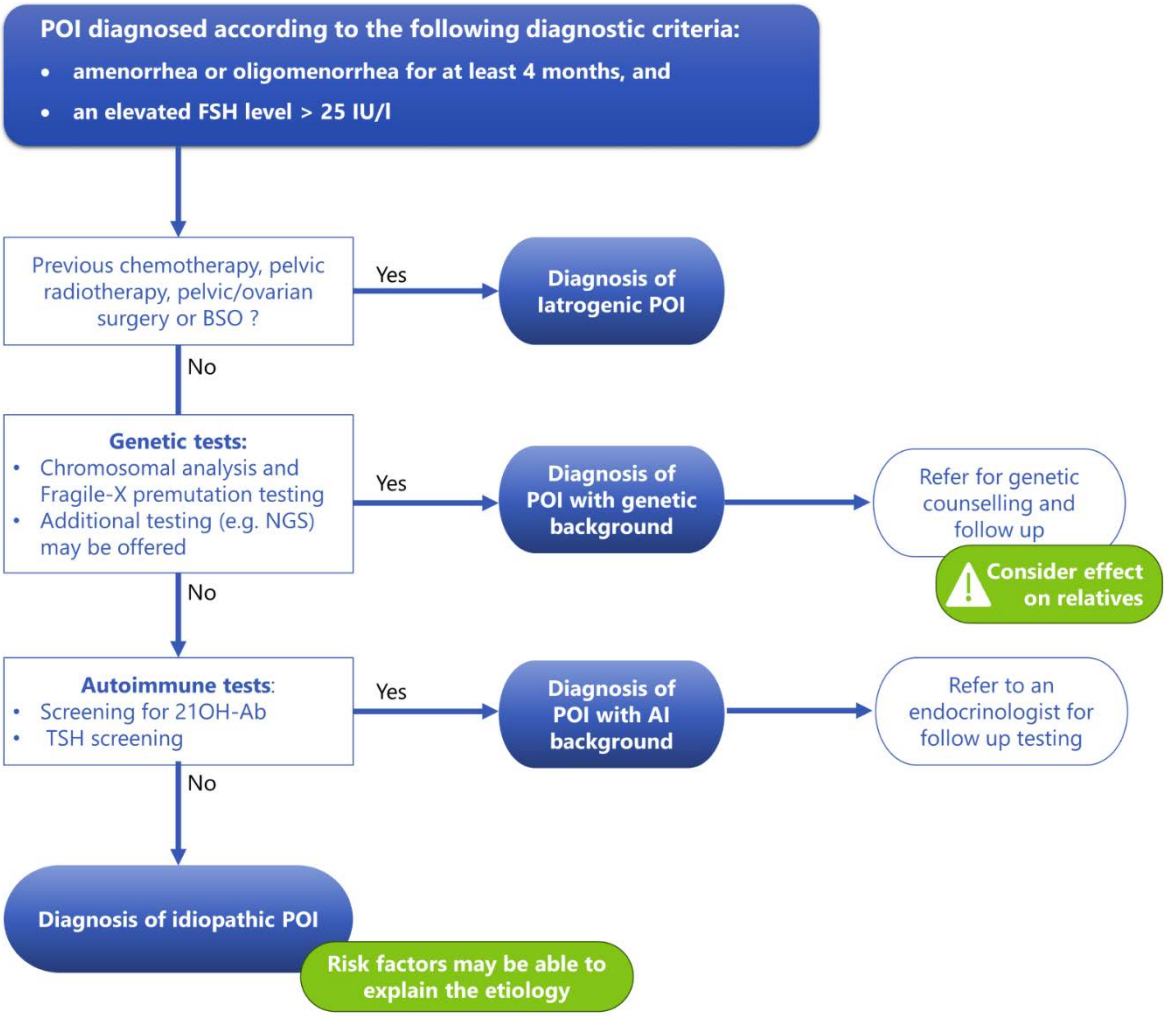
Recommendations

Women with POI and positive 21OH-Ab should be referred to an endocrinologist for testing of adrenal function.	⊕◯◯◯	**STRONG**
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.	⊕◯◯◯	**STRONG**
Women with POI with abnormal TSH levels should be referred to an endocrinologist for evaluation and treatment for thyroid hormone disorders.	⊕◯◯◯	**STRONG**

Justification

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. However, there is no evidence regarding the natural history of autoimmunity in women with POI who have negative autoantibodies at initial screening. Further autoantibody testing is only indicated if symptoms of disease are present.

FIGURE 7 SUMMARY OF TESTING TO ESTABLISH A CAUSE FOR POI



II.4 Care for women with POI after diagnosis

The journey of a woman diagnosed with POI is one that necessitates comprehensive and compassionate care from HCPs. In addition, POI does not only affect the individual diagnosed; it can have ripple effects on family members and dynamics. HCPs are instrumental in helping women and their families understand and adapt to this diagnosis and should provide support and guidance. There is also a significant need for greater community awareness and education regarding POI to reduce the perceived impact, stigma, and marginalization of POI, improve patient outcomes, and better support patients (McDonald *et al.*, 2022, Vincent *et al.*, 2024).

Dissatisfaction with care, related to multiple factors including unmet information needs, manner of delivery of the diagnosis, delayed diagnosis, discontinuity of care, negative clinical interactions, and perceived unsympathetic HCPs, has been reported and contributes to impaired quality of life (Alzubaidi *et al.*, 2002, Deeks *et al.*, 2011, McDonald *et al.*, 2022)(see Figure 11). A scoping review (McDonald *et al.*, 2022) identified factors including mental health counselling, compassionate HCPs, sensitive revelation of the diagnosis of POI, individualised care and continuity of care as positively influencing quality of life for women with POI.

As discussed, a diagnosis of POI can have a significant impact on psychological wellbeing and quality of life (see VIII. POI and psychological wellbeing). HCPs should use care both while delivering the diagnosis of POI, but also afterwards. Therefore, the guideline group has formulated the following recommendations for the organisation of care in POI (see also Figure 7).

Care for family members of women with POI is addressed in III. Implications for relatives of women with POI.

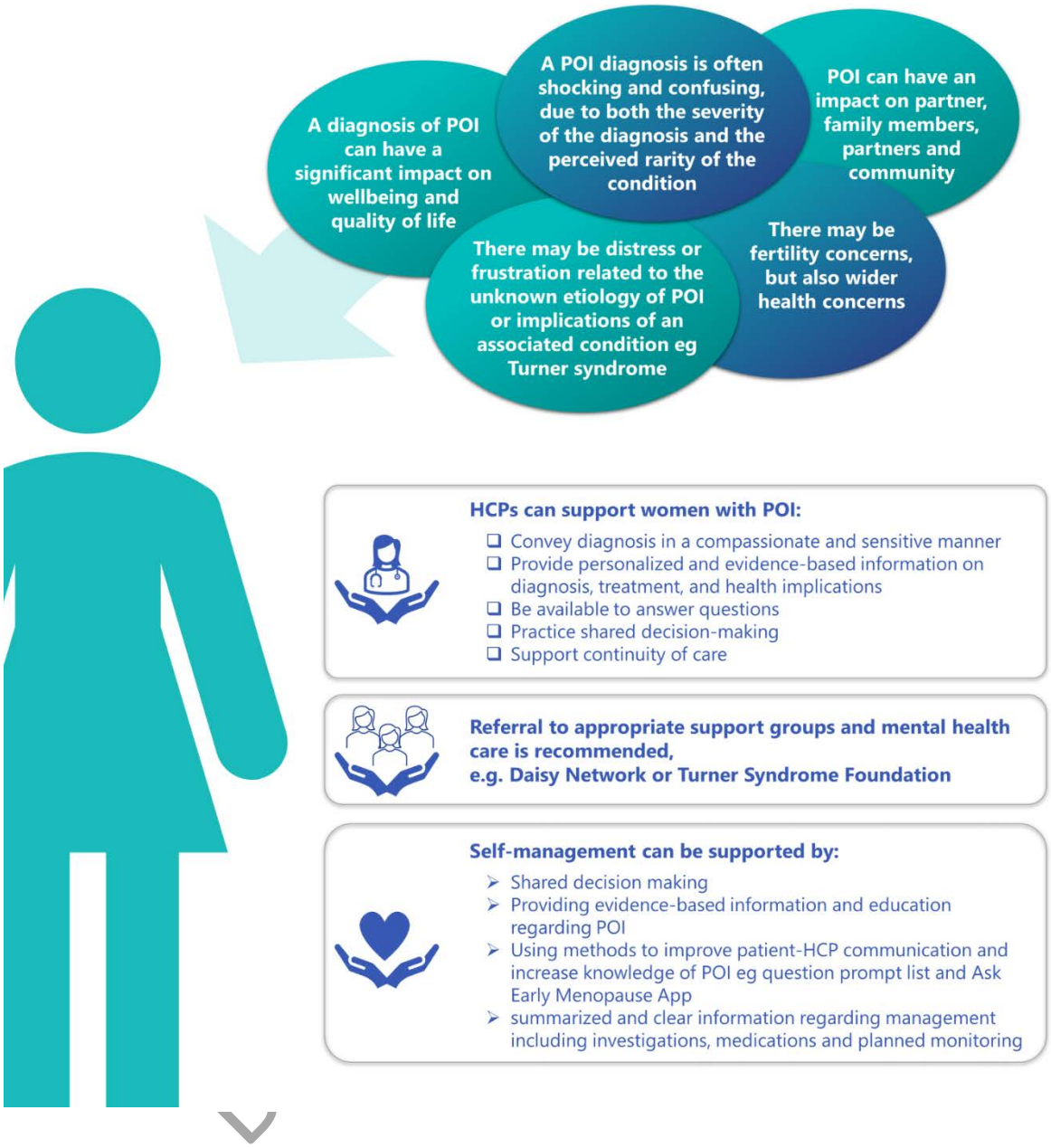
Recommendations

The guideline group recommends that HCPs convey the diagnosis of POI in a compassionate and sensitive manner, provide personalised evidence-based information about the condition and ensure enough time for the women to ask questions.	**GPP**
The guideline group recommends shared decision making and support for continuity of care in managing POI.	**GPP**
The guideline group recommends referral of women with POI to appropriate support groups and mental health care.	**GPP**

Justification

POI has a significant impact on multiple aspects of an individual's life requiring long-term medical management. Positive patient experience and outcomes are promoted by empathic, supportive HCPs and shared decision making.

1217 **FIGURE 8 SUPPORTIVE CARE FOR WOMEN WITH POI**



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III. Implications for relatives of women with POI

Non-iatrogenic POI can occur sporadically, but it has also been observed that women diagnosed with POI often have at least one (first-degree) relative with POI or early menopause. This risk is particularly heightened when multiple family members are affected. Research from various countries including the US, UK, Finland, and China has corroborated these findings, showing increased odds of POI and early menopause among relatives of women with POI. A recent USA study quantified the risks using data linkage. They reported that the risk of POI was increased 18-fold in first degree relatives, 4-fold in second degree relatives and 2.7-fold in third degree relatives of women with POI compared with controls (Verrilli *et al.*, 2023). Data on this topic are discussed in section Family history and demographic factors.

In families with two or more affected females, a genetic aetiology is suggested, but the genetic association with POI cannot always be identified (Barros *et al.*, 2020). Irrespective of a genetic background, women with POI may ask their HCPs questions on the implications of their diagnosis for their relatives (sisters, children), including the chances of their relatives developing POI, and measures for prevention and/or postponement of POI and infertility. Another aspect is intrafamilial egg donation, aspects of which are discussed in section Oocyte donation to achieve pregnancy in women with POI.

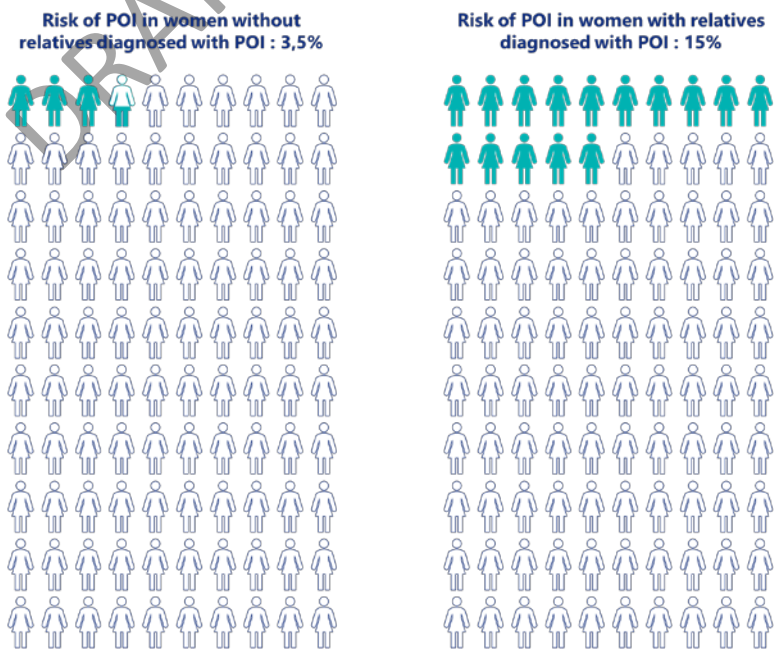
PICO Question: What are the implications for relatives of women with POI?

Chances of relatives developing POI

The relative risk of POI among relatives of women with POI was 4.6 (95% CI 3.3 to 6.5) compared to relatives of women without POI (Silvén *et al.*, 2022). A US study reported that the risk of POI was increased 18-fold in first degree relatives, 4-fold in second degree relatives and 2.7-fold in third degree relatives of women with POI compared to controls (Verrilli *et al.*, 2023).

As mentioned before, the prevalence of POI was estimated around 3.5% in recent reviews (Golezar *et al.*, 2019, Li *et al.*, 2023a). This implies that the likelihood of POI under the age of 40 among the relatives of women with POI is approximately 15% (Figure 9).

Figure 9 Risk of POI in relatives of women with POI and in the general population.



Relatives of women with POI who are concerned about their risk of developing POI should be informed (Webber *et al.*, 2016):

- They are at increased risk of developing POI.
- There is currently no proven predictive test to identify women who will develop POI, unless a genetic mutation known to be related to POI is detected.
- There are no established methods for preventing or predicting POI.
- About the symptoms and signs of POI such as menstrual disturbance or symptoms of estrogen deficiency. They should also be advised that long term use of hormonal contraception may mask these symptoms and signs.
- Fertility preservation could be considered, although data remain limited (see V.2. Fertility preservation)
- Their potential risk of earlier menopause should be taken into account when planning a family.

Follow-up of relatives of women with 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 *et al.*, 2022), such as bone loss or other sequelae of POI that could have been prevented by prompt institution of HT.

Family members of women with POI may require support to cope with their newfound risk of POI.

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).

Family planning and fertility preservation

While in women with established POI the opportunity for fertility preservation is missed, it is worth considering it for women who are at risk of developing POI, such as sisters of women with the condition. Additionally, for women at risk of POI, it may be advisable not to delay pregnancy, even if it needs to be acknowledged that the decision to start a family is complex and influenced by multiple factors.

It has been suggested that close monitoring of these women and their ovarian reserve can guide fertility preservation and family planning (Jiao *et al.*, 2017, Martyn *et al.*, 2017, La Marca and Mastellari, 2021). However, assessment of AMH level has limitations for predicting fertility and menopause. This is further discussed in chapter V.2. Fertility preservation.

Oocyte cryopreservation and/or embryo cryopreservation are established options for fertility preservation. However, data on the effectiveness of these techniques in women at risk of POI are not available (La Marca and Mastellari, 2021).

Recommendations

The guideline group recommends that relatives of women with the Fragile X premutation or other identified genetic causes of POI should be offered genetic counselling and testing.		**GPP**

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	⊕⊕◯◯	**STRONG**

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	**GPP**

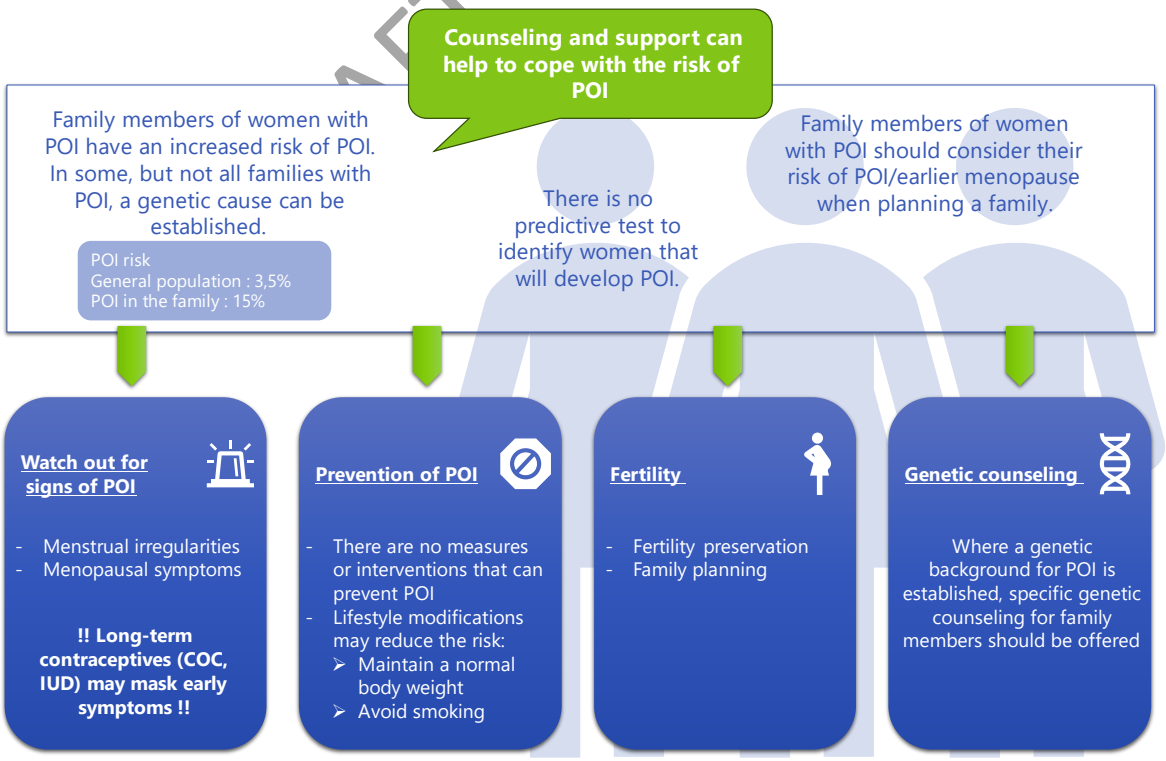
The guideline group recommends that female relatives (such as sisters or daughters) of women with non-iatrogenic POI should be informed of the signs and symptoms of POI and should promptly seek medical advice if this occurs.	**GPP**

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.	**GPP**

Justification

Although there seems to be a familial factor in POI and there is evidence of heritability of age of 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. 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.

FIGURE 10. SUMMARY OF INFORMATION FOR FAMILY MEMBERS OF WOMEN WITH POI



Research recommendation.

Research into methods for reliable prediction of POI and monitoring of ovarian function in relatives of women with non-iatrogenic POI is needed. Further research into the outcomes of fertility preservation in the specific group of women with a family history of POI is indicated.

PART C: Sequelae of POI

IV. POI and life expectancy

POI affects not only fertility, but also impacts bone health, cardiovascular health, and neurological function, as described in the relevant chapters. Awareness that these effects may have long-term consequences has led to the hypothesis that POI, and early menopause, may be associated with higher mortality rates. Furthermore, POI can be associated with a number of autoimmune diseases, can be caused by treatment for cancer, or by risk reducing bilateral oophorectomy in women with high risk of developing cancer, which again may largely affect mortality. This chapter reviews the available evidence and considers whether a diagnosis of POI has significant consequences for life expectancy.

PICO Question: What are the consequences of POI for life expectancy?

A recent study in a US population of approximately 160,000 people reported that among 36 women with POI, 32 (88.9%) had induced (iatrogenic) POI, and for 28 of them (77.8%) the cause was bilateral salpingo oophorectomy (Rocca *et al.*, 2023). Remarkably, in this general population, bilateral salpingo oophorectomy was the most frequent cause of POI (Rocca *et al.*, 2023). However, the distribution by causes of POI may vary across countries because of differences in gynaecologic practice. It is not surprising that most of the evidence on long-term outcomes of POI comes from observational studies of women who have undergone bilateral oophorectomy, usually at the time of hysterectomy for a benign gynaecological disease (e.g., fibromas or excessive bleeding), or as a risk reducing surgery for familial cancer risk. Some more recent evidence comes from cohort studies of women with spontaneous (non-iatrogenic) POI. The outcomes in women who undergo oophorectomy may differ from the outcomes in women who have experienced non-iatrogenic POI, which typically has a gradual onset and prolonged fluctuating course, compared to the immediate onset and profound estrogen-deficiency caused by surgical menopause.

Bilateral oophorectomy and mortality

A 2021 paper from Canada included a detailed review of 8 cohort studies on bilateral oophorectomy and mortality (Cusimano *et al.*, 2021). The cohort studies differed in several methodologic details and were conducted in 4 countries (United States, United Kingdom, Australia, and Canada). The most important difference was the selection of the referent women that were compared to the women who underwent bilateral oophorectomy. In 4 studies, the referent women were women who had not undergone bilateral oophorectomy (most women had no gynaecological surgery) (Rocca *et al.*, 2006, Gierach *et al.*, 2014, Wilson *et al.*, 2019, Tuesley *et al.*, 2020). In the remaining 4 studies, the referent women were women who had undergone hysterectomy with ovarian conservation (Parker *et al.*, 2009a, Jacoby *et al.*, 2011, Parker *et al.*, 2013, Mytton *et al.*, 2017, Cusimano *et al.*, 2021). Therefore, the question addressed in the two groups of studies was somewhat different (surgical management decision vs. broader public health perspective). In addition, the age cut-off used to define premature or early menopause caused by bilateral oophorectomy differed across studies (e.g., <45; <50, <40; ≤45; 35-45; <35; 35-44 years). In any event, 7 of the 8 studies confirmed that bilateral oophorectomy at younger age was associated with an increased overall mortality. As an example of the magnitude of the effect, the Canadian study showed a hazard ratio (HR) of 1.31 (95% CI 1.18 to 1.45; p<0.001) for women aged 45 years or younger at the time of surgery. The number needed to harm was 71 oophorectomies (measured at 20 years of follow-up) (Cusimano *et al.*, 2021). Therefore, for every 71 women who underwent bilateral oophorectomy, 1 additional death associated with bilateral oophorectomy was expected within 20 years of follow-up.

Only the Women's Health Initiative Observational Study did not report a significant association between bilateral oophorectomy before age 40 years and mortality (Jacoby *et al.*, 2011). However, women were recruited at an average age of 63 years (approximately 20 or more years after the bilateral oophorectomy, which had occurred at or before 40 years of age) and followed for a short time (mean 7.6 years, SD 1.6). Therefore, women were relatively young at the end of follow-up (mean age 70.6 years). In addition, the analyses were adjusted for a number of cardiovascular risk factors and conditions present at the time of recruitment in the study. Therefore, the cardiovascular risk factors and conditions were most likely mediating events in the chain of causality between the original oophorectomy and mortality, and they should not have been included in the model. In conclusion, the study by Jacoby and colleagues does not provide strong contradictory evidence.

Specific causes of death were addressed in some of the 8 cohort studies considered above. For example, in the Mayo Clinic Cohort Study of Oophorectomy and Aging, bilateral oophorectomy before age 45 years was associated with increased cardiovascular mortality, especially cardiac mortality (Rivera *et al.*, 2009a). In the same study, oophorectomy before age 45 years was also associated with increased mortality for neurological and mental diseases (Rivera *et al.*, 2009b). In the Nurse's Health Study, oophorectomy at age 50 years or younger was associated with reduced risk of ovarian cancer mortality but with increased risk of total cancer mortality. Cardiovascular disease mortality and coronary heart disease mortality were also increased (Parker *et al.*, 2013).

A 2023 study from Denmark confirmed the higher risk of all-cause mortality after bilateral oophorectomy before age 45 years compared to women who underwent hysterectomy with ovarian conservation. However, the differences at 10 and 20 years of follow-up were not statistically significant (Gottschau *et al.*, 2023). Another 2023 study from Norway confirmed the higher risk of all-cause mortality or of cardiovascular mortality after bilateral oophorectomy before age 40 years compared to women with no gynaecologic surgery, but the differences were not statistically significant (Michelsen *et al.*, 2023). Finally, a 2023 systematic review confirmed the association of bilateral oophorectomy before age 50 years with all-cause mortality both using women with hysterectomy and ovarian conservation or women with no gynaecologic surgery as the referent group. However, there was substantial heterogeneity across studies (Hassan *et al.*, 2024). In particular, the Women's Health Initiative Observational Study discussed above reported inconsistent findings (Jacoby *et al.*, 2011).

Non-iatrogenic POI and mortality

We found 4 systematic reviews of studies on the association between non-iatrogenic POI and overall mortality. Three reviews were published in 2016 and a more recent review in 2021 (Gong *et al.*, 2016, Muka *et al.*, 2016, Tao *et al.*, 2016, Huan *et al.*, 2021). The most recent review by Huan and colleagues included 16 studies and 321 233 women. The magnitude of the association was measured by relative risk (RR) or HR. In analyses comparing non-iatrogenic POI with spontaneous menopause at age 49-52 years (reference category), the association with all-cause mortality was significant both including follow-up intervals in the model (adjusted HR 1.10; 95% CI 1.01 to 1.21; p=0.034) and not including follow-up intervals in the model (adjusted RR 1.34; 95% CI 1.08 to 1.66; p=0.007). Marginal significance was reported for cardiovascular mortality after including follow-up intervals in the model (HR 1.09; 95% CI 1.00 to 1.19; p=0.045). Subgroup analyses indicated that geographic location and follow-up intervals were possible causes of heterogeneity across studies. There was an overall low probability of publication bias (Huan *et al.*, 2021).

A 2022 study based on the UK Biobank reported an increased risk of cardiovascular mortality, but not of cancer mortality, when comparing POI with spontaneous menopause at age 50-52 years (Xu *et al.*, 2022). A 2023 study from the United States confirmed the association between POI (spontaneous or iatrogenic) and increased all-cause mortality compared to non-premature menopause (all other ages at

menopause). The association between age of menopause and all-cause mortality was not linear, and particularly strong for menopause before age 37.5 years (Xing *et al.*, 2023). Finally, a 2023 study from Korea confirmed the association between POI (spontaneous or iatrogenic) and increased all-cause mortality compared with menopause after age 49 years. The association was particularly strong for menopause at ages 30-34 years. The risk was also increased in women who underwent early menopause (age 40-45 years) (Lee *et al.*, 2023a).

Interaction of POI with other risk factors

Evidence for possible interactions between POI and other risk factors for mortality such as obesity, smoking, or chronic diseases remains limited. For example, one study suggested a possible interaction between cardiovascular risk factors and early menopause in increasing mortality (Li *et al.*, 2021c). Another study showed that women who smoked and underwent early menopause were at particularly high risk of lung cancer or lung diseases (Zhai *et al.*, 2022).

Hormone therapy in POI

There are no clinical trials examining the long-term effects of hormone therapy (HT) on mortality after POI. The evidence available comes once again from observational studies of women who underwent bilateral oophorectomy and did or did not receive estrogen replacement therapy. For example, in the Mayo Clinic Cohort Study of Oophorectomy and Aging, increased overall mortality was observed mainly in women who had undergone bilateral oophorectomy before age 45 years and had not received estrogen replacement therapy (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)(Rocca *et al.*, 2006). In the Nurses' Health Study, the increased overall mortality, lung cancer mortality, cardiovascular mortality, and coronary heart mortality were higher in women who did not receive estrogen replacement therapy compared to women who did (significant interaction tests) (Parker *et al.*, 2013). Finally, in the Women's Health Initiative study, unopposed estrogen initiated at age 50-59 years in women who underwent bilateral oophorectomy and hysterectomy reduced overall mortality during a cumulative 18-year follow-up period (HR 0.68; 95% CI 0.48 to 0.96). However, this randomized controlled trial was not designed to test the effect of estrogen replacement therapy on POI (Manson *et al.*, 2019). Therefore, the results should be interpreted with caution.

Recommendations

Women with POI should be informed that POI without hormone therapy is associated with reduced life expectancy, largely due to cardiovascular disease.	⊕⊕◯◯	**STRONG**
Women with POI should be offered hormone therapy at least until the usual age of menopause as primary prevention to reduce risk of overall morbidity and mortality.	⊕◯◯◯	**STRONG**
The guideline group recommends that, in addition to hormone therapy, women with POI are advised to reduce cardiovascular risk by avoidance of smoking, healthy diet, regular exercise, and maintaining a healthy weight range		**GPP**

Justification

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.

Patients asking whether POI has an impact on their life expectancy can be informed about interventions that help reduce mortality in the general population.

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 *et al.*, 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.

V. POI, fertility, and pregnancy

As POI is characterised by cessation of ovarian function, loss of fertility is one of the key accompanying features of the diagnosis.

In the current chapter, the consequences of POI for fertility are described, and the options for women with POI wishing to achieve pregnancy. In the second part of this chapter, obstetric complications in women with POI, and the potential for mitigation of these complications by assessing fitness prior to pregnancy are explored. Additionally, the issue of fertility preservation in women with POI is covered.

V.1. Fertility and fertility treatments

PICO Question: What are the consequences of POI for fertility?

Much of the literature consists of case reports demonstrating the potential for natural pregnancy in women with POI related to specific aetiologies.

What is the chance of natural pregnancy with a diagnosis of POI?

Information on this can be derived from the natural pregnancy rate of women with POI awaiting oocyte donation. In an analysis of 200 consecutive women, 5 (2.5%) conceived within 2-8 years after diagnosis (Sauer, 1995). A review of the literature up to 1999 showed marked differences in pregnancy rate according to the design of the study, with 4.8% of women achieving pregnancy in observational studies compared to 1.5% in controlled studies (van Kasteren and Schoemaker, 1999). Subsequent analyses have reported pregnancy rates of between 2.2 and 14.2%, although mostly under 10% (Bachelot *et al.*, 2017, Fraison *et al.*, 2019, Cambray *et al.*, 2023).

An analysis of 358 consecutive women with idiopathic POI revealed that 25% showed subsequent evidence of ovarian function (at least 2 consecutive menstrual cycles or pregnancy), the great majority within 1 year of diagnosis. Pregnancy occurred in 4.8%. Predictive factors included markers of ovarian activity at diagnosis, a family history of POI and secondary amenorrhea (Bidet *et al.*, 2011). A more recent study showed a similar rate of resumption of ovarian activity (117/507; 23%), with 53% of these women continuing to have ovarian function at the end of the follow-up period, a mean of 3.4 years later. Women with resumption of ovarian activity had lower FSH levels at initial evaluation and were younger than those who did not. They also had a significantly higher pregnancy rate of 15.3%, vs 3.5% for the whole cohort (Bachelot *et al.*, 2017).

Oocyte donation can significantly improve the pregnancy rate and live birth rate of women with POI. However, studies have shown that only women with POI with underlying genetic factors tend to choose oocyte donation, and women with idiopathic and iatrogenic POI prefer to use their own oocytes to obtain pregnancy (Cambray *et al.*, 2023).

Recommendations

Women with non-surgical POI should be informed that ovarian activity may occur. This is associated with a chance of natural conception.	⊕◯◯◯	**STRONG**

Women with non-surgical POI should be advised to use contraception if they wish to avoid pregnancy.	⊕◯◯◯	**STRONG**

Justification

Ovarian activity may occur in women with non-surgical POI, especially early in the natural history of the condition. This gives the possibility for natural conception, which occurs in up to 15% in those women, although probably in <5% overall. The cause of POI should be considered in a woman who has a natural pregnancy, in case it has implications for the pregnancy and child (e.g. FMR1 premutation).

PICO QUESTION: WHAT FERTILITY INTERVENTIONS ARE EFFECTIVE?

Treatments to increase natural pregnancy rate in women with POI.

A range of treatments including estrogens, gonadotrophins, and corticosteroids have been explored as potential treatments to increase the chance of pregnancy. A review of 7 controlled trials of therapies in POI concluded that none showed a statistically significant increase in ovulation (the primary end point in all) or pregnancy rates (van Kasteren *et al.*, 1999). Meta-analysis was not possible due to heterogeneities in design, patient selection, and intervention. Only one study included a placebo group (Taylor *et al.*, 1996). A more recent systematic review including two randomized controlled trials, two observational studies, and 11 interventional studies also concluded that no treatment had been shown to increase the pregnancy rate in women with POI (Fraison *et al.*, 2019). One of these RCTs has been withdrawn (Badawy *et al.*, 2007).

The remaining RCT involved administration of ethinyl estradiol in the context of gonadotropin administration (Tartagni *et al.*, 2007). They randomized 50 women with POI to 0.05 mg ethinylestradiol (EE) versus placebo three times a day for 2 weeks before and during gonadotrophin treatment, with the main outcome being ovulation (Tartagni *et al.*, 2007). Eight out of 25 women treated with EE ovulated and 4 of them conceived. None of the 25 women in the placebo group ovulated ($p<0.005$). Sub-analysis demonstrated that ovulation only occurred in women with FSH<15IU/l during EE treatment. It seems likely that this subgroup had greater ovarian activity, reflecting the often-fluctuating nature of POI especially early in its natural history.

These data confirm the high rate of follicle development and potentially of ovulation in women with POI, especially with a shorter duration of amenorrhoea; this may also underline the apparent relationship between EE suppression of FSH and ovulation, the basis of which is unclear. Further RCTs are required to confirm the potential beneficial effect of gonadotrophin suppression (using either estrogen or GnRHa) pre-treatment and hormone replacement therapy, with pregnancy as the main outcome measure.

There have been many recent interventional studies of novel approaches aiming to enhance fertility in women with POI, but generally without appropriate study designs (notably the inclusion of controls) or with sufficient power to allow any conclusions. Many also include populations of women with reduced ovarian reserve as well as POI. Several recent reviews have been published providing more details on the proposed mechanisms and individual studies (Rosario and Anderson, 2021, Zhang *et al.*, 2021, Pellicer *et al.*, 2023). Most of these interventions fall into the following categories:

1. In vitro activation of follicle growth in biopsied ovarian tissue.
2. Administration of mesenchymal stem cells.
3. Injection of platelet rich plasma into the ovary.

In vitro activation ~~(IVA)~~ was originally described as a joint surgical/pharmacological treatment to activate the growth of remaining follicles in the ovaries of women with POI (Kawamura *et al.*, 2016), involving surgical removal of ovarian tissue, its fragmentation and pharmacological treatment, and surgical

replacement. A pharmacological treatment-free version has also been described (Ferreri *et al.*, 2020), as has the surgical procedure in combination with administration of stem cells (Tinjić *et al.*, 2021).

Stem cell-based treatments have used mesenchymal stem cells derived from bone marrow, placenta, and umbilical cord. Injection of platelet rich plasma has also been used in several studies, including one of 311 women (Cakiroglu *et al.*, 2020), generally without adequate control groups.

A recent RCT of platelet rich plasma administration versus no intervention in women with diminished ovarian reserve has been presented in abstract form (Herlihy *et al.*, 2023); 83 women were randomised, with no differences in the number of metaphase II oocytes or blastocysts obtained after subsequent ovarian stimulation. Thus, at present none of the approaches can be recommended for women with POI.

Oocyte donation to achieve pregnancy in women with POI.

It is clear that oocyte donation is the most successful treatment for women with POI desiring pregnancy. Successful pregnancy was first reported in 1984 (Lutjen *et al.*, 1984) and since then it has become a 'routine' treatment. The pregnancy rate from oocyte donation is not greatly affected by the recipient's age (Sauer *et al.*, 1994, Templeton *et al.*, 1996, Hogan *et al.*, 2019).

Oocytes may be donated altruistically, or from a known donor (often a sister). A comparison of treatment cycles where 'egg-sharing' was used (i.e. the donor was an infertile woman undergoing IVF for her own treatment at the same time) with altruistic donors showed no difference in clinical pregnancy rate (n=353 cycles overall) (Oyesanya *et al.*, 2009).

Sisters or other near relatives are often oocyte donors for women with POI. There are specific ethical considerations in sibling donation, and in addition, sisters will have a high genetic homology to the woman with POI, which may be of relevance if there is a possible genetic cause or component to the aetiology of the POI, which may not be clinically apparent in the donor sister. This is supported by an analysis of donation by sisters (n=13) with altruistic donors (n=66), which showed that sisters had a 5-fold increased risk of cycle cancellation (30.7% vs 6.1%). However, in completed cycles the number of oocytes obtained was similar, as were pregnancy and miscarriage rates (Sung *et al.*, 1997). These issues, including the sister's own plans for pregnancy, should be discussed with the potential donor sister before proceeding with donation.

Sex steroid replacement therapies are used to ensure endometrial development and receptivity at the time of embryo replacement. Most studies have investigated this in women without POI. One small RCT in women with POI (n=17 completed the study, with a range of aetiologies including idiopathic, post chemotherapy and TS) compared transdermal estradiol plus vaginal progesterone with oral ethinylestradiol plus norethisterone (O'Donnell *et al.*, 2012). Endometrial thickness was greater in the former group, with no significant differences in uterine volume or blood flow. The significance of this for establishment of pregnancy was not assessed.

However, while oocyte donation is a technically straightforward procedure for IVF clinics, oocyte donation pregnancies are associated with some obstetric risks, which may be related to maternal factors, particularly the cause of POI (*see section* V.3. Pregnancy).

Abnormal uterine function and thus the potential for early and late pregnancy complications is a well-established consideration in women who have received radiotherapy (including total body irradiation) to the uterus *(see section 6.3).* Radiotherapy in childhood causes failure of uterine growth and in some women reduced responsiveness to exogenous sex steroids (Critchley *et al.*, 1992). There may be a relationship between the risk of pregnancy complications and age at irradiation and uterine volume (Larsen *et al.*, 2000), but series of sufficient size on which to base clinical advice are lacking.

Special considerations apply in women with Turner Syndrome (TS) in relation to comorbidity (especially cardiovascular), which results in high rates of complications in pregnancy (*see section* V.3. Pregnancy). Implantation and pregnancy rates in women with TS have been comparable to those in women with other POI aetiologies in most (Foudila *et al.*, 1999, Bodri *et al.*, 2006, Alvaro Mercadal *et al.*, 2011), but not all series (Yaron *et al.*, 1996). Women with TS may have higher rates of early pregnancy loss compared to other groups with POI (early miscarriage 60% versus 8.7%), indicating reduced endometrial and uterine function (Yaron *et al.*, 1996). A cohort study of 57 women having 124 pregnancies from a population of 482 Swedish women with TS described a miscarriage rate of 45% in spontaneous pregnancies compared to 26% in oocyte donated pregnancies (Bryman *et al.*, 2011).

Recommendation

Women with POI should be informed that there are no interventions that have been reliably shown to increase ovarian activity and natural conception rates.	⊕⊕⊕◯	**STRONG**
Women with POI should be informed that oocyte donation is an established option to achieve pregnancy after a diagnosis of POI	⊕⊕◯◯	**STRONG**
Women with non-iatrogenic POI considering oocyte donation from sisters should be informed that this includes shared genetic risk and carries a higher risk of ovarian stimulation cycle cancellation.	⊕⊕◯◯	**STRONG**

Justification

There are no known treatments which reliably increase ovarian activity, ovulation rate, and the possibility of conception. Several novel approaches have been described, but study design precludes reliable interpretation, particularly in the light of the prevalence of resumption of ovarian activity in women with POI. Robust studies of these approaches are required so that if effective, they can be more widely used or if ineffective, not be offered to vulnerable women.

Oocyte donation is the treatment of choice in women wishing to conceive (efficacy shown in observational studies). As pregnancies after oocyte donation are associated with obstetric complications, the guideline group strongly recommends that these pregnancies are followed with adequate obstetric involvement, although no studies have been performed showing the effect of obstetric care on complications in these patients.

While there may be personal reasons why a sister (or other close relative) would be a suitable donor, sisters have a higher donation cycle cancellation rate due to low response to ovarian stimulation. This is likely to reflect that siblings may have a shared genetic risk of low ovarian reserve/POI.

There are special considerations regarding oocyte donation in women with TS. While establishment of clinical pregnancy can be achieved, severe maternal morbidity and maternal mortality during and after pregnancy is a critical issue. This is discussed more fully in *section* V.3. Pregnancy.

V.2. Fertility preservation

PICO QUESTION: What therapies are effective for fertility preservation and /or prevention of POI?

This aspect is reviewed in detail in the ESHRE Guideline 'Fertility Preservation in Women' (Anderson *et al.*, 2020) thus only a brief summary is given here.

The diagnosis of POI indicates the loss of the ovarian follicle pool; thus, fertility preservation interventions (oocyte, embryo or ovarian tissue cryopreservation) would appear futile. However, the variable course of the condition, especially in its early course, indicate the potential for a window of opportunity for this approach. While this is advocated in reviews of the subject (Baker, 2011), there are no data available as to success rates. These considerations also apply to highly selected women with Turner Syndrome (TS), who may have an opportunity during adolescence and early adulthood for fertility preservation treatments. Both oocyte and ovarian tissue cryopreservation (including IVM and combining both approaches) have been described in case reports (Lau *et al.*, 2009, Balen *et al.*, 2010) (Gayete-Lafuente *et al.*, 2023) and series (Borgstrom *et al.*, 2009, Mamsen *et al.*, 2018, Mamsen *et al.*, 2019, Nadesapillai *et al.*, 2023); while a clinical pregnancy has been reported after ovarian tissue cryopreservation and replacement, live birth was not achieved (Dunlop *et al.*, 2023).

Women with auto-immune POI may show some preservation of antral follicle growth in the early stages of the condition. The possibility of aspiration of immature oocytes from such follicles, with in vitro maturation and cryopreservation and subsequently successful warming, fertilisation and pregnancy has been described (Grynberg *et al.*, 2020).

Fertility preservation may also be considered for women at risk of POI, either because of a naturally low number of follicles in the ovary, or where it is low as a result of disease or medical treatment. These might include sisters of women with POI, women with Fragile X/TS and survivors of childhood and adolescent cancer who have not yet developed POI, although data remain limited (Zajicek *et al.*, 2023). While available biomarkers of ovarian reserve have some predictive value of time to menopause (e.g.(Broer *et al.*, 2011, Freeman *et al.*, 2012)), evidence linking reduced ovarian reserve in young women to fertility is limited, but indeed suggests that regularly cycling women with low AMH levels do not have reduced fecundability (Hagen *et al.*, 2012, Steiner *et al.*, 2017). Many women will conceive naturally after treatment for childhood or young adult cancer (Chow *et al.*, 2016, Anderson *et al.*, 2022b). Some will have low AMH levels after such treatment: the limited evidence suggests that such low AMH levels can be maintained over many years, indicating ongoing ovarian function and thus the potential for conception (Cameron *et al.*, 2019, Su *et al.*, 2020b).

Recommendation

The guideline group recommends that fertility preservation is discussed with women at risk of POI. In women with established POI, the opportunity for fertility preservation has passed.	**GPP**

Justification

Where a risk of POI has been identified, there will be concern about the risk to fertility. This will be modified by age and imminent vs distant family intentions. Discussion of future fertility and the possibility of fertility preservation interventions is therefore appropriate, recognising the limitations of tests such as AMH that might predict POI (see section XI.2. Risks of hormone therapy). Where POI is established, there is complete or near-complete exhaustion of the follicle pool and fertility preservation interventions are not recommended.

V.3. Pregnancy

PICO QUESTION: WHAT ARE THE OBSTETRIC RISKS ASSOCIATED WITH POI?

Pregnancy-related risks are associated with the cause of POI and to some extent, whether the pregnancy is natural, or the result of oocyte/embryo donation.

After idiopathic POI

There are case reports of natural pregnancies occurring, but it is difficult to draw any detailed conclusions regarding the outcomes. The risk of miscarriage is probably the same as in women with normal ovarian function (van Kasteren *et al.*, 1999). A pilot study of 20 women and 20 age-matched controls, examining the aneuploidy rates in embryos from women with prematurely declining ovarian function (not POI) showed this to be the same as that for women with age-appropriate ovarian function (Weghofer *et al.*, 2007).

After cancer treatment

The obstetric risks associated with pregnancy after cancer treatment (chemotherapy/radiotherapy) – independent of POI - were earlier summarized in the ESHRE Guideline on Female Fertility Preservation (Anderson *et al.*, 2020).

Reports from large registry data from the Scottish Cancer Registry (van der Kooi, et al., 2018), the North Carolina Central Cancer Registry (CCR) (Anderson *et al.*, 2017a), the Finnish Cancer Registry (Madanat-Harjuoja *et al.*, 2013, Melin *et al.*, 2019) and the Cancer registry of Norway (Fosså *et al.*, 2005) concluded that women previously treated for cancer had higher rates of postpartum haemorrhage, operative or assisted delivery, and preterm birth. Furthermore, their offspring were more likely to require monitoring or care in a neonatal intensive care unit. The risks of early death or stillbirth were not increased after adjustment for prematurity, and there was no increased risk of congenital or chromosomal abnormality (Winther *et al.*, 2012, Nielsen *et al.*, 2018, van der Kooi *et al.*, 2018, van der Kooi *et al.*, 2019). Data from the Swedish Cancer Register (10 017 births in female cancer survivors) identified an increased risk of stillbirth within three years after the cancer diagnosis (OR 1.92; 95% CI 1.03 to 3.57). However, the risk of stillbirth and neonatal death was significantly decreased among second children as compared to the first born, suggesting that any adverse effect associated with cancer treatments may diminish with time (Ji *et al.*, 2016).

A meta-analysis of data from cohort studies and registries came to similar conclusions (van der Kooi *et al.*, 2019). Their calculations showed that cancer survivors had an increased risk of prematurity (RR 1.56; 95% CI 1.37 to 1.77), low birth weight (RR 1.47; 95% CI 1.24 to 1.73), emergency caesarean section (RR 1.22; 95% CI 1.15 to 1.30), elective caesarean section (RR 1.38; 95% CI 1.13 to 1.70), and postpartum haemorrhage (RR 1.18; 95% CI 1.02-1.36). They reported a non-significant difference in small-for-gestational-age-babies (RR 0.99; 95% CI 0.81 to 1.22), and antepartum haemorrhage (RR 1.06; 95% CI 0.88-1.29). From this meta-analysis, they also concluded that the incidence of congenital abnormalities was not higher in children from cancer survivors, with an apparent increase due to the statistical artefact know as Simpson's paradox (van der Kooi *et al.*, 2019).

Effect of chemotherapy

No systematic reviews were found on the effect of different chemotherapy regimens in adult women on subsequent pregnancy. Chemotherapy has not been associated with adverse pregnancy outcomes (van Dorp *et al.*, 2018). Akhtar and colleagues retrospectively assessed 176 patients (age 14-40 years) who underwent high dose chemotherapy and autologous stem cell transplant without total body irradiation (TBI) for diffuse large B-cell lymphoma and Hodgkin lymphoma (Akhtar *et al.*, 2015). Twenty-six patients (65%) became pregnant 50 times (range 1-6 times), resulting in 43 (86%) live births, 7 (14%)

miscarriages, including 1 still birth (at 28 weeks). There was a significantly higher incidence of successful pregnancies after autologous stem cell transplant in patients younger than 40 years. Other single studies were of very small patient groups, precluding accurate interpretation.

Large prospective cohort and population-based studies have evaluated the effects of chemotherapy for childhood cancer on subsequent pregnancy outcomes, whereas data are more limited for adult cancer patients. One relevant publication reported outcomes of 4922 births to cancer survivors and concluded that women who conceived ≥1 year after starting chemotherapy without radiation or ≥2 years after chemotherapy with radiation did not have an increased risk of preterm birth (Hartnett *et al.*, 2018). Women who conceived ≤1 year after starting chemotherapy had higher risks of preterm birth than controls (chemotherapy alone: RR 1.9; 95% CI 1.3-2.7; chemotherapy with radiation: RR 2.4; 95% CI 1.6 to 3.6).

Anthracyclines (e.g. doxorubicin, daunorubicin) and mediastinal radiotherapy (including that for breast cancer, as the heart can fall within the area of scatter) are both associated with cardiomyopathy and heart failure. The risk is greatest when either is used at higher doses or in combination with each other. Anthracyclines can be cardiotoxic at all doses, and it is not entirely clear at what dosage the risk increases significantly, but it is likely to between a cumulative dose of 250 mg/m^2 (Scottish Intercollegiate Guidelines Network (SIGN), 2013) and 300 mg/m^2 (Hudson, 2010). The overall risks for heart failure are low (1.7%), most severely in those with pre-existing cardiac dysfunction (Nolan *et al.*, 2020).

Effect of Pelvic radiotherapy

There are robust data that radiotherapy to a field that includes the uterus is associated with adverse pregnancy outcomes in women who had been exposed during childhood and adolescence, but the data following adult exposure are much more limited. Females treated with pelvic radiation for childhood cancers have an increased rate of uterine dysfunction leading to pregnancy loss, preterm birth, and low birth weight (Critchley and Wallace, 2005). These pregnancy-related complications are related with reduced uterine volume, damage of uterine vessels, myometrial fibrosis, endometrial injury (Critchley and Wallace, 2005, Teh *et al.*, 2014). Doses of 14 to 30Gy can lead to irreversible uterine dysfunction in young female patients (Critchley and Wallace, 2005).

A large retrospective cohort study, performed between 1970 and 1986, enrolled 1774 women younger than 21 years at initial cancer diagnosis, who had survived for at least 5 years after diagnosis and who had received radiotherapy, found that high-dose pelvic irradiation can permanently impair growth and blood flow to the uterus resulting in a reduced uterine volume; these effects of radiation are dependent on age (Signorello *et al.*, 2010). Sixty stillbirths or neonatal deaths, and 3077 live births were reported. Uterine or ovarian irradiation with doses ≥2.5 Gy greatly increased the risk of stillbirth or neonatal death (12-fold) in women treated before menarche. Therefore, careful management is warranted for pregnant women treated with high doses of pelvic irradiation particularly before they have reached puberty.

In a study reporting on the effect of adulthood radiation effect on pregnancy, the incidence of spontaneous miscarriage (37% versus 7%) and preterm birth (63% versus 18%) were significantly higher in total body irradiation (TBI) recipients when compared to the chemotherapy-only group (Sanders *et al.*, 1996). The 13 preterm births resulted in 10 low birth weight (1.8 to 2.24kg) and three very low birth weight (≤ 1.36kg) infants, for an overall incidence of 25%, which is higher than the expected incidence of 6.5% for the general population. Four Gy appears to be the threshold dose.

Radiotherapy-induced structural and functional changes to the uterus (> 5Gy) may adversely affect implantation and maintenance of pregnancy increasing the risk of placental attachment disorders (placenta accreta or placenta percreta), low birth weight (OR 3.64; 95% CI 1.33 to 9.96; in survivors after abdominopelvic radiation; OR 6.8; 95% CI 2.1 to 22.2); small for gestational age (OR 4.0; 95% CI 1.6 to

9.8) ; preterm birth (OR 3.5; 95% CI 1.5 to 8.0); and perinatal death and foetal malposition (Tarín *et al.*, 2016).

In conclusion, uterine exposure to radiotherapy during childhood reduces adult uterine volume and leads to an increased risk of pregnancy complications and adverse pregnancy outcomes. Preconceptional assessment and appropriate obstetric monitoring is warranted (van de Loo *et al.*, 2019).

For oocyte donated pregnancies

Oocyte (or embryo) donation is an established fertility treatment, and most IVF units report similar pregnancy, implantation, and live birth rates as their cycles using women's own oocytes when egg age is similar. Pregnancies following oocyte donation (OD) are at increased risk for obstetrical and neonatal complications. In a large systemic review and meta-analysis (Storgaard *et al.*, 2017) singleton OD pregnancies, compared with singleton IVF pregnancies, had increased risk for hypertensive disorders of pregnancy (AOR 2.11; 95% CI 1.42 to 3.15), caesarean section (AOR 2.20; 95% CI 1.85 to 2.60), post-partum haemorrhage (AOR 2.40; 95% CI 1.49 to 3.88), preterm birth (AOR 1.75; 95% CI 1.39 to 2.20), and low birth weight (AOR 1.53; 95% CI 1.16 to 2.01). There was no increased risk for gestational diabetes.

The greatest risk for oocyte donor cycles seems to be the risk for pre-eclampsia (PE). A large systemic review and meta-analysis evaluated data from 27 studies and over 7000 donor cycles and 70 000 IVF cycles to establish risk (Keukens *et al.*, 2022). The risk was 13.5 to 18% in OD pregnancies compared to 5.9% in autologous IVF, with risk for severe PE of 6.8 to 12% vs. 3.3%, respectively. Interpretation of these data are complicated by the fact that a higher percentage of the OD pregnancies were multiples compared with autologous IVF, and that the OD pregnancies were conceived in a medicated cycle. Recent data have suggested the absence of the corpus luteum in medicated cycles, compared with natural cycle, or transfer in a fresh egg retrieval cycle, increases PE risk (Conrad *et al.*, 2022). Lastly, women with POI, based on the cause of the POI, may have unique risk factors, such as prior abdomino-pelvic radiation, chemotherapy, and estrogen deficiency.

The risk of aneuploidy is related to the age of the donor, not the recipient, and should be taken into consideration during antenatal aneuploidy screening (Bowman and Saunders, 1994, Donnenfeld *et al.*, 2002).

In women with Turner Syndrome (TS) (see also Table IV)

Pregnancies in women with TS are high risk due to the underlying increased morbidity and mortality of the condition. Although not common, spontaneous pregnancies can occur, especially in women with a mosaic karyotype rather than 45,X, and these may be lower risk than oocyte donated pregnancies (Hadnott *et al.*, 2011). Hadnott and colleagues reported 7 spontaneous pregnancies in 5 women with spontaneous menses out of a population of 276 TS women (Hadnott *et al.*, 2011). All 7 pregnancies resulted in live births without any maternal complications, although one of the offspring had cerebral palsy. None had congenital or karyotypic anomalies. A much larger cohort study of 57 women having 124 pregnancies from a population of 482 Swedish women with TS described a miscarriage rate in spontaneous pregnancies of 45% compared to 26% in oocyte donated pregnancies (Bryman *et al.*, 2011). The higher miscarriage rate is consistent with a higher rate of karyotypic abnormalities in natural pregnancies (Birkebaek *et al.*, 2002, Bernard *et al.*, 2016). Assessment of anti-mullerian hormone (AMH) levels is a reliable marker of ovarian function in women with Turner syndrome to assess chances for natural pregnancy and/or options for fertility preservation (Kalra *et al.*, 2019).

1757 **TABLE IV THE PREVALENCE OF COMPLICATIONS IN PREGNANCIES IN WOMEN WITH TURNER SYNDROME**

	Pregnancies with own oocytes				Pregnancies with donated oocytes					
	(Hadnott *et al.*, 2011)	(Bryman *et al.*, 2011).	(Bernard *et al.*, 2016)	(Birkebaek *et al.*, 2002)	(Hadnott *et al.*, 2011)	(Bryman *et al.*, 2011).	(Chevalier *et al.*, 2011)	(Foudila *et al.*, 1999)	(Bodri *et al.*, 2006)	(Hagman *et al.*, 2013)
Nr of TS women	5	27	27	33[2]	5	30		18	21	106
Unassisted / IVF / UIU	5 / 0	23 / 3 / 1	27	32 / 1						
Nr of Pregnancies	7	82	52	61	6	42	82	20	17	
Deliveries (children)	7 (7)	36 (37)	30 (30)	61 (64)	6 (7)	31 (31)	71	11 (12) (1 ongoing)	7 (8) (1 ongoing)	122 (131)
Pregnancy complications										
Multiple pregnancy	0/7	1/82	0/52		1/6	0/42		1/20		13/122
Miscarriage		37/82 (45)	16/52 (30.8)			11/42 (26)		8/20 (40)	8/17 (47)	
Legal abortion		8/82 (10)	2/52 (3.8)			0				
Medical interruption			3/52 (5.8)							
Extrauterine pregnancy		1/82 (1.2)				0				
Intrauterine foetal death			1/52 (1.9)						1/17 (5.6)	
Stillbirth										1/131 (0.8)
Maternal complications										
Aortic dissection	0	1	0/30		0		2/93 (2.2)			1/117 (0.8)
Other cardiovascular complications										1/117 (0.8)[3]
⇨ Maternal death		0					2			0
Pregnancy-associated hypertensive disorders (PAHD)	0		4/30 (13.3)		0		31/82 (37.8)	6/18 (33)	5/8 (62.5)	17/117 (14.5)
Pre-eclampsia	0		2/30 (6.7) (included in PAHD)		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)

[2] This includes 1 patient pregnant after Oocyte donation for which the results/data could not be excluded.
[3] heart regurgitation and left ventricular dilatation.

Gestational diabetes	0		1/30 (3.3)	0/6		3/82 (3.6)			11/117 (9.4)
Intrahepatic cholestasis of pregnancy			1/30 (3.3)			1/82 (1.2)			8/117 (6.8)
C-section	4/7 (57.1)	17/27 (63)	14/30 (46.7)	6/6 (100)	24/30 (80)	58/71 (81.7)	11/11 (100)	7/7 (100)	100/122 (82.0)
Neonatal complications									
Placental complications							1 /11 (twin)		5/118 (4.2)
Perinatal mortality									3/131 (2.3)
Preterm delivery (<37wks)	0			2		28/73 (38.3).[4]		4/8 (50)	15/122 (12.3)
Low birth weight (<2500g)	0			4/7					23/131 (17.6)
Chromosomal anomalies	0			0					
Birth defects	1/7.[5]	4.[6]	0		1				8/131 (6.1%).[7]
Abnormal Karyotype			2 TS /11 girls tested	6 /25 tested.[8]					
Other adverse neonatal outcomes				0		7/87			

1758

[4] ≤35 wg

[5] cerebral palsy

[6] 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.

[7] Of which 5/131 (3.8) were considered serious birth defects

[8] 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.

Overall risk for death related to pregnancy for a patient with Turner Syndrome is ~1% (Bondy, 2014). Pregnancy increased the risk of aortic dissection by an estimated two to five times for women with TS while a recent systematic review found 14 reported cases of death from aortic dissection with a concurrent or recent pregnancy (Hynes *et al.*, 2020). Rates of death, and serious complications, have declined with good pre-pregnancy screening (excluding from pregnancy for those with high risk) and careful monitoring of those with lesser risk as aortic dissection can occur even with a normal pre-pregnancy cardiac evaluation.

A cohort study of oocyte donated pregnancies in 106 TS women in 3 Nordic countries (1992-2011) similarly showed these pregnancies to be high risk (Hagman *et al.*, 2013). Hypertensive disorders of pregnancy were the most common complication (35%). Life-threatening events occurred in 4 pregnancies (3.3%), one of which was an aortic dissection, although there were no maternal mortalities. Neonatal complications appeared less common than suggested by previous studies; in singleton pregnancies the preterm birth rate was 8.0% with low birth weight in 8.8%. Perinatal mortality was 2.3% overall. It is not known how many women were declined treatment based on an unfavourable pre-conception assessment and the same proportion of women was 45,X as in the Hadnott & Bondy review (44%) (Hadnott *et al.*, 2011). Only 63.5% of cases had a prior cardiac review (although 100% of the Swedish group - 31 deliveries) and only 48.7% of assessments were within 2 years of pregnancy (71% in Sweden).

Other issues

A case report of post-partum depression in a woman with POI (Shea and Wolfman, 2017) raises the concern for the impact of rapid changes in hormones that occur post-partum and differential affect in women with chronic estrogen deficiency and potential sensitivity to mood alterations. Transdermal estrogen can be given post-partum without impact on lactation and may be of benefit (Moses-Kolko *et al.*, 2009, Wisner *et al.*, 2015). A recently approved medication, specifically for post-partum depression (zuranolone) may offer benefit but has not yet been tested in this population.

Recommendations

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.	⊕⊕⊕◯	**STRONG**
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 with their obstetric team.	⊕⊕◯◯	**STRONG**
Pregnancies after radiation to the uterus are at high risk of obstetric complications and should be managed in an appropriate obstetric unit.	⊕⊕◯◯	**STRONG**
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.	⊕⊕◯◯	**STRONG**

A cardiologist should be involved in care of pregnant women who have received anthracyclines and/or cardiac irradiation.	⊕◯◯◯	**STRONG**

Justification

Unassisted pregnancies after idiopathic POI or after most forms of chemotherapy are probably not any higher risk than the general population (moderate quality of evidence). Pelvic irradiation is associated with increased obstetric risks due to poor uterine function, especially when exposure occurred before menarche. Anthracycline chemotherapy and cardiac irradiation are associated with cardiac failure, which may become clinically apparent in pregnancy.

Oocyte donated pregnancies, regardless of recipient's age, indication for treatment or ovarian function, are associated with pregnancy-induced hypertensive disorders, threatened miscarriage, caesarean section, and possibly postpartum haemorrhage. Fetal growth restriction may be more common in oocyte donated pregnancies in women with POI. Therefore, the guideline development group strongly recommends that these pregnancies are followed with adequate obstetric surveillance, although no studies have been performed showing the effect of obstetric care on complications in these patients. (Good practice point)

Low dose aspirin (150mg) has been shown to reduce risk of pre-eclampsia (Duley *et al.*, 2019). Aspirin is most effective if started prior to 16 weeks but can be started earlier based on proposed mechanism. The recommendation is that 2 or more moderate risk factors, an example of which is first pregnancy, should be an indication for aspirin (NICE clinical Guideline, 2010). Although oocyte donation is not given as a specific risk factor, consideration of prescribing aspirin should be given in these pregnancies, especially when it is the first pregnancy or in a woman with Turner Syndrome. A recent randomized trial (Mendoza *et al.*, 2023) suggests that stopping treatment at 24 – 28 weeks in those with a normal sFlt-1:PlGF ratio does not negative impact pre-eclampsia risk.

Pregnancies in women with Turner Syndrome are high risk and may have a maternal mortality as high as 3.5%, with newer studies reporting lower risk. Reporting bias may make the true incidences of complications uncertain. Pre-conception screening, especially for cardiac risk factors, may help reduce maternal risks in pregnancy as well as identify those in whom pregnancy might be considered best avoided. Women with TS should be appropriately counselled regarding the risks of reproduction, and this should include contraceptive advice when pregnancy is considered contra-indicated, especially in those with spontaneous menses.

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

Women with POI seeking to embark on pregnancy should be given the same pre-conception advice as any woman with regard to ensuring immunity to rubella, varicella, and measles and, ideally, have optimized body mass index (BMI). Treatment of co-existing medical conditions should be optimized, any medication should be reviewed, and folic acid commenced. If either partner is a smoker, they should be advised to stop.

No evidence of effectiveness or otherwise for any intervention prior to pregnancy in POI was identified, except for women with Turner Syndrome (TS). Given that oocyte donation pregnancies appear to be high risk (see section V.3. Pregnancy), it would be reasonable to consider a general assessment for all women prior to oocyte donation with measurement of blood pressure and renal function, starting with creatinine.

Specific investigations are indicated according to the cause of POI.

Co-existing endocrinopathies associated with autoimmune POI should be sought and treated as described in section II.3.3 Autoimmune causes of POI. Specifically, thyroid function should be tested, as should adrenal antibodies. Genetic analysis should also be performed, if not already known, in view of the significance of Turner Syndrome in pregnancy.

Cardiotoxicity may result from prior treatment with anthracyclines, high dose cyclophosphamide or mediastinal irradiation, including chest wall irradiation for breast cancer, and the effects may be subclinical (see section V.3. Pregnancy). While risk for women without pre-existing, cardiac dysfunction is low (0.24%, 95% CI 0.00 to 0.81%), the risk with during pregnancy, and post-partum, with pre-existing disease is significantly increased (28.4%; 95% CI 15 to 44%) (Nolan *et al.*, 2020). Therefore, echocardiogram and assessment of left ventricular ejaculatory function (LVEJ) is recommended pre-pregnancy for all women exposed to anthracyclines or chest radiation (Bansal *et al.*, 2022, Ehrhardt *et al.*, 2023). 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 (Felker *et al.*, 2000).

Only one study was identified that considered pregnancy outcome in relation to myocardial function (Bar *et al.*, 2003). Fractional shortening values of 30% or more pre-pregnancy in women treated with doxorubicin in childhood were associated with no deterioration in cardiac function during pregnancy. Those with lower fractional shortening had a non-significant decrease after pregnancy but more maternal admissions to the intensive care unit and neonatal admissions to the neonatal intensive care unit as well as a higher rate of induction of labour (Bar *et al.*, 2003). However, it is not clear whether these differences were a result of clinical reaction to the known impaired cardiac function or were driven by the deterioration.

Pregnancy in women with TS is high risk. Women with TS considering pregnancy (spontaneous or oocyte donation) should have a thorough medical assessment with special consideration paid to the cardiovascular system (Gravholt *et al.*, 2017). Thyroid and liver function should be updated and screening for diabetes performed (Gravholt *et al.*, 2017) (Bondy and Turner Syndrome Study Group, 2007, Cabanes *et al.*, 2010). Resting blood pressure must be measured, and Cabanes and colleagues suggest ambulatory monitoring in addition (Cabanes *et al.*, 2010).

Congenital and acquired cardiac abnormalities should be screened for using MRI and echocardiography (Gravholt *et al.*, 2017). Women with aortic size index (ASI) > 2.5cm/m^2 should be advised against pregnancy. This is a conservative recommendation and may reflect publication bias (pregnancies with adverse outcomes being more likely to be reported). Additionally, in most of the reported case series, the proportion of women who had a cardiology assessment was relatively low and outcome may be improved when this is performed. Transthoracic echocardiography is recommended at least once during pregnancy for those without observed risk and more frequently for those with ASI > 2 or other risk factors. CT/cardiac magnetic resonance should be performed during pregnancy for suspicion of disease of the distal ascending aorta, aortic arch, or descending aorta (Gravholt *et al.*, 2017).

Aortic dissection occurred in 33% of TS women with an aortic root over 2.5 cm/m^2 in a series of 166 TS women with the average age of 36 years over a 3-year period (Matura *et al.*, 2007). The French review of practice recommends this as the cut-off above which pregnancy should be avoided or suggest a level of > 2.0cm/m^2 in those with additional risk factors including bicuspid aortic valve (BAV), coarctation of the aorta, elongated transverse arch, uncontrolled hypertension and/or liver disease (Fiot *et al.*, 2022). A previous ASRM guideline offered a more conservative recommendation with a cut-off value of 2.0 cm/m^2 (Practice Committee of American Society For Reproductive Medicine., 2012). The consensus is

that aortic root measurement is best expressed as aortic size index (ASI) due to the short stature of the affected women (Matura *et al.*, 2007).

It is also recommended a renal ultrasound scan for structural abnormalities and, if hypertensive, for renal artery stenosis along with measurement of urea and electrolytes be performed (Cabanes *et al.*, 2010).

Recommendation – see also Table V Summary – assessing fitness for pregnancy in POI

Women presenting for oocyte donation who are suspected of having POI should be fully investigated prior to oocyte donation, including thyroid and adrenal function as well as genetic testing.	⊕⊕◯◯	**STRONG**
Women previously exposed to anthracyclines, high dose cyclophosphamide or mediastinal irradiation should have an echocardiogram prior to pregnancy, and referral to a cardiologist if indicated.	⊕◯◯◯	**STRONG**
Thorough cardiac screening and appropriate counselling by a maternal–foetal medicine specialists and cardiologists with expertise in managing women with Turner Syndrome is recommended prior to planning a pregnancy, especially if oocyte or embryo donation is considered.	⊕⊕◯◯	**STRONG**
Women with POI should have their cardiometabolic and thyroid function assessed prior to pregnancy.	⊕◯◯◯	**STRONG**
Pregnancy in some women can be of such high risk that clinicians may consider oocyte donation pregnancy to be life threatening and therefore inappropriate.	⊕◯◯◯	**STRONG**

Justification

Oocyte donation pregnancies appear to be at high risk of obstetric complications, especially in women with POI and a history of chemotherapy and/or cardiac irradiation, or women with Turner syndrome.

Although no evidence was found on the effectiveness of any intervention prior to pregnancy in POI, the guideline development 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 Turner syndrome patients.

In addition to the assessment of fitness for pregnancy based obstetric risk factors, an oncology assessment to rule out recurrence prior to pregnancy could be recommended in women with POI after treatment for cancer.

TABLE V SUMMARY – ASSESSING FITNESS FOR PREGNANCY IN POI

	Idiopathic POI	Turner Syndrome	Fragile X premutation	POI after cancer treatment		POI after surgery
				chemotherapy only	chemotherapy + radiotherapy	
Standard antenatal assessment	√	√	√	√	√	√
Echocardiogram				√[1]	√[2]	
Evaluation by cardiologist		√				
Renal function	√	√	√	√	√	√
Thyroid function	√	√	√	√	√	√
Genetic evaluation[3]	√	√	√	√	√	√
Adrenal function	In case of oocyte donation					
Uterine doppler / MRI / EMBx					√ If Pelvic RT, esp. pre-pubertal	

[1] If exposed to anthracyclines or high dose cyclophosphamide.

[2] In case of mediastinal irradiation

[3] Karyotype for all + WES when clinically available

VI. POI and musculoskeletal health

Muscle and bone form an integrated locomotor unit and both menopause and aging impact musculoskeletal health. During the menopausal transition and early post-menopause, rapid bone loss in the range of 2-5% per year occurs which then slows after approximately 10 years, and thereafter is similar to that of eugonadal age-matched men, i.e. bone loss is age-related rather than reflecting hormone deficiency after that time point (Eastell *et al.*, 2016). Accelerated bone loss around menopause predominately affects trabecular bone; however, the subsequent age-related slower bone mass decline affects both cortical and trabecular bone. This is reflected in the onset of fragility fractures where spine fractures occur earlier than hip fractures (Eastell *et al.*, 2016). Peak muscle mass and strength is attained in young adulthood, being greater in men than women. The age-related decline in muscle mass accelerates after usual menopause reflecting the impact of estrogen deficiency, decreasing by approximately 1-2 % per year after age 50 and from the mid-seventies by about 0.7% per year (Cruz-Jentoft and Sayer, 2019). A greater decline in muscle strength also occurs, decreasing 10-15% per decade to age 70 and then accelerating to 25-40% (Cruz-Jentoft and Sayer, 2019).

The beneficial effects of estrogen on bone have long been recognized; however, it is increasingly recognised that estrogen is important for muscle mass and function as well. Estrogen is important for bone accrual during puberty/adolescence with attainment of peak bone mass during early adulthood (Samad *et al.*, 2020). Human and animal studies have shown that estrogen receptors α and β are expressed in multiple cell types in both muscle and bone. Estrogen signals via both classical nuclear genomic and non-genomic membrane G-protein-coupled receptor pathways (Samad *et al.*, 2020). However, the details remain unclear. Bone-muscle crosstalk via myokines and osteokines influence musculoskeletal function, growth, and repair (Samad *et al.*, 2020). Bone loss secondary to estrogen deficiency results from greater bone resorption versus formation due to decreased osteoblast function, decreased osteocyte mechano-sensing, increased osteoclast number and activity and increased T cell activation leading to increased cytokines and reactive oxygen species (Eastell *et al.*, 2016). Estrogen deficiency is also associated with: (i) loss of muscle mass via increased muscle apoptosis and protein turnover; and (ii) loss of muscle strength via loss of type II (fast twitch) fibres, dysregulated muscle metabolism, lipid infiltration and impaired myosin function (Samad *et al.*, 2020). In addition, reduced levels of other hormones including, testosterone, insulin-like growth factor-1 and dehydroepiandrosterone, may also contribute to loss of muscle mass and function. Lower muscle mass and function is associated with bone microarchitecture abnormalities, decreased bone size, and bending strength (Kirk *et al.*, 2020).

Clinical consequences of these interacting musculoskeletal changes are an increased incidence of osteoporosis (low bone mass with deteriorated microarchitecture leading to fragility fractures (de Villiers and Goldstein, 2021), sarcopenia (loss of skeletal muscle mass and function) (Cruz-Jentoft and Sayer, 2019) and osteosarcopenia (sarcopenia associated with bone loss) (de Villiers and Goldstein, 2021). Osteosarcopenia is associated with increased morbidity, including cardiometabolic disease, and mortality.

VI.1. Skeletal health

PICO Question: What are the consequences of POI for skeletal health?

The effect of POI on skeletal or bone health is among the most clearly established adverse consequences of the condition and a key concern for women (Deeks *et al.*, 2011). Underlying mechanisms for POI associated low bone mass include: (i) reduced bone accrual and failure to achieve peak bone mass; (ii)

increased bone resorption associated with estrogen deficiency; (iii) presence of POI associated co-morbidities that increase the risk of osteoporosis such as rheumatoid arthritis or coeliac disease; and (iv) factors specific to the cause of POI, for example Turner Syndrome (TS) (Gravholt and Backeljauw, 2017, Samad *et al.*, 2020). The relative contributions of reproductive (estrogen deficiency), socioeconomic, health behavioural, and genetic factors to bone health in POI must be considered and many details have yet to be determined.

Bone mineral density (BMD)

The World Health Organization (WHO) has defined 'osteoporosis' as a condition where BMD values fall by 2.5 standard deviations below those of young, healthy women (represented by a T-score<-2.5), whereas 'osteopenia' refers to T-score -1.0 to -2.5 (International Society for Clinical Densitometry, 2019, de Villiers and Goldstein, 2021). Using BMD to assess fracture risk in young adult populations, including those with POI, can be problematic since the correlation between BMD and fracture risk in such cohorts is not fully established. The International Clinical Densitometry Society has suggested avoiding the terms "osteopenia" and "osteoporosis" for premenopausal women under 50 years of age and instead use "low bone mass" when BMD is 2.0 standard deviations below age and sex-matched populations (Z-score ≤-2.0) (International Society for Clinical Densitometry, 2019). However, the International Osteoporosis Foundation proposed that BMD T-score ≤-2.5 may be used to diagnose osteoporosis in young adults with chronic conditions known to influence bone metabolism as long as peak bone mass has been achieved (Ferrari *et al.*, 2012). In addition, reduced height is characteristic of TS and BMD should be adjusted to allow for this as otherwise BMD would be underestimated.

Reduced BMD compared to reference populations has been established in many studies investigating women with POI of different aetiologies. This includes women with idiopathic POI, TS, galactosemia, Fragile X premutation, gonadal dysgenesis, iatrogenic POI and in populations of mixed aetiology (Gravholt and Backeljauw, 2017). However, the magnitude varies reflecting differences in POI aetiology, ethnicity, study design, reference population, duration of amenorrhoea, HRT use and presence of other osteoporosis risk factors.

A 2023 systematic review of eight studies assessing the effect of HT on BMD in women with POI (including 977 women with idiopathic POI, 698 premenopausal controls, and 55 postmenopausal controls) reported that women with POI had lower lumbar spine (mean difference ranged from 0.028 to 0.43 g/cm^2) and femoral neck (mean difference ranged from 0.025 to 0.047g/cm^2) BMD than control subjects (Costa *et al.*, 2023). African, American, and Asian women with POI were found to have a greater risk of having Z-score< -2.0 (Costa *et al.*, 2023). Similar findings have been reported in other studies. A study of 70 Indian women with non-iatrogenic POI reported 11.5%, 11.4%, and 9.1% lower mean BMD values at the lumbar spine, hip, and forearm respectively ($p<0.01$) compared to 70 age-matched controls (Dhakate *et al.*, 2023). A case-control study observed that mean lumbar spine and femoral BMD was lower in 240 Chinese women with spontaneous normal karyotype POI compared to 260 perimenopausal controls, but higher than 260 postmenopausal controls (Luo *et al.*, 2018). A retrospective study of 162 Italian women with POI of diverse causes observed lower BMD in primary versus secondary amenorrhoea (Bakhsh *et al.*, 2015).

Later induction of puberty was associated with lower BMD in women with POI including TS (Nakamura *et al.*, 2015, Gravholt and Backeljauw, 2017, Nguyen *et al.*, 2017, Cardona Attard *et al.*, 2019).

Women with TS have increased prevalence and risk (OR 9.8; 95% CI 1.9 to 49.9 adjusted for height and BMI) of low bone mass compared to controls (Nguyen *et al.*, 2017). Lumbar spine BMD (but not total hip BMD) was significantly lower in 267 TS women compared to 67 women with POI (Cardona Attard *et al.*, 2019). TS women who have spontaneous menses have higher spine BMD than those with primary amenorrhoea (Nakamura *et al.*, 2015). Late initiation of HRT after 18 years or non-use of HRT was

associated with lower lumbar spine BMD (Nakamura *et al.*, 2015). Although BMD does not appear to be associated with TS karyotype (Gravholt and Backeljauw, 2017), recent studies reported variation in femoral neck bone density with estrogen receptor 1 (ESR1) polymorphism pattern (Scalco *et al.*, 2019) and an association between low BMD and variants in the CYP27B1 gene (Barrientos-Rios *et al.*, 2019).

Bilateral oophorectomy (BO) was associated with decreased lumbar spine BMD by up to 8% and at the hip by up to 5.7% within 2 years post-surgery in a prospective longitudinal study (Jiang *et al.*, 2021). Similar reductions in lumbar spine (7.8%) and hip (5.2%) BMD at 2 years follow-up were reported in women (mean age 42.8 years) with early surgical menopause secondary to risk reducing BO and not treated with HT (Jiang *et al.*, 2021).

A substantial difference in BMD (8.3%) was reported between chemotherapy-associated POI (24 women treated for lymphoma) and age-matched controls (Ratcliffe *et al.*, 1992). In a study of women with POI following chemotherapy for cancer assessed at a mean age of 37, 21% (7 of 33) had a Z-score of <-2 for at least one of 4 skeletal sites surveyed, only 1 of whom was taking estrogen replacement (Howell *et al.*, 1998). As BMD in a cohort of 26 women treated for lymphoma who did not have POI was similar to controls, the decreased BMD was not attributed to the drugs involved in treatment (Ratcliffe *et al.*, 1992), although there had been an interval of several years since treatment. However, in prospective analysis of changes in BMD during chemotherapy for early breast cancer and in relation to ovarian function, an adverse effect of the chemotherapy in addition to the effect of loss of ovarian function was identified (Cameron *et al.*, 2010).

A study of 985 Serbian women, median age 64 years, reported that those with early menopause defined as ≤ 45 years) reported lower median femoral neck BMD in both women with and without previous fracture compared to those with menopause after age 45 years (Minaković *et al.*, 2023).

Prevalence of low bone mass and osteoporosis

A higher prevalence of low bone mass[9] and osteoporosis[10] () is reported in women with POI; however, the extent and study quality varies according to study design, sample size, comparators, diagnostic criteria used, presence of co-morbidities and cause of POI. A cohort study of Canadian women (n= 12329; mean age 65 years at follow-up) observed a higher rate of self-reported osteoporosis in women with POI versus normal age menopause (21.9% versus 16.7%) (Shea *et al.*, 2021). Similar findings were reported in an Australian prospective cohort of 5107 women; spontaneous menopause ≤40 years (mean age 38.2 years) was associated with the highest prevalence of osteoporosis (26.5%) at age 59-64 and an increased risk of osteoporosis (OR 2.54; 95% CI 2.63 to 3.96) compared to menopause at age 50-51 years (Xu *et al.*, 2020). Women with POI were more likely to have multiple co-morbidities, smoke, have low levels of physical activity and be less educated (Xu *et al.*, 2020).

The reported prevalence of DXA defined osteoporosis in spontaneous normal karyotype non-iatrogenic POI varies from 5-14% (Bachelot *et al.*, 2009, Popat *et al.*, 2009, Podfigurna *et al.*, 2020, Beitl *et al.*, 2021, Shea *et al.*, 2021, Samad *et al.*, 2022). A Canadian study of 374 women with POI indicated osteoporosis prevalence of 9.3% with a 69% increased risk of osteoporosis compared to women with usual age menopause (aOR 1.69; 95% CI 1.07 to 2.66) (Shea *et al.*, 2021). An osteoporosis prevalence of approximately 17% associated with non-iatrogenic POI was observed in a Brazilian (n=72; excluding those with primary amenorrhoea)(Benetti-Pinto *et al.*, 2015a) and a European cohort (n=195) (Vogt *et al.*, 2022). The reported prevalence of low bone mass varied from 13% (Samad *et al.*, 2022) to 85% in an Indian cohort (n=20) with 75% having vitamin D deficiency (Dutta *et al.*, 2016). A higher prevalence of low bone mass was observed in women with non-iatrogenic POI compared with controls including

[9] Low bone mass is defined as Z score <-2 unless otherwise indicated.

[10] Osteoporosis is defined as T score <-2.5 unless otherwise indicated.

lumbar spine (35.7% versus 11.4% ; P<0.01), hip (20% versus 4.3%; P=0.01) and forearm (15.2% versus 0%; P < 0.01)(Dhakate *et al.*, 2023). The prevalence of self-reported osteoporosis was 26.4% in a cohort of 87 women with Fragile X premutation POI (Allen *et al.*, 2020).

A Danish national registry study (n=1156 women with TS and 115577 age matched controls) reported a seven-fold increased risk of osteoporosis after TS diagnosis compared to controls (incidence rate ratio 6.6; 95% CI 4.4 to 9.9)(Viuff *et al.*, 2020). A study of 150 women with TS (mean age 31 years) reported the prevalence of DXA defined osteoporosis as 12% and 52% had osteopenia (Freriks *et al.*, 2011). A study of 26 women with TS treated with hormone therapy (HT) (mean age 23.5 years) reported osteoporosis in 10.4% (Faienza *et al.*, 2015). Low lumbar spine bone mass was observed in 26% of TS participants in an Australian cohort (n=58, mean age 28.5 years) (Nguyen *et al.*, 2018). In contrast, 89.5% of 19 Turkish adolescents with POI (predominately due to TS, mean age 14.2 years) had low bone mass (Özbek *et al.*, 2016).

The prevalence of osteoporosis in iatrogenic POI was 12.2% in a cross-sectional European study, lower than the prevalence in non-iatrogenic POI (p=0.034)(Vogt *et al.*, 2022). The prevalence of osteoporosis was 18% in a study of 27 women with POI following bone marrow transplantation, mean age 31 years, of whom only one was taking estrogen replacement (Castaneda *et al.*, 1997). A systematic review reported an osteoporosis prevalence of 9-13% in premenopausal women (although not confined to women under age 40 years) undergoing risk reducing BO (Gaba and Manchanda, 2020). Bilateral oophorectomy and chemotherapy for gynaecological cancer has also been associated with a higher prevalence of low BMD in comparison to oophorectomy for benign indications (39% versus 15%; p=0.009) (Stavraka *et al.*, 2013).

Fracture

There are substantial data linking low BMD to fracture risk in postmenopausal women (Eastell *et al.*, 2016) but there is limited data specifically assessing fracture in women with POI and findings are mixed. A 2019 systematic review assessing fracture risk and menopausal age reported no significant difference in fracture risk or hip fracture incidence between women with POI compared with menopausal women over 45 or 50 years of age on the basis of two studies (Anagnostis *et al.*, 2019). However, early menopause was associated with an increased fracture risk (OR 1.36; 95% CI 1.11 to 1.66; p<0.002) (14 studies included) and this finding persisted when only fragility fractures were included (OR 1.48, 95% CI 1.11 to 1.97; p=0.007) (Anagnostis *et al.*, 2019). Consistent with this, a study of 985 Serbian women, median age 64 years, reported increased risk of hip fracture calculated by FRAX scores (OR 1.6; 95% CI 1.14 to 2.34) in women with early menopause (defined as ≤45 years) compared to women with menopause occurring after age 45 years (Minaković *et al.*, 2023). A recent Indian cohort study of 70 women with non-iatrogenic POI observed a higher prevalence of vertebral fractures (15.7% versus 4.3%; P=0.045) compared to 70 controls (Dhakate *et al.*, 2023).

Women with TS have an increased risk of fracture (reported risk ratios ranging from 1.35 to 3.2) (Gravholt and Backeljauw, 2017, Viuff *et al.*, 2020). Fracture risk is further increased in women aged >45 years, co-existing hearing impairment, balance problems and low BMI, but reduced in those with spontaneous menstruation (Gravholt and Backeljauw, 2017, Wasserman *et al.*, 2018, Cardona Attard *et al.*, 2019). A cross-sectional UK study assessing 267 women with TS and 67 karyotypically normal POI reported that women with TS had a higher prevalence of major osteoporotic fractures compared to those with normal karyotype POI (52.7% versus 30.2%; p=0.012) although the overall fracture prevalence was similar (30.7% versus 32.8%)(Cardona Attard *et al.*, 2019). Overall self-reported fracture prevalence was similar in a USA study of 711 TS women compared to 231 controls (41.8% versus 29.4%; p>0.05); however, in those aged 25 years or older, fracture prevalence was higher in TS women (57.7% versus 46.4%; p=0.03)(Wasserman

et al., 2018). Fracture prevalence was also higher in TS women aged 25 years or older who discontinued HT compared to those who continue HT (67.4% versus 47.7%; p=0.003)(Wasserman *et al.*, 2018).

Risk factors for reduced BMD and fracture.

Identified risk factors for low BMD and osteoporosis in women with POI include: primary amenorrhoea, longer duration of amenorrhoea/ menopause, age <20 years at onset of irregular menses, >1 year delay in diagnosis, African or Asian ethnicity, low serum vitamin D concentrations, low dietary calcium intake, smoking, non-adherence or shorter duration of estrogen replacement, lower BMI and lack of exercise (Bachelot *et al.*, 2009, Popat *et al.*, 2009, Bakhsh *et al.*, 2015, Nakamura *et al.*, 2015, Nguyen *et al.*, 2017, Wasserman *et al.*, 2018, Cameron-Pimblett *et al.*, 2019, Cardona Attard *et al.*, 2019, Samad *et al.*, 2020, Beitl *et al.*, 2021, Costa *et al.*, 2023, Dhakate *et al.*, 2023, Minaković *et al.*, 2023). Abnormal autoimmune screening was associated with a lower T score (p=0.01) in a study of idiopathic POI (n=76) (Beitl *et al.*, 2021) (see Figure 11).

Other Bone assessment modalities

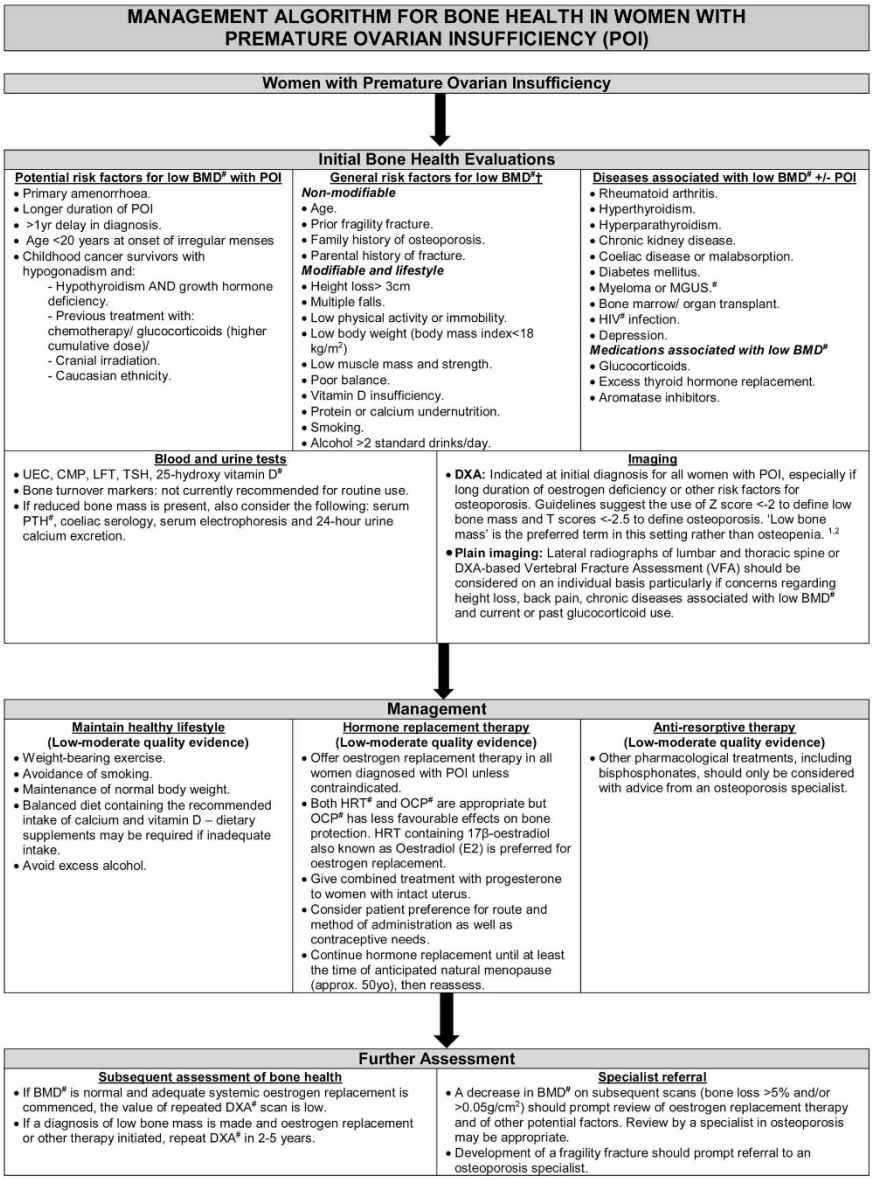
DXA derived BMD only provides a measure of 60-80% of bone strength. Other imaging techniques such as trabecular bone score, quantitative ultrasound (QUS), quantitative computed tomography (QCT) provide greater insights into bone geometry and microarchitecture. However, studies in POI are few and relevance to fracture risk is yet to be established.

Trabecular bone score (TBS)

Trabecular bone score (TBS) provides a DXA-derived analysis of the lumbar spine trabecular microarchitecture, is an independent predictor of fracture risk and is now incorporated into fracture risk tools (International Society for Clinical Densitometry, 2019). However, this tool is not recommended for women younger than 20 years old or those with a BMI over 37 kg/m2 (International Society for Clinical Densitometry, 2019). A higher prevalence of degraded TBS is reported in women with POI of mixed causes including non-iatrogenic POI, iatrogenic POI and TS compared with controls (Nguyen *et al.*, 2018, Samad *et al.*, 2022, Dhakate *et al.*, 2023). Fracture prevalence was greater in women with degraded TBS in women with TS or non-iatrogenic POI (Nguyen *et al.*, 2018, Dhakate *et al.*, 2023). TBS was a superior predictor of fracture in women with TS compared to BMD (Nguyen *et al.*, 2018). Age, duration of amenorrhea, and HRT use were significant predictors of TBS in women with POI (Nguyen *et al.*, 2018, Dhakate *et al.*, 2023).

Quantitative CT Although not widely available, peripheral (pQCT) and high resolution QCT (HRQCT) have advantages over DXA as they provide three-dimensional measures of volumetric BMD, bone geometry and morphometry of separate bone compartments, mechanical properties, and integral bone strength without being influenced by bone size (Samad *et al.*, 2020). Studies involving pQCT and HR QCT have shown compromised microarchitecture and lower bone strength in women with TS (Hansen *et al.*, 2012, Gravholt and Backeljauw, 2017). This may explain the increased fracture risk that is observed in TS women with 'normal' DXA defined areal BMD (Gravholt and Backeljauw, 2017). Significant decreases in volumetric cortical BMD and bone strength measures were observed at 24 months follow-up in women with early menopause following risk reducing BO who did not use HRT compared to HRT users or age matched controls (Jiang *et al.*, 2021).

FIGURE 11 MANAGEMENT ALGORITHM FOR BONE HEALTH IN WOMEN WITH POI (REPRODUCED FROM (KIRIAKOVA *ET AL.*, 2019), PERMISSION PENDING)



† FRAX risk calculator is not validated for use in women<40 years.

BMD – Bone mineral density, MGUS – Monoclonal gammopathy of undetermined significance, HIV – Human immunodeficiency virus, CMP - Calcium, magnesium, phosphate, UEC - Urea, electrolytes, creatinine, LFT - Liver Function tests, TSH - Thyroid stimulating hormone, PTH – Parathyroid hormone, HRT – Hormone replacement therapy, OCP – oral contraceptive pill, FRAX – Fracture risk assessment tool.

1. ESHRE Guideline Group on POI, et al. "ESHRE Guideline: management of women with premature ovarian insufficiency." *Human Reproduction* 31.5 (2016): 926–937.

2. Ferrari, S., et al. "Osteoporosis in young adults: pathophysiology, diagnosis, and management." *Osteoporosis International* 23.12 (2012): 2735–2748.

Recommendations

Women with POI and HCPs should be aware that POI is associated with abnormal bone microarchitecture and reduced bone mineral density (BMD)	⊕⊕◯◯ **STRONG**

It is suggested that HCPs inform women that POI may be associated with an increased risk of fracture later in life, although this has not been adequately demonstrated	⊕◯◯◯ CONDITIONAL

Justification

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.

VI.2 Bone protection and improvement

PICO Question: What are the treatment options for bone protection and improvement?

A systematic appraisal of guidelines regarding management of bone health in women with POI reported variable quality and evidence and recommendation gaps (Kiriakova *et al.*, 2019).

Non-pharmacological approaches

Low serum Vitamin D, physical inactivity, low calcium intake and smoking have been identified as risk factors for low BMD in women with POI. A balanced diet, adequate calcium and vitamin D intake, weight-bearing exercise, maintaining a healthy body weight and cessation of smoking and moderation of alcohol intake are primary goals in reducing fracture risk in postmenopausal women (Eastell *et al.*, 2019, Camacho *et al.*, 2020, de Villiers and Goldstein, 2021). While there are few data directly relating to women with POI, it is considered that the same beneficial effects will apply.

An observational study of 70 Indian women with idiopathic POI reported that vitamin D deficiency increased vertebral fracture risk and fracture risk decreased 9% for every 2.5nmol increase in Vitamin D levels (OR 0.910; 95% CI 0.837 to 0.988; p=0.025) (Dhakate *et al.*, 2023). Addition of eldecalcitol, a vitamin D analogue, to HRT (0.625mg dose CEE or 0.72mg transdermal estradiol patch) increased spine bone density after 12 months compared to baseline (–2.37 ± 0.57g/cm^2 versus –2.62 ± 0.55 g/cm^2; P<0.05) in an uncontrolled study of Japanese women with TS with vitamin D deficiency (Tsuburai *et al.*, 2018).

Although not specific to POI, a systematic review which included five cohort studies in Asian populations reported that higher consumption of soy containing foods was associated with a reduced risk of fracture in pre-and perimenopausal women and postmenopausal women within 10 years of menopause (Akhavan Zanjani *et al.*, 2022).

A randomised study involving 32 BRCA positive breast cancer survivors (not taking adjuvant endocrine therapy or HRT) with early surgical menopause investigating a commercially available online lifestyle program, which included strength training, assessed bone health as a secondary outcome and observed increased cortical volumetric bone density (+0.3mg/cm^3 versus -0.4 g/cm^3; P=0.02), but not total body BMD, compared to a waitlist control group at 12 months follow-up (Sturgeon *et al.*, 2017).

A survey of 316 women with POI/ EM indicated that osteoporosis knowledge, beliefs and self-efficacy predicted calcium intake, physical activity, and osteoporosis screening behaviours (Goh *et al.*, 2019). These findings indicate the importance of providing information regarding bone health to women and the codesigned consumer website/App 'Ask Early Menopause' was developed in response to this (www.askearlymenopause.org).

Hormone therapy

An extensive evidence base and guidelines exist for the role of HRT in management of osteoporosis in postmenopausal women (Zhu *et al.*, 2016, Eastell *et al.*, 2019, de Villiers and Goldstein, 2021). In contrast, studies of the effects of HRT on BMD in women with POI are heterogenous, many with small sample sizes and methodological limitations. No RCTs have fracture as a primary outcome. Non-use, delayed initiation, interrupted and/or shorter duration of estrogen therapy is associated with reduced BMD and increased risk of fracture.

A 2022 systematic review of 14 studies (6 RCT and 8 cohort studies; n=4004, median age 31 years) investigating the effect of HRT on BMD in women with POI of diverse aetiologies reported that HRT increased or maintained BMD (Gonçalves *et al.*, 2022). In five studies, HRT was superior to non-treatment, placebo, calcitriol or calcium supplementation and meta-analysis (4 studies; n= 197 women) reported 3.27% (95% CI 1.89 to 4.65) increase in mean difference lumbar spine BMD per year with HRT compared to controls (Gonçalves *et al.*, 2022). An earlier systematic review of women with diverse POI aetiologies and some differences in the included studies, reported mixed findings with significant increases reported in 3/6 studies with bone outcomes and otherwise no significant effect or inconclusive findings (Burgos *et al.*, 2017). A recent observational study of 70 Indian women with non-iatrogenic POI reported higher prevalence of low bone mass in HRT non-users compared to users (51.9% vs. 25.6%; p=0.04) (Dhakate *et al.*, 2023). Lumbar BMD and TBS increased with duration of HRT (p<0.001). However, in the stratified analysis there was no difference in frequency of vertebral fractures and TBS between women with or without HRT (Dhakate *et al.*, 2023). A cross-sectional UK study indicated that women with POI using HRT had higher spine BMD than non-users (−1.1 g/cm^2 ; 95% CI −4.3 to 2.7 versus -1.4 g/cm^2; 95% CI −3.4 to 2.2; p=0.031)(Cardona Attard *et al.*, 2019). Follow-up (mean 7.4 years) of a French cohort (n=162) with idiopathic POI observed a significant reduction in femoral BMD in women who had ceased their HRT for more than one year compared to women who continued HRT (-57 mg/cm^2 per year versus -13 mg/cm^2 per year; P= 0.009)(Bachelot *et al.*, 2016). Similarly, interrupted HRT use was associated with declines in femoral neck BMD (-0.020g/cm^2 per year,95% CI -0.037, 0.0030; P=0.025) and TBS (-0.0070 per year, 95% CI −0.011, −0.0020), P=0.007) (Samad *et al.*, 2022). A lower risk of osteoporosis was observed with current (OR 0.65 (95% CI: 0.46 to 0.91) and past (OR 0.76 (95% CI: 0.63 to 0.90) HRT use in a large cohort of Canadian women (Shea *et al.*, 2021).

A 2023 systematic review examined the effect of hormone preparation on BMD in women with idiopathic POI (TS excluded) included 9 studies with varying HRT regimens including use of the combined oral contraceptive (COC). The authors reported increased femoral neck and lumbar spine BMD with regimens containing 2 mg estradiol, 1.25 mg CEE, 100 µg transdermal estradiol or continuous 30 µg ethinyl estradiol COC: but not with lower doses of estradiol/ CEE, tibolone or non-continuous COC use (Costa *et al.*, 2023). These findings are consistent with a 2022 meta-analysis (28 studies, n=4004) which reported that HRT use was associated with a greater BMD effect compared to non-continuous COC (mean difference 1.95% per annum; 95% CI 0.48-3.43)(Gonçalves *et al.*, 2022).

A national registry study reported that HRT treatment in TS women was associated with a significantly lower risk of hospital admissions for osteoporotic fractures (HR 0.37; 95% CI 0.14 to 0.99) compared to those not treated with HRT and was similar to general population controls (HR 1.3; 95% CI 0.7 to 2.4) (Viuff *et al.*, 2020). A significant increase in lumbar spine BMD was reported with estradiol (mean difference 0.09 g/cm^2; 95% CI 0.04 to 0.14), but not CEE or ethinyl estradiol, in a systematic review of studies (12 RCTs and 13 observational studies) involving women with TS aged under 40 years (Cintron *et al.*, 2017). Later age at initiation of estrogen and interrupted use of HRT is associated with lower BMD and TBS (Nguyen *et al.*, 2018, Wasserman *et al.*, 2018, Cardona Attard *et al.*, 2019). A UK cohort of 799 TS women showed that bone density T-scores of the hip and spine were negatively correlated with age at estrogen initiation (r = 20.20 and r = 20.22 respectively; p≤0.001) (Cameron-Pimblett *et al.*, 2019).

Meta-analysis of 2 studies (n=52 adolescents) concluded that transdermal estrogen was associated with a greater increase in whole body BMD z-score that oral estrogens (Zaiem *et al.*, 2017, Cameron-Pimblett *et al.*, 2019). Increased BMD over time was observed in a five- year RCT involving 20 women with TS (mean age 19 years) with no difference between those randomised to 2 or 4 mg estradiol (Cleemann *et al.*, 2017).

An observational Korean study of 234 females with POI post allogeneic hematopoietic stem cell transplantation, median age 30.8 years, reported that lumbar spine BMD gains was significantly greater in the HRT group (2 mg estradiol) compared with the non-HRT group, after the first (4.16 ± 4.39% versus +2.61 ± 7.50%, P =0.033) and second year of treatment (5.42 ± 5.86% vs 3.80 ± 6.00%; p=0.047) (Ha *et al.*, 2020). No significant changes were observed in hip/ femoral BMD(Ha *et al.*, 2020). At two years follow-up, early initiation within 12 months was associated with greater spine BMD (6.31±3.89% versus 3.10±4.94%; p=0.013) and total hip BMD gains (3.35±3.99% versus 1.39±3.94%; p=0.002) compared to delayed HRT initiation (Ha *et al.*, 2020). Similar findings were reported in 38 French women with POI secondary to chemo-radiotherapy for haematological malignancies treated with HRT (9–13-year follow-up) where an increase in spine BMD (+0.015g/cm^2 per year; 95% CI 0.002 to 0.028) but not hip BMD was observed (Naessén *et al.*, 2014). In contrast, an earlier Italian RCT, reported no significant change in spine or femoral BMD with HRT containing 2 mg estradiol in women with POI secondary to allogenic stem cell transplantation (Tauchmanovà *et al.*, 2006). A prospective cohort study reported that HRT use attenuated BMD loss in women with early menopause secondary to risk reducing bilateral salpingo oophorectomy (BSO)(Jiang *et al.*, 2021).

No specific evidence was found regarding optimal progestogen regimen with POI in regard to bone health (see XI.3. HT – treatment options).

Testosterone

Following non-iatrogenic and iatrogenic POI, ovarian testosterone production is low/lost, with a 50% reduction in testosterone levels (Soman *et al.*, 2019). A recent systematic review concluded that testosterone replacement improves sexual function in postmenopausal women; however, the effect on bone is mixed which may reflect small sample sizes and differing testosterone preparations used (Islam *et al.*, 2019a). Limited data exists regarding androgen replacement and bone health in women with POI. No significant alteration in BMD gain was found with the addition of testosterone to HRT (mean difference 0.05; 95% CI -2.45 to +2.55) as reported in a meta-analysis of two studies involving 145 women with non-iatrogenic POI and the other study including 15 women with TS (Gonçalves *et al.*, 2022). No studies were identified on DHEA treatment and bone density outcomes for surgically menopausal women or those with non-iatrogenic POI (see also XI.5. Testosterone Therapy).

Pharmacological approaches

Bone specific therapies including bisphosphonates, selective estrogen receptor modulator raloxifene, denosumab, romosozumab, teriparatide and abaloparetide reduce fracture risk in postmenopausal women (Eastell *et al.*, 2019, Kanis *et al.*, 2019, Camacho *et al.*, 2020, de Villiers and Goldstein, 2021, North American Menopause Society, 2021). Combined calcium and vitamin D supplements in a daily dose of 0.5–1.0 g and 400–800 IU, respectively, are generally recommended in patients receiving bone-specific therapy, since most randomised controlled trial evidence for the efficacy of interventions is based on co-administration with calcium and vitamin D supplements (Eastell *et al.*, 2019, Kanis *et al.*, 2019, Camacho *et al.*, 2020, de Villiers and Goldstein, 2021).

A RCT involving women with POI secondary to chemotherapy for stem cell transplantation reported significant lumbar spine BMD gains at 12 months with weekly oral risedronate (5.8±2.1%; p<0.05) and intravenous (a monthly infusion for three consecutive months) zoledronate (8.6±7%; p<0.05) compared

to HRT or calcium/ vitamin D supplementation alone (Tauchmanovà *et al.*, 2006). Femoral neck BMD also increased with zoledronate (5.4±2.2%) but not risedronate therapy. Zoledronate is effective in preventing bone loss in premenopausal women with chemotherapy induced amenorrhoea and/or adjuvant endocrine therapy for breast cancer (Shapiro *et al.*, 2011, Waqas *et al.*, 2021, Ebeling *et al.*, 2022). A non-randomised clinical study of 86 Japanese women, mean age 42 years, with BSO for management of benign or malignant gynaecological disease, reported higher femoral neck and spine BMD at 12-, 24- and 36-month's follow-up in patients treated with the bisphosphonate, minodronic acid (1mg/day) compared to no treatment (HT users were excluded) (Okumura *et al.*, 2022). Bisphosphonates remain incorporated in bone for a long period of time, especially zoledronate, which has led to concern over use in young women, and particularly in relation to future pregnancy. There is no direct trial evidence, but it is regarded as prudent to withdraw oral bisphosphonate therapy prior to pregnancy. However, the recommended duration cited varies from three to twelve months (Stathopoulos *et al.*, 2011, Schreiber *et al.*, 2023). Bisphosphonate use was higher in women with TS compared to non-iatrogenic POI (9.8% versus 2.2%; p=0.006)(Cardona Attard *et al.*, 2019).

There are no trials of other bone specific agents in women with POI. Selective estrogen receptor modulators (SERMs) have mixed functional estrogen receptor agonist or antagonist activity, depending on the target tissue, and this varies between drugs. Conjugated estrogens (0.45mg) combined with bazedoxifene improves bone density in postmenopausal women (de Villiers and Goldstein, 2021, North American Menopause Society, 2021) but has not been investigated in women with POI. Tamoxifen is beneficial for bone health in postmenopausal but not premenopausal women (Ebeling *et al.*, 2022). Other bone specific agents have been used in small studies/ case reports of younger women with secondary hypogonadism with mixed results (Ebeling *et al.*, 2022).

Recommendations

The guideline group recommends that HCPs advise women with POI regarding bone health.		**GPP**
The guideline group recommends that osteoporosis risk factors should be identified.		**GPP**
The guideline group recommends that women with POI should be advised to maintain a healthy lifestyle, involving weight-bearing exercise, avoidance of smoking, and maintenance of normal body weight to optimize bone health.		**GPP**
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 value in women with low BMD.	⊕⊕◯◯	CONDITIONAL
Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.	⊕⊕◯◯	**STRONG**

A daily dose of HT containing at least 2mg oral estradiol or 100 µg transdermal estradiol or equivalent is suggested to optimise bone density.	⊕◯◯◯	CONDITIONAL
Delayed initiation and non-adherence of estrogen replacement should be avoided.	⊕◯◯◯	STRONG
The combined oral contraceptive pill may be appropriate for some women. A continuous or extended regimen is recommended.	⊕⊕◯◯	CONDITIONAL
Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies to women desiring pregnancy.	⊕⊕◯◯	STRONG

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.

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 is 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 suggests no benefit for bone health with the addition of testosterone therapy to HRT.

There is little data regarding the use of bone-specific therapies for osteoporosis in POI.

VI.3. Monitoring of skeletal health

PICO QUESTION: How should skeletal health be monitored in women with POI?

Initial and ongoing assessment of bone health should identify and address modifiable risk factors (Kiriakova *et al.*, 2019).

Dual-Energy X-ray Absorptiometry (DXA) is the key investigation in the diagnosis and management of women with suspected osteoporosis (Eastell *et al.*, 2019, International Society for Clinical Densitometry, 2019, Kanis *et al.*, 2019, Camacho *et al.*, 2020, de Villiers and Goldstein, 2021). While DXA is considered the 'gold standard' method of BMD measurement, it has limitations including (very low) use of ionizing

radiation, large size of the equipment, high cost, and limited availability in some regions. However, there is a paucity of evidence regarding the use of other imaging techniques in POI.

DXA scan is suggested by most guidelines to provide a baseline measurement at POI diagnosis (Kiriakova *et al.*, 2019) especially in the setting of long duration of estrogen deficiency or other risk factors (e.g. history of low impact fractures). If a baseline DXA is performed, BMD is within the normal range and women are receiving adequate estrogen replacement, it is unclear when BMD measurement should be rechecked. DXA involves X-rays, which should be avoided unless there is a specific indication, although radiation exposure from DXA is very low. Postmenopausal osteoporosis guidelines vary regarding the interval at which repeat DXA measurement should be performed; ranging from every 1-2 years (Camacho *et al.*, 2020), 3 years (Eastell *et al.*, 2019, North American Menopause Society, 2021) or 5 years (Kanis *et al.*, 2019). Non-adherence or suspicion of continuing bone loss due to secondary factors e.g., antihormonal therapy in breast cancer patients or in the initial phase of treatment of women with moderate to severe osteoporosis, this time interval should be shortened.

FRAX® is a computer-based algorithm (http://www.shef.ac.uk/FRAX) that calculates the 10-year probability of a major fracture (hip, lumbar spine, humerus, or wrist fracture) and the 10-year probability of hip fracture from age, body mass index and dichotomized risk factors. BMD data can also be added to improve predictive accuracy. Because fracture probability differs markedly by geography, FRAX is calibrated to those countries where the epidemiology of fracture and death is known. An important consideration in POI is the lower age for which this tool is applicable is currently 40 years.

Biochemical markers of bone resorption (C-telopeptide (CTX) and urinary N-telopeptide (NTX)) and bone formation (procollagen type 1 N propeptide (PINP) and bone specific alkaline phosphatase (BSAP)) are useful for the prediction of fractures and rapid bone loss and are recommended for monitoring the treatment of osteoporosis (adherence and response) (Eastell *et al.*, 2019, Kanis *et al.*, 2019, Camacho *et al.*, 2020). The use of bone turnover markers to aid assessment of response to treatment is based on their more rapid response (typically within 3 months) than changes in BMD. However, assay variability and poor standardization have limited the use of bone turnover markers in clinical practice. There is limited data regarding POI and bone turnover markers. In the RCT conducted by Cartwright et al., both P1NP and CTX declined after the administration of COC and HRT (2mg estradiol) for 6, 12, and 24 months when compared to the baseline levels in women with non-iatrogenic POI, with no significant difference between hormone therapies during follow-up (Cartwright *et al.*, 2016). Three months after commencing HRT containing 100 µg estradiol patch, there was no difference in bone resorption marker levels (CTX) between women with idiopathic POI and controls (Popat *et al.*, 2014) however, the bone formation marker (BSAP) was significantly higher in women with idiopathic POI (12.6 versus 11.4 ng/ml; p=0.04)(Popat *et al.*, 2014). Similar findings were observed in a randomised crossover study involving 34 women with diverse causes of POI where a reduction in bone resorption markers was observed with 12 months treatment with both the cyclic COC and HRT (100 µg estradiol patch) compared to baseline (Crofton *et al.*, 2010). However, the pattern of bone formation marker response (P1NP and BSAP) varied with significant increases observed with transdermal estradiol but decreases with COC use. These findings may help to explain the differences in BMD results observed between cyclic COC and HRT regimens (Costa *et al.*, 2023).

Recommendations

It is important to consider bone health at diagnosis of POI, and during ongoing care. Osteoporosis risk factors should be identified and addressed.	⊕◯◯◯ **STRONG**

Where available, measurement of BMD at initial diagnosis of POI is recommended for all women.	⊕⊕◯◯	**STRONG**

In case of a diagnosis of osteoporosis or low bone mass in women with POI, BMD measurement should be repeated within 5 years. A decrease in BMD should prompt review of estrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate.	⊕◯◯◯	**STRONG**

If BMD is normal and adequate systemic estrogen replacement is commenced, the value of repeated DXA scan within 5 years is low.	⊕◯◯◯	**STRONG**

Assessment of bone turnover markers can be considered as it may be useful in monitoring response and adherence to therapy.	⊕◯◯◯	**CONDITIONAL**

Justification

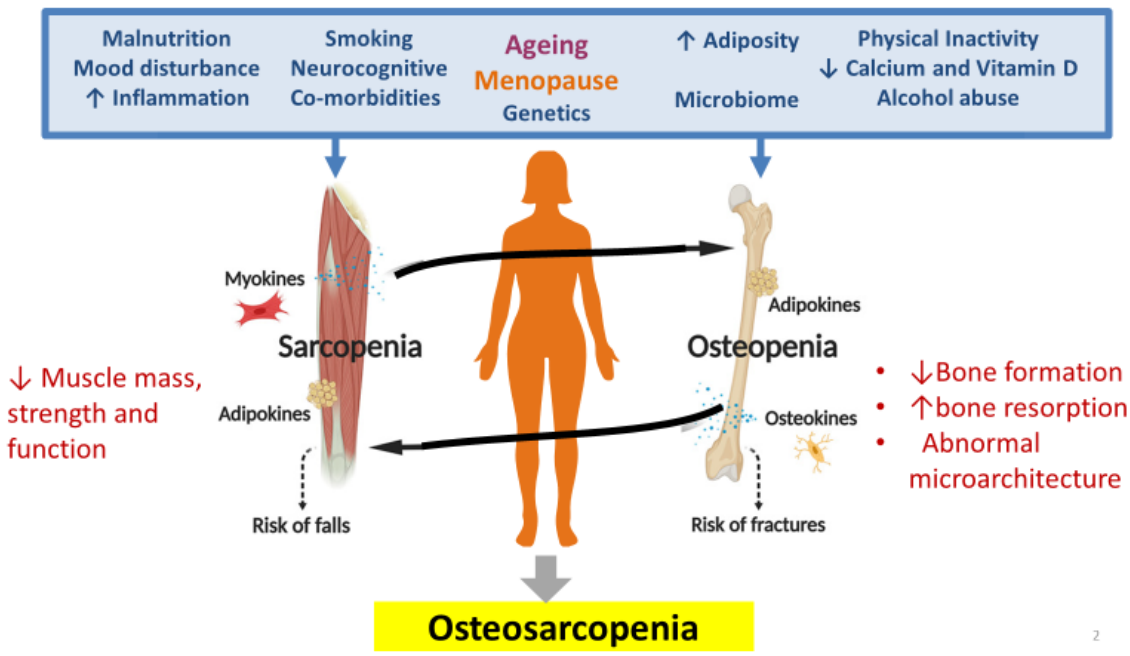
Based on the evidence that women with POI have reduced BMD (see section VI.1. Skeletal health), BMD measurement should be considered at POI diagnosis. Dual-Energy X-ray Absorptiometry (DXA) is the most reliable assessment for BMD and the amount of ionising radiation used is very small. The optimal interval at which DXA should be repeated is unclear 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 if the results will influence a management decision, 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.

VI.4. Muscle health

PICO Question: what are the consequences of POI for muscle health?

POI is likely to adversely affect muscle mass and function although this remains under-researched and poorly understood. Multiple factors have been identified as contributors to sarcopenia in older populations including genetic, nutritional, behavioural, co-morbidities, neurocognitive function, microbiome, hormonal and aging (Figure 11). Sarcopenia is associated with increased morbidity and mortality in older populations (de Villiers and Goldstein, 2021). However, there is a lack of consensus regarding sarcopenia definitions, diagnostic criteria, and treatment guidelines (Cruz-Jentoft and Sayer, 2019, Chen *et al.*, 2020, de Villiers and Goldstein, 2021). The prevalence and impact of sarcopenia in women with POI is unclear.

Figure 12 Factors associated with development of adverse musculoskeletal health outcomes. Adapted from (Kirk *et al.*, 2020) and used with permission (Open Access Creative Commons CC BY licence).



A 2023 systematic review of 6 observational studies (n=18291) reported lower muscle mass (DXA derived appendicular skeletal muscle mass (ASM)/BMI) in women with early menopause in two studies of Asian women compared with age of menopause >45 years (standardized mean difference (SMD) -0.14 ± 0.03; 95% CI -0.20 to -0.07; p=0.001) (Divaris *et al.*, 2023). There was insufficient data regarding muscle mass and POI. POI was associated with lower muscle strength as assessed by hand grip strength (SMD -0.3; 95% CI -0.58, -0.01; p=0.04) and lower muscle performance as assessed by gait speed (SMD -0.13; 95% CI -0.23 to -0.04; p=0.004) compared with age of menopause >45 years (Divaris *et al.*, 2023); however, only the difference in gait speed persisted after adjusting for age. Subgroup analysis indicated that women with non-iatrogenic POI, but not surgical POI (one study), had lower gait speed compared with menopause at usual age. In contrast, a study of USA women reported that bilateral oophorectomy before age 45 years (n=1365) was associated with a mean 2.86% reduction in DXA derived total lean mass compared to women without surgery (adjusted for age, race, BMI, parity, lifestyle factors, and post-surgery HRT use) (Karia *et al.*, 2021).

A case-control study of 240 Chinese women with idiopathic POI (mean age 31.6 years) compared to 240 age matched controls and 520 peri/postmenopausal controls (mean age 45.5 and 50.1 years respectively) observed significantly decreased lower limb muscle strength in women with POI compared with controls but lower limb muscle strength was similar to perimenopausal women and increased compared with the postmenopausal group (Luo *et al.*, 2018). Lower limb muscle mass (muscle distributing coefficient) was significantly lower in women with POI compared to all groups. Lower limb muscle strength was a significant predictor of femoral BMD in multivariate analysis adjusted for age and BMI (Luo *et al.*, 2018). No difference in DXA derived lean mass indices was observed in a study of 70 Brazilian women with normal karyotype POI (mean age 36.3 years), all using HRT for the past year, compared with age matched controls (Freitas *et al.*, 2021). A recent cross-sectional study of 59 Chinese women with idiopathic POI (mean age 37 years; 75% using HRT) reported lower DXA derived appendicular skeletal muscle mass compared with 57 age matched controls (ASM/height^2 5.71 ± 0.64 versus 6.15 ± 0.62; BMI p < 0.001) (Li *et al.*, 2023b). This relationship persisted after adjusting for age, BMI, and lifestyle factors. The prevalence of low muscle mass (defined as ASM/height^2<5.4 was greater in Chinese women with idiopathic POI compared with premenopausal controls (32.2% versus 8.77% kg/m^2; p=0.002) (Li *et al.*, 2023b). The Asian Working Group for Sarcopenia definition includes low muscle mass ASM/height^2<5.4 kg/m^2 (DXA-derived ASM) and reduced grip strength (<18kg) (Chen *et al.*, 2020). Muscle strength/function was not assessed; however, based on the reported prevalence of low muscle mass, one-third of POI participants in this study could be considered "pre-sarcopenic" or "sarcopenic" depending on normal or reduced muscle strength respectively. Lower muscle mass was observed in 60 women with spontaneous or iatrogenic POI versus 60 age matched controls (6.17 versus 6.15 versus 7.08 kg/m2 respectively; p<0.001) (Samad *et al.*, 2022). In contrast, a prospective study showed no significant change in DXA derived lean body mass at two years follow-up in 54 women following risk reducing BSO, at mean age 42 years, compared to 81 premenopausal controls, mean age 40 years (Price *et al.*, 2023).

Women with TS have lower lean body mass compared with age and BMI matched controls (Gravholt and Backeljauw, 2017, Samad *et al.*, 2020). A cross-sectional study of 54 Danish women with TS, mean age 42.5 years, reported reduced muscle mass, oxygen uptake, and physical activity versus 55 premenopausal controls (Gravholt *et al.*, 2006). Normal muscle force (Fmax) but reduced power (Pmax) was observed in a cross-sectional study of 60 adolescent TS girls compared with healthy controls (Soucek *et al.*, 2015). There was no association with menarcheal stage, karyotype, or HRT duration (Soucek *et al.*, 2015). Consistent with this, a study of 15 TS women (mean age 13.9 years) demonstrated greater anaerobic stress during exercise contributing to increased muscle fatigue compared with 16 age, activity and BMI matched healthy controls (Wells *et al.*, 2013).

Recommendations

Women with POI and HCPs should be aware that POI is associated with lower muscle mass, strength, and performance.	⊕⊕◯◯	**STRONG**

The guideline group recommends that HCPs be aware that POI may be associated with an increased risk of sarcopenia.	**GPP**

Justification

Limited evidence suggests that POI is associated with reduced muscle mass, strength and performance which may vary according to cause of POI and ethnicity. Women with POI may be at increased risk of

sarcopenia. This has implications for morbidity, including bone and cardiometabolic health, and mortality. There is an urgent need for more research.

VI.5.Muscle protection and improvement

PICO Question: What are the treatment options for MUSCLE protection and improvement?

Proposed lifestyle interventions for management of sarcopenia/osteosarcopenia incorporate adequate nutrition (including protein intake ≥1.2g/kg/day), creatine supplementation 3-5g/day, and calcium and vitamin D supplementation if deficient (Kirk *et al.*, 2020, de Villiers and Goldstein, 2021). Increased lean body mass, muscle strength and performance with resistance exercise have been demonstrated in meta-analyses, although study quality varied (Thomas *et al.*, 2021, Sá *et al.*, 2023). Whole body vibration has shown benefits in regard to muscle strength in separate meta-analyses of postmenopausal and younger population (Samad *et al.*, 2020). There are no specific studies in women with POI.

Meta-analyses indicate a positive effect in postmenopausal women of HRT on muscle strength but not lean body mass (potentially reflecting variable study methodology, HRT regimens, time since menopause or prior HRT) (Greising *et al.*, 2009, Javed *et al.*, 2019). Although estrogen therapy is important in bone health in women with POI (see VI.1. Skeletal health), data is lacking regarding muscle parameters and HRT exposure. A longitudinal analysis indicated that continued HRT use was associated with an increase in muscle mass (ALM/ height^2+47.3 g/m^2 per year; 95% CI 25,4,69.23); whereas no change was seen in those with interrupted HRT (Samad *et al.*, 2022). In contrast, no difference was observed between HRT users and non-users in women with non-iatrogenic POI (Li *et al.*, 2023b) or following RR BSO (Price *et al.*) which may reflect small sample sizes. A five-year RCT reported increased lean mass in TS women taking high dose 4mg estradiol but not 2mg estradiol per day (Cleemann *et al.*, 2017).

A systematic review found no benefit in regard to lean body mass with testosterone therapy in postmenopausal women (Islam *et al.*, 2019a). A positive effect of testosterone therapy on lean body mass was observed in a pilot study of 14 women with TS (Zuckerman-Levin *et al.*, 2009).

There are no pharmacologic interventions approved by government regulatory agencies (e.g. FDA) for prevention/ treatment of sarcopenia. A small study in postmenopausal women, mean age 65 years, reported increased muscle strength and lean mass with denosumab but not with bisphosphonate or placebo therapy (Bonnet *et al.*, 2019).

Recommendations

The guideline group recommends that HCPs consider informing women with POI about muscle health.		**GPP**
HCPs should identify modifiable risk factors for muscle health in women with POI. Maintaining a healthy lifestyle, involving adequate nutrition, regular exercise, avoidance of smoking, and maintenance of normal body weight is likely to benefit muscle health	⊕◯◯◯	**STRONG**

Dietary supplementation of calcium and vitamin D may be required in women with inadequate vitamin D status and/or calcium intake and may benefit muscle health.	⊕⊕◯◯	CONDITIONAL

Resistance training can be considered as it increases muscle mass, strength and performance in other populations and is likely to be of benefit in POI	⊕◯◯◯	CONDITIONAL

The effect of HT on muscle parameters in women with POI is uncertain but treatment may be of benefit and can be offered.	⊕◯◯◯	CONDITIONAL

The effect of other therapies, including testosterone, on muscle health in women with POI is uncertain and they should not be offered.	⊕◯◯◯	STRONG

Justification

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. There is an urgent need for more research.

VI.6. Monitoring of muscle health

PICO Question: How should muscle health be monitored in women with POI?

The 2019 European Working Group on Sarcopenia in Older People (EWGSOP2) (Cruz-Jentoft and Sayer, 2019) updated recommendations on definition and diagnosis of sarcopenia provide an operational diagnosis of sarcopenia:

Probable sarcopenia is identified by Criterion 1. **Diagnosis is confirmed by additional documentation of Criterion 2.** **If Criteria 1, 2 and 3 are all met, sarcopenia is considered severe**
(1) Low muscle strength
(2) Low muscle quantity and quality
(3) Low physical performance

A variety of tools have been proposed to assess sarcopenia (Cruz-Jentoft and Sayer, 2019, Samad *et al.*, 2020). The EWGSOP2 recommended pathway for diagnosis of sarcopenia in clinical practice includes: (i) initial assessment of muscle strength via grip strength and/or chair stand test (ii) confirmation of low muscle mass via DXA derived total body or ASM, adjusted for BMI or height; and (iii) determine severity via measurement of physical performance assessed via either gait speed, Timed Up and Go test or Short Physical Performance Battery. However, cut off points depend on the measurement technique and

population studied and there are no cut-off values for women aged<45 years (Samad *et al.*, 2020). In the absence of validated POI specific thresholds, current sarcopenia cut-off values (as used in publications referred to in VI.5.Muscle protection and improvement) (Cruz-Jentoft and Sayer, 2019, Chen *et al.*, 2020) could be used.

DXA is recommended for women with POI at diagnosis to assess bone health and this provides an opportunity to also assess muscle mass. Despite limitations (Cruz-Jentoft and Sayer, 2019, Samad *et al.*, 2020), DXA-derived total or ASM (adjusted for BMI or height) combined with grip strength and gait speed could potentially provide useful information regarding the presence of sarcopenia in women with POI. There are no data regarding whether or when these tests should be repeated.

Recommendation

The guideline group recommends that HCPs consider assessment for sarcopenia at POI diagnosis.	**GPP**

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. Further research regarding muscle health and POI is need.

Conclusion

Adverse effects of POI on BMD are well recognised although the impact on fracture requires further clarification. Risk factors for bone loss in women with POI have been identified and support the key role of HT in maintaining bone mass. Newer evidence has provided guidance regarding the estrogen doses/ regimens needed to prevent bone loss. The evidence regarding therapeutic options where HT is contraindicated is limited and referral to a bone specialist should be considered. 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.

Research recommendation.

Further research is required to (i) clarify fracture risk associated with POI and the effect of HT on this outcome; (ii) determine the best strategies for monitoring of bone health including screening interval, role of bone turnover markers and newer imaging modalities; (iii) investigate the effect of exercise on muscle parameters and bone density in women with POI; (iv) clarify the role bone specific agents in managing POI associated osteoporosis; (v) clarify the changes in muscle mass and function associated with POI; (vi) identify strategies for assessment and monitoring of muscle health in this population including defining sarcopenia; and (vii) examine the role of HT and other strategies to maintain muscle health.

VII. POI and cardiometabolic health

Early loss of ovarian function (i.e., POI, early menopause before the age of 45 years and surgical menopause) has emerged as a female-specific risk factor for cardiovascular disease (CVD). Since the end of the 1950's, it has been recognised that women undergoing premenopausal oophorectomy show increased cardiovascular morbidity (Robinson *et al.*, 1959, Parrish *et al.*, 1967). Indeed, all meta-analyses show that women with POI, surgical menopause and early menopause are at higher risk for CVD and death, probably due to the shorter exposure to cardioprotective endogenous estrogen.

Studies evaluating cardiovascular problems in women with POI or Turner Syndrome are summarised in the first part of this chapter. Whether cardiovascular disease and mortality may be prevented by estrogen replacement therapy or screening and monitoring of risk factors is explored in the second part of the chapter.

VII.1. Impact of POI on cardiometabolic health

PICO Question: What are the consequences of POI for the cardiovascular system?

All published studies, consistently, have shown that women with POI have increased risk for earlier onset of coronary artery disease (CAD) (Atsma *et al.*, 2006) and increased cardiovascular disease (CVD) mortality (Zhu *et al.*, 2019, Okoth *et al.*, 2020). This increased risk is evident in women with POI, early menopause (at age 40-45 years) and surgical menopause. A meta-analysis with pooled data from 310329 women (derived from 32 observational studies), showed that 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) (Muka *et al.*, 2016). Interestingly, pooled individual-level data from 15 observational studies suggested that 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 (Zhu *et al.*, 2019). Lower premenopausal AMH levels and/or greater declines in AMH over the menopausal transition were found to be associated with greater atherosclerotic risk (El Khoudary *et al.*, 2023).

The risk of stroke is also increased in women with early loss of ovarian function. A recent study involving 1.159,405 Korean postmenopausal women showed that women with POI have 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), compared with women with menopause in the normal age range (Lee *et al.*, 2023a) .

Initially, a systematic review of cohort studies published in English between 2006 and 2010 examined the risk of early lack of endogenous estrogen, through either surgical menopause or spontaneous ovarian cessation before the age of 50 years, on stroke and found that estrogen is protective for stroke in women younger than 50 years (Rocca *et al.*, 2012a). Age at ovarian failure was more important than type of estrogen loss, i.e., either natural or induced ovarian failure (Rocca *et al.*, 2012a). A Korean population-based cohort study of 135575 women aged 40-49 years (median follow-up 7.9 years) showed that the 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) (Yuk *et al.*, 2023). Finally, a systematic review showed that hysterectomy with bilateral oophorectomy before the age of 45 years is associated with 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) (Hassan *et al.*, 2024).

These findings were confirmed by a recent meta-analysis of 20 cohort studies, which showed that women with POI or early menopause (at age 40-45 years) have a higher risk for CHD, ischemic and haemorrhagic stroke and total cardiovascular event compared to women with menopause at age > 45 years (Liu *et al.*, 2023b).

In a cohort study (UK biobank) of 144260 postmenopausal women, POI was 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 (Honigberg *et al.*, 2019). The hazard ratio was 1.36 for non-iatrogenic POI and 1.87 for surgical premature menopause (Honigberg *et al.*, 2019). The finding of increased risk of heart failure and atrial fibrillation in women with POI was further confirmed in a cohort study of 1401175 Korean women (Shin *et al.*, 2022). A recent meta-analysis of 9 cohort studies also found that women with POI or early menopause (before the age of 45 years) have a higher risk of heart failure and atrial fibrillation compared with women with menopause in the normal age range (Liu *et al.*, 2023a).

Women undergoing risk reducing bilateral oophorectomy before the age of 40 consistently showed an increased risk for cardiovascular disease (Lokkegaard *et al.*, 2006, Rocca *et al.*, 2006, Parker *et al.*, 2009b, Barrett-Connor, 2013, Honigberg *et al.*, 2019, Hassan *et al.*, 2024). Bilateral oophorectomy before the age of 45 is associated with a 2-fold increase in cardiovascular risk (Atsma *et al.*, 2006, Parker *et al.*, 2009b, Rivera *et al.*, 2009a, Ingelsson *et al.*, 2011). It should be pointed out that hysterectomy along with any oophorectomy (unilateral or bilateral) has also been associated with an increased risk of CVD (Farland *et al.*, 2023).

Interestingly, a study of 130254 postmenopausal women showed that women with POI have a shorter leukocyte telomere length, a marker of cellular aging (Schuermans *et al.*, 2023). In that study, leukocyte telomere length and age of menopause were independently associated with CAD (Schuermans *et al.*, 2023).

Cardiovascular effects of spontaneous and surgical POI

Women with POI develop earlier signs of endothelial dysfunction (Kalantaridou *et al.*, 2004) and premature atherosclerosis (Clarkson, 2007). Surgical menopause in premenopausal women (aged 46-53 years) induced an increase in total, low-density lipoprotein cholesterol (LDL-C), and lipoprotein(a) within the next 2-3 months; HDL cholesterol decreased significantly for 3 months (Bruschi *et al.*, 1996).

A meta-analysis of 20 cohort studies showed that women with POI and early menopause have a higher risk of type 2 diabetes (RR 1.32; 95% CI 1.08 to 1.62 and RR 1.17; 95% CI 10.91 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), both aspects of metabolic syndrome, compared with women with usual age menopause (Liu *et al.*, 2023b). The prevalence of the metabolic syndrome increases with ovarian failure and may also contribute to the acceleration of CVD thereafter.

The adverse effects of early loss of ovarian function in metabolic parameters has also been shown in the following studies: A small cross-sectional study of 118 Chinese Women with POI and 151 age-matched controls, showed that women with POI have significantly increased triglyceride levels, fasting glucose and insulin and HOMA-IR (Jin *et al.*, 2023). A recent meta-analysis of 21 studies, also showed that women with POI had significantly higher waist circumference, total cholesterol, LDL-C, triglycerides, and fasting glucose (Cai *et al.*, 2022).

Alteration of haemostatic factors and markers of platelet function was observed in another group of premenopausal women 6 weeks after surgical menopause (Lip *et al.*, 1997). A smaller study in 26 females with POI and 31 healthy controls suggested that QT dynamicity is impaired in patients with POI despite the absence of overt cardiovascular involvement (Canpolat *et al.*, 2013).

Turner Syndrome

Women with Turner Syndrome (TS) have a 3-fold increased mortality risk compared with the general population, mainly due to cardiovascular disease (Gravholt *et al.*, 2023). Women with TS have a higher prevalence of congenital cardiac malformations such as aortic coarctation (11%) and bicuspid aortic valve (16%), thus being at higher risk for infective endocarditis and, over time, the bicuspid aortic valve may deteriorate leading to clinically significant aortic stenosis or regurgitation (Bondy, 2008). A bicuspid aortic valve is also associated with aortic wall abnormalities including ascending aortic dilatation, aneurysm formation, and aortic dissection. Women with TS have an increased risk of CVD, including arrythmia, CAD, hypertension, stroke, and hyperlipidaemia (Gravholt *et al.*, 2023). A major concern in TS remains the rare but often fatal aortic dilatation, dissection, or rupture in relatively young women. The prevalence of aortic dilatation increases with age but dilatation in TS can already be present in the second decade of life (Sharma *et al.*, 2009). Women with TS present an increased risk of hypertension, diabetes mellitus, celiac disease, osteoporosis and disorders of the thyroid and the parathyroid gland (Gravholt *et al.*, 2023). The majority of girls with TS will require pubertal induction (see XIII. Puberty Induction). Cardiovascular health is of great importance, especially in pre-pregnancy assessment (see V.3. Pregnancy.

Recommendations

HCPs should be aware that women with POI are at increased risk of cardiovascular disease, including coronary artery disease, heart failure and stroke.	⊕⊕⊕◯	**STRONG**
The guideline group recommends that women with POI should be advised of cardiovascular risk factors that they can modify through behavioural change (e.g. by avoidance of smoking, heart healthy diet, regular exercise, and maintenance of normal body weight).		**GPP**
All women diagnosed with Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease, especially prior to and during pregnancy.	⊕⊕◯◯	**STRONG**

Justification

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.

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.

VII.2 Hormone treatment for cardiovascular health

PICO QUESTION: Is estrogen replacement cardio-protective?

Spontaneous and surgical POI

Oophorectomy and early menopause are associated with a markedly increased incidence of CAD in young women (Manson, 1994). Premenopausal women with premature coronary artery disease have significantly lower plasma estradiol concentrations compared with controls (Hanke *et al.*, 1997). Recent findings indicate that lower premenopausal AMH levels and/or greater declines in AMH over the menopausal transition are associated with greater atherosclerotic.

In women with spontaneous and surgical POI, estrogen has beneficial effects on vascular endothelium and lipid parameters (Kalantaridou *et al.*, 2004). In experimental animals, the most robust inhibition of postmenopausal atherosclerotic progression was found in animals given contraceptive steroids premenopausally and subsequently given conjugated equine estrogens postmenopausally (Clarkson, 1994). There are inadequate prospective data regarding hormone therapy in women with POI. Most reports suggesting an increased risk of CVD in women with POI also suggest a protective effect of hormone therapy . Existing data regarding hormone therapy in women experiencing menopause at the usual age should not be extrapolated to women experiencing POI and initiating hormone therapy at that time (Rees, 2008). The risks attributable to hormone therapy used by these young women are likely smaller and the benefits potentially greater than those in older women who commence hormone therapy beyond the usual age of menopause (Utian *et al.*, 2008). Recent studies suggest that the increased CVD morbidity and mortality observed after the menopause cannot be fully explained by changes in plasma lipoproteins only and support the concept that sudden ovarian hormone deprivation has a widespread impact on the cardiovascular system with a direct harmful effect on vessel wall physiology (Mercuro *et al.*, 2004). Similarly, Kalantaridou and colleagues reported that young women with POI (age range 23-40 years) have significant endothelial dysfunction (Kalantaridou *et al.*, 2004). Oral estrogen/progestogen cyclic treatment for 6 months restored endothelial function in these patients. However, the risks and benefits of HT in women with POI have not been studied in long-term trials (Hendrix, 2005, Kalantaridou *et al.*, 2006b).

In the observational Danish female nurses' study, an increased risk of ischemic heart disease was found among women having their ovaries removed before the age of 40 compared with those having their ovaries removed after the age of 45, as well as among women who had spontaneous menopause before age 40 compared with those after the age of 45 (Lokkegaard *et al.*, 2006). For the group of women experiencing menopause after bilateral oophorectomy, a threefold increase in ischemic heart disease was observed among never users compared to ever users of hormone therapy. However, this finding was based on few cases. The effect of hormone therapy was most pronounced for the subgroup of current users and among women who started treatment within 1 year of menopause.

Estrogens have effects on ventricular myocyte contractile function (Ren *et al.*, 2003) and on intracellular Ca^{2+} kinetics in coronary endothelial cells thus having antiarrhythmic effects in cardiac myocytes (Nakajima *et al.*, 1999). There is also evidence that estrogen decrease insulin resistance (Sumino *et al.*, 2003) and protect against lipid peroxidation (Ayres *et al.*, 1998).

During menopause, plasma lipids change in an unfavourable way to a more atherogenic pattern with increased total and LDL-cholesterol and decreased HDL cholesterol concentrations. There is evidence that short-term HRT beneficially affects plasma lipids and reverses some of these changes (Sack *et al.*, 1994, Rajman *et al.*, 1996, Darling *et al.*, 1997).

Clinical and experimental data indicate that there may be different effects of hormone therapy in younger women (e.g. women with POI and healthy vessels without established atherosclerosis starting HT), in comparison with older women (e.g. women with age of menopause over 50 years, starting treatment 10 years after their final menstrual period) (Clarkson, 1994, Atsma *et al.*, 2006, Mikkola and Clarkson, 2006, Ouyang *et al.*, 2006). In blood vessels with established atherosclerosis, oral estrogen administration has negative effects via its prothrombotic effects, thus contributing to plaque instability (Clarkson, 1994, Walsh *et al.*, 2000). In comparison with a 12-month standard regimen (oral ethinylestradiol and norethisterone), physiological sex-steroid replacement therapy (transdermal estradiol 100 µg + vaginal progesterone) in a randomized, controlled crossover study resulted in lower blood pressure, better renal function, and less activation of the renin-angiotensin system in 18 women aged 19-39 years with POI (Langrish *et al.*, 2009).

In a group of 25 young hypogonadal women (mean age 31.9 years; range 18.5-42.2), increasing doses of hormone therapy (17β-estradiol at 1 mg, 2 mg, and 4 mg) resulted in a reduction of carotid intima-media thickness along with increased serum HDL and decreased plasma glucose (Ostberg *et al.*, 2007).

Turner Syndrome

Almost all women with TS need appropriate HT until the age of natural menopause, following induction of puberty, i.e. approximately for 40 years. A Danish cohort study showed that women with TS treated with HT had a significantly lower use of antihypertensives, antidiabetics, and thyroid hormones and significantly reduced hospitalization rates for stroke and osteoporotic fractures (Viuff *et al.*, 2020). A small study showed that increasing doses of HT result in a reduction in carotid IMT and plasma glucose, along with increased serum HDL (Ostberg *et al.*, 2007). Studies have shown no increased risk for neoplasia in women with TS receiving HT, including breast cancer (Schoemaker *et al.*, 2008, Larizza *et al.*, 2016, Viuff *et al.*, 2021).Women with spontaneous and surgical POI, as well as TS are not only estrogen deficient; they are also testosterone deficient (Kalantaridou *et al.*, 2006a, Viuff *et al.*, 2022, Gravholt *et al.*, 2023) However, there are no clinical studies showing the effect of testosterone addition to standard HT regarding CV health..

Recommendation

Despite a lack of data from randomised controlled trials, hormone therapy with early initiation is recommended in women with POI to control future risk of cardiovascular disease. Hormone therapy should be continued at least until the usual age of menopause.	⊕⊕◯◯ **STRONG**

Justification

Hormone therapy in POI has beneficial effects on plasma lipids, blood pressure, insulin resistance, and vascular endothelial function. There is a need for long-term randomized prospective studies to determine the optimal routes, doses, and regimens of HT. In the absence of long-term randomized prospective data, treatment should be individualized and carefully monitored.

Research recommendation.

There is a need for long-term randomized prospective studies to determine the optimal routes, doses, and regimens of HT. In the absence of long-term randomized prospective data, treatment should be individualized and carefully monitored.

VII.3. Monitoring of cardiovascular risk factors

Premature estrogen deficiency is associated with increased risk of CAD, stroke, and overall CVD and increased CVD mortality, CAD mortality and all-cause mortality.

Starting hormone therapy soon after the diagnosis of POI and achieving a healthy lifestyle (i.e., not smoking, maintaining normal BMI, having regular exercise program, and a healthy diet) are important parameters and are associated with normal lipid profile and blood pressure and less progression of subclinical atherosclerosis (Mehta and Manson, 2024). Regular CVD follow-up is essential including cardiologist review according to individual needs and availability.

PICO QUESTION: SHOULD CARDIOVASCULAR RISK FACTORS BE MONITORED?

Spontaneous and surgical POI

Women with POI have an increased risk for CAD, heart failure, type 2 diabetes, hypertension, dyslipidaemia, and stroke. Clinical data has shown that hormone therapy reduces the risk for CAD, and stroke and improves insulin sensitivity and lowers glucose levels, thus decreasing the risk for type 2 diabetes in postmenopausal women (Mehta and Manson, 2024).

Annual follow-up is essential for monitoring HT, blood pressure (BP), BMI, and lipid and glucose levels. Because of the impact on CV risks, screening for thyroid function, by measuring TSH, should be performed according to individual needs. Regular cardiovascular follow-up is also important, which may require referral to a cardiologist. Achieving and maintaining a healthy lifestyle, along with transdermal HT until the usual age of menopause, will reduce the risk for CVD (Mehta and Manson, 2024) (see also XII.3. Lifestyle management options).

Turner Syndrome

In addition to the burden of congenital heart defects, women with TS have an excess of several cardiovascular risk factors including hypertension, obesity, impaired glucose tolerance, type 2 diabetes, and hyperlipidaemia.

Women with Turner Syndrome have a 50% risk of developing impaired glucose tolerance and a fourfold increase in the relative risk of developing type 2 diabetes (Gravholt *et al.*, 1998). Impaired glucose tolerance is thought to result from a combination of insulin deficiency (Bakalov *et al.*, 2004) and insulin resistance (Salgin *et al.*, 2006), and both are independent of body composition although, if obesity is present, it will further aggravate insulin resistance. A more atherogenic lipid profile is usually found in women with TS compared with those who have a normal karyotype and POI (elevation of LDL and triglycerides).

Annual screening for these risk factors should be performed and, if relevant, smoking cessation should be discussed. Standardized multidisciplinary evaluation is effective; girls with Turner Syndrome benefit from a careful transition to ongoing adult medical care (Freriks *et al.*, 2011).

Close monitoring of CVD factors by specialized cardiologists is essential (Gravholt *et al.*, 2023).

Recommendations

The guideline group recommends that cardiovascular risk should be assessed in women diagnosed with POI.	**GPP**

The guideline group recommends that all women with POI should have annual monitoring of blood pressure, weight and smoking status, and where available blood tests for lipid profile and diabetes screening. Other tests for assessing cardiovascular risk can be performed upon indication.	**GPP**

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

Psychological wellbeing is an essential component of quality of life (QoL) that is a key endpoint in medical and health research. QoL is a broad concept measurable with multiple scales assessing an overall score and domain score, with no universal accepted definition. The WHO has created a scale with six domains: physical health, psychological state, levels of independence, social relationships, environmental features, and spiritual concerns. Any condition or intervention able to modify the individual status may influence one or more dimensions of QoL that are generally interconnected. Several conceptual and methodological challenges emerge in the literature, mostly related to definitions, theoretical backgrounds, and design of validated instruments (Haraldstad *et al.*, 2019). Measures of health-related quality of life (HRQoL) take generally into account physical, psychological, and social dimensions contributing to wellbeing, and they are effective in clinical practice when retaining the ability to capture the specificity of health conditions or interventions under investigation in a multidimensional perspective. In many circumstances, including menopause, the final goal is to understand individual feelings and behaviours associated with the health status and the level of intra-personal and inter-personal distress in a specific socio-cultural context (Kotz *et al.*, 2006).

VIII.1. Impact of POI on psychological wellbeing

PICO Question: What are the consequences of POI on psychological wellbeing and quality of life?

General aspects

Over the years intensive research has been conducted on the most appropriate and validated instruments to measure global, health and menopause related QoL regarding the impact of hormone therapy on symptoms and conditions that may variably affect women at this life stage. The main challenge associated with menopause is the assessment of QoL in a real multidimensional perspective that should consider several biopsychosocial modulators influencing the individual perception of a natural transition, not a disease (Utian and Woods, 2013). On the other hand, chronic illnesses underlying iatrogenic POI may influence psychological wellbeing and QoL by itself, in addition to typical menopausal symptoms (Woods and Utian, 2018), which are generally more severe (Kotz *et al.*, 2006).

Within the POI literature on QoL, few studies had set out to specifically and systematically examine QoL patterns and their physical and psychosocial predictors. A meta-analysis including only six studies with 645 women with POI and 492 normal-ovarian control subjects under 40 years reports 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 (see IX. POI and sexuality). Collectively, the data suggest the importance of developing condition-specific questionnaires based on POI-related constructs (Li *et al.*, 2020b). A sample of Chinese women with POI after hematopoietic stem cell transplantation (HSCT) for hematologic diseases showed milder symptoms in comparison with the norm group, but non-specific scales to assess QoL were used (Su *et al.*, 2023). Recently, Golezar *et al.* developed and evaluated the psychometric properties of POI QoL scale (POIQoL) which consists of six subscales including psychological effects, coping strategies, hormone therapy complications, fears and concerns, self-conception, and sexual function (Golezar *et al.*, 2022).

The criticism goes beyond the validity of the QoL measure used. POI is not a homogenous and fixed state, and most importantly is not natural because, even when a specific cause is not identified, it occurs early in the life course and assumes the characteristics of a chronic health problem requiring long-term care. It is currently unclear to what extent women with POI can be compared to other long-term medical conditions associated with a higher prevalence of psychological and mental health difficulties (The British Psychological Society & The Royal College of Psychiatrists., 2010). With these limitations in mind, studies of varying quality and scale appear to point to a higher prevalence of psychological distress (Nappi *et al.*, 2019). Distinct aspects of POI such as the absence or presence of previous cancer diagnosis/risk increase, concurrent unrelated health problems, vasomotor symptoms, as well as current treatment (e.g. fertility treatment) may impact upon different QoL domains in distinctive ways. These effects may be mitigated by a number of variables, such as the absence or presence of a stable and satisfying relationship and/or children, and pre-POI mental health.

Importantly, social, and economic status is associated with access to social privileges and can powerfully influence QoL domains, so that the confounding effects of education, occupation, and income may need to be controlled for. A fair example is a retrospective study with women who had undergone risk reducing salpingo-oophorectomy. The authors found that younger women were at a higher risk for poorer long-term wellbeing outcomes, and that sport participation and a stable weight had a protective effect (Touboul *et al.*, 2011). However, the potential confounding effects of educational level and executive occupation – markers of socio-economic success and privilege - were measured and reported as results rather than considered for their potentially overriding influence on wellbeing outcome.

Quality of Life and menopausal symptoms

The research on POI and QoL has not yet reached the stage of being able to map specific aspects of POI across different dimensions of QoL, mainly because of the paucity of instruments specifically designed for these women (Li *et al.*, 2020b). Generic HRQoL instruments may not appropriately assess the variety of biopsychosocial elements described in women with non-iatrogenic POI (Nappi *et al.*, 2019). In a non-clinic-based sample of members of a POI-specific support group, symptom scores did not substantially decrease with time since diagnosis or correlate with age at POI diagnosis. Of note, women with POI report many symptoms not adequately captured by the symptom checklists created for age-appropriate postmenopausal women (Allshouse *et al.*, 2015). For instance, iatrogenic POI, especially before the age of 41 years, is associated with a poor QoL namely in sexual and vasomotor domains (Gosset *et al.*, 2022). On the other hand, research in menopause at usual age suggests there are important cognitive, emotional, and behavioural variations in vasomotor symptom experience and reporting, so that their impact on women can be expected to be highly variable (Hunter and Mann, 2010). A total of 140 relatively healthy mid-aged women with vasomotor symptoms (at least ten hot flushes/night sweats) report reduced HRQoL compared to age-matched normal subjects and a general sample of menopausal women. Poor HRQoL is associated with younger age, current psychosocial concerns, poor general health, and higher body mass index (Ayers and Hunter, 2013).

Quality of Life and psychological wellbeing

Poor female identity emerges in women with POI undergoing qualitative research (Moukhah *et al.*, 2023). Body image changes are also important factors to consider regarding adaptation to surgery with an impact on feminine perception (Pearce *et al.*, 2014). A study that compared women who have experienced natural and surgical menopause for benign conditions found that HRQoL is worse for women who have had a surgical menopause (Bhattacharya and Jha, 2010), whereas risk reducing bilateral salpingo-oophorectomy (RRBSO) in women with pathogenic BRCA variants is not associated with significant changes in QoL, but with lower global health status, as compared with an expectant management (Zilski *et al.*, 2023). Of note, in a non-randomized controlled trial risk reducing

salpingectomy with delayed oophorectomy in premenopausal women who had completed childbearing is associated with better menopause-related QoL than with RRBSO, without significant differences in HRQoL (Steenbeek *et al.*, 2021). Individual experiences of RRBSO are variable and influenced by multiple factors but psychosexual problems are common and often cause significant distress to the women with POI and their partners (Hickey *et al.*, 2021a). A recent review addresses the psychosocial impact of the decision-making process in women candidate to risk reducing surgery pointing to the need of methodological standards (Alves-Nogueira *et al.*, 2023) to counteract the suboptimal clinical care after premenopausal RRBSO in high-risk women (Nebgen *et al.*, 2023).

Also, the relationship between oophorectomy and depression may vary depending on the type of iatrogenic POI affecting the population of women and on the instruments used to assess psychological wellbeing. A large-scale telephone interview follow-up study of women who had undergone bilateral oophorectomy before the onset of menopause for a non-cancer indication shows the participants to be at an increased long-term risk of depressive and anxiety symptoms compared to an age-matched referent group (Rocca *et al.*, 2008). This report highlights that a reduction in psychological wellbeing is not always accountable in terms of cancer diagnosis and risk. Different trajectories of depressive symptoms across menopause stages have been described in a large prospective longitudinal cohort of midlife women, including in those with surgical menopause and taking menopause hormone therapy (Hickey *et al.*, 2016). In a recent retrospective cohort study performed using a national database in South Korea, menopause at an earlier age showed an increased risk of depression, as well the use of menopause hormone therapy for more than 5 years (Kim *et al.*, 2023). A cross-sectional study conducted in the same country showed that suicidal ideation was present in middle-aged women with POI, regardless of a positive diagnosis of major depressive disorder (Ryu *et al.*, 2022)

Women with iatrogenic POI are more affected in term of depression and anxiety as compared with non-iatrogenic POI and controls (Deeks *et al.*, 2011). Among women at an elevated risk of ovarian cancer, the surgery did not increase self-reported depression and antidepressant use in a prospective study (Kotsopoulos *et al.*, 2020), whereas in another study (using a validated instrument risk of depressive symptoms) depression doubled within 3 months of premenopausal RRBSO and remained elevated in the 3 to 12 months after RRBSO (Hickey *et al.*, 2017). In a nationwide population-based cohort study using Danish National Registries including women after RRBSO for a family history of cancer (n=2002) and an age-matched reference group (n=18 018), surgery was likely associated with the use of antidepressants, especially in women treated with hormone therapy (Bräuner *et al.*, 2022). Interpretation of results should always consider that pre-existing mood disorders are associated with increased risk of bilateral oophorectomy in overall analyses and also in women ≤45 years of age (Gazzuola Rocca *et al.*, 2019). Moreover, intrapersonal experiences, including adverse childhood and adult experiences, might play a role in the association between mental health and gynaecologic symptoms that eventually lead to bilateral oophorectomy (Rocca, *et al.,* 2021).

An early cross-sectional observational study using standardised questionnaires with 64 attendees at a POI clinic showed that women report higher levels of depression and perceived stress, and lower levels of self-esteem and life satisfaction, compared to normative data. Very important factors affecting the degree of reported distress were age, age at diagnosis, time since diagnosis, already having children, being in a long-term relationship, or having psychological treatment in the past or present (Liao *et al.*, 2000). Levels of psychological distress were high in women with POI in both users and non-users of hormone therapy, as shown in a cross-sectional study comparing women with Turner syndrome, POI women with normal karyotype and healthy controls. The psychosocial profile was similar with increased shyness, social anxiety, and depression, and decreased self-esteem (Schmidt *et al.*, 2006). Non-iatrogenic POI is associated with an increased lifetime risk for major depression, probably sharing a common vulnerability (Schmidt *et al.*, 2011). A cross-sectional questionnaire-based study showed a high

rate of negative impact on self-image and confidence in women with POI (Singer *et al.*, 2011). Another cross-sectional opportunistic descriptive study involving clinic patients and support group members also suggested poorer psychosocial adjustment in women with POI and the presence of vasomotor symptoms explains only a small amount of the variance in psychosocial functioning (Mann *et al.*, 2012). Other symptoms such as poor sleep quality and insomnia seemed to be linked to depression, but interpersonal factors (being married, having more children) seem to mediate this link (Ates *et al.*, 2022). Lifestyle factors, for example smoking, may also play a mediator role. Indeed, in a sample of non-hysterectomized 31435 women aged 45 and above, POI was positively associated with insomnia and depression and negatively associated with cognition, with a more significant association among those who consumed tobacco (Kundu and Acharya, 2023).

A study found that scores on *Illness Uncertainty*, *Purpose in Life* and *Stigma* are significantly implicated in scores on Anxiety and Depression, whilst scores on *Goal Reengagement* and *Purpose in Life* are associated with scores on Positive Affect (Davis *et al.*, 2010). A significant positive relationship between spiritual and functional wellbeing is evident in women with non-iatrogenic POI (Ventura *et al.*, 2007). However, they perceive lower levels of social support (Orshan *et al.*, 2009). A systematic review and meta-analysis confirmed a high risk of depression and anxiety in women with POI (Xi *et al.*, 2023). A qualitative study exploring factors affecting QoL of women with POI identified profound effects on different aspects of biopsychosocial health, including fears for short- and long-term consequences and ambivalence towards hormone therapy. Distorted self-concept, mainly deriving from amenorrhea, changes in maternity expectations and signs of aging, is also a major topic (Golezar *et al.*, 2020). A heterogeneous sample of midlife women diagnosed with early menopause at age 38 ± 5 years described the condition with words having negative connotations and referring to symptoms, especially hot flushes (36.8%), mood swings (20.5%), and infertility (16.8%) (Yeganeh *et al.*, 2020a).

Quality of Life and fertility concerns

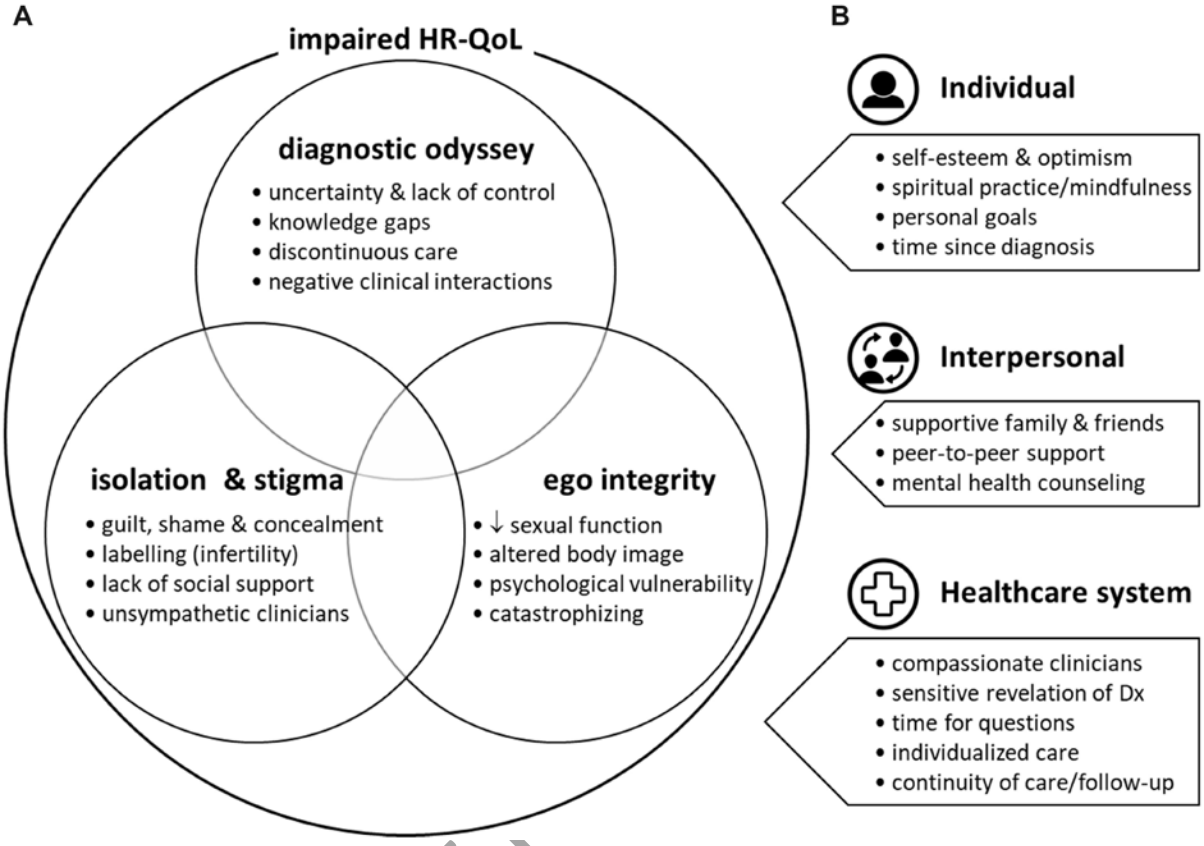
Fertility concerns were reported by 71% of a descriptive study sample involving clinic patients and support group members, but a strong relationship with self-reports of psychosocial functioning measures was not demonstrated (Mann *et al.*, 2012). However, infertility is one of the most disturbing aspects of the "silent grief" of women with POI, with feelings of guilt and shame (Singer *et al.*, 2011). In a longitudinal investigation on 102 women with POI, avoidance to acknowledge stress deriving from infertility, regardless of parity status, seems the most important factor to negatively cope with the POI condition following 12 months (Driscoll *et al.*, 2016). Difficulties in forming new relationships or fears of losing current partner, along with the awareness that a fundamental component of femininity is missing, make POI a very special form of infertility requiring comprehensive care (Singer, 2019). A case-control study showed that male partners of women with POI report significantly higher anxiety and depression, and experience worse marital relationship in several aspects. Most male partners had inadequate and inaccurate knowledge about their partners' disease, and this lack of understanding correlated with mood status and level of communication (Chu *et al.*, 2021).

A recent systematic scoping review of the literature on HRQoL in women with non-iatrogenic POI is extremely useful to identify relevant categorical themes and associated dimensions, as well as individual factors, interpersonal influences or healthcare system factors that can modulate the level of impairment of HRQoL and are important promoters of effective coping with a POI diagnosis (McDonald *et al.*, 2022)(Figure 12).

This updated review sets the stage for further development in providing adequate care to women with POI who very often report feelings of loneliness and experiences of negative interactions with health care providers (HCPs). Discontinuing of care, knowledge gaps and inadequate support are very relevant to psychosexual distress. All these themes (diagnostic odyssey, isolation and stigma, and ego integrity)

and associated dimensions should be targets of effective counselling to make informed choices in the management of the POI condition (McDonald *et al.*, 2022).

FIGURE 13 THEMES AND DIMENSIONS RELATED TO IMPAIRED HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN WOMEN WITH POI (MCDONALD *ET AL.*, 2022)(PERMISSION PENDING)



Themes and dimensions related to impaired health-related quality of life (HR-QoL) in women with primary ovarian insufficiency (POI). Synthesizing the results of the scoping review identified potential targets for interventions to improve health-related quality of life (HR-QoL) in women with primary ovarian insufficiency (POI). (A) Three interacting themes (bold text in overlapping circles: diagnostic odyssey, isolation and stigma, ego integrity) contributed to impaired HR-QoL in women with POI (i.e. anxiety, depression, psychological distress, diminished health status). Dimensions for each theme are depicted by bullets. (B) Several mitigating factors were identified from the literature and are categorized at the individual, interpersonal and healthcare system levels. Protective factors are noted by bulleted points for each respective level. Dx, diagnosis.

Recommendations

HCPs should be aware that a diagnosis of POI can have a significant impact on psychological wellbeing and quality of life	⊕◯◯◯	**STRONG**

The guideline group recommends offering assessment of psychological health and quality of life to all women with POI.	**GPP**

Justification

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.

Authoritative data is 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 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.

Research recommendation.

QoL research is needed involving prospective studies with the use of comprehensive scale validated in women with spontaneous and iatrogenic POI.

VIII.2. Management options

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

A large variety of therapeutics are available to support women with POI and the crucial point is to understand how to investigate QoL outcomes following intervention. POI is a physical health condition that affects multiple body systems so that some impact on HRQoL may be expected at some time point. The effect may be mild or moderate, transient, or prolonged, depending on a wide range of variables. It should not be implied that every woman reporting a reduction in QoL should be medically or psychologically treated. Psychological distress in response to (aspects of) POI is normal. Coping with a level of adversity across the lifespan is intrinsic to human development.

In some situations, a caring professional attitude may be the best form of clinical management. A telephone interview study based on findings from focus groups suggested that the manner in which women are informed about their diagnosis could significantly affect their level of distress, and they expressed a need for HCPs to spend more time with them and provide more information about their condition (Groff *et al.*, 2005).

A recent review including 19 studies involving a total of 10856 participants with various chronic conditions points to the importance of personalised care planning (Coulter *et al.*, 2015). Having a conversation, or series of conversations, in which patients and HCPs identify and discuss problems caused by or related to a given chronic condition leads to improvements in certain indicators of physical and psychological health status, and people's capability to self-manage their condition when compared to routine care (Coulter *et al.*, 2015). Ideally, HCPs should be able to integrate personalised care planning into routine consultations to empower women with POI in the decision-making regarding their condition with the ultimate goal of enhancing QoL.

A very important aspect of empowering women with POI to take individual decisions on pharmacological and non-pharmacological strategies to improve QoL and psychological wellbeing is the development of co-designed instruments to help them to understand the condition and to facilitate the communication with HCPs (Yeganeh *et al.*, 2020b). A study in 2017 indicates the need for higher-quality internet resources for women seeking information on early menopause (Aleksova *et al.*, 2017). A question prompt list -a structured list of questions- has been developed to assist women with early menopause in acquiring relevant information and facilitating communication with HCPs. Both women

and HCPs found it useful to overcome communication difficulties related to sexual function (vaginal/urinary symptoms) and psychological impact (Yeganeh *et al.*, 2020c). A recent study using a co-designed early menopause digital resource shows an improvement in women's health-related empowerment, illness perception, menopause symptoms, risk perception, and knowledge (Yeganeh *et al.*, 2022). This approach has the potential to further improve QoL in women with POI that may feel part of a community as well as perceive a shared reality of their condition with HCPs.

The guiding principle in daily practice should be individualized care (Figure 12).

Medical interventions

An early review that focused specifically on the effects of hormone interventions on QoL concluded that estrogen with or without testosterone may improve general wellbeing in some surgically menopausal women for whom the level of serum estrogen was within a premenopausal range. They further observed that adding testosterone to estrogen therapy may provide additional improvements in wellbeing in some women but only at supra-physiological levels of total testosterone and physiological levels of free testosterone (Kotz *et al.*, 2006). A recent systematic review and meta-analysis (Gonçalves *et al.*, 2022) assessing several endpoints of hormone therapy (HT) in women with POI included two RCTs evaluating QoL (Zuckerman-Levin *et al.*, 2009, Guerrieri *et al.*, 2014). These studies were designed to compare groups treated with and without testosterone and showed that women with POI treated with estrogen plus progestogen had stability or improvement in the QoL scores after 1 year. One study (Zuckerman-Levin *et al.*, 2009) was conducted in 14 young (age range: 17-27 years) women with Turner Syndrome treated with estrogen/progestogen replacement therapy and receiving oral 1.5 mg methyl testosterone or placebo for 1 year and the alternative for another year. QoL, including general health, coping with stress, and sexual desire, were significantly improved by using androgen treatment, which was safe when given for 1 year. The other study was conducted in 128 women with 46,XX non-iatrogenic POI over a 12-month period (Guerrieri *et al.*, 2014). The research team concluded that augmentation of standard estrogen/progestogen therapy with physiologic low-dose testosterone (150-µg patch) in young women with POI did not change reported QoL or self-esteem and had minimal impact on mood. It was suggested that other pathways were likely to be involved in any mood alterations associated with POI. Another study in adults with Turner Syndrome explored long-term psychological functioning after androgen exposure (oxandrolone) during childhood in terms of neurocognition, QoL and social-emotional functioning (Freriks *et al.*, 2015). Results suggest that early androgen treatment has long-term effects on adult QoL (higher anxiety and depression levels) and social-emotional functioning (lower emotion perception for fearful faces without effect on interpersonal behaviour) (Freriks *et al.*, 2015).

A cross-sectional study of 61 women with POI receiving HT and 61 aga-matched women with preserved ovarian function showed that women with POI receiving HT have poor sleep quality, take longer to fall asleep and have a higher fatigue index (Benetti-Pinto *et al.*, 2019). The same research team showed that women with POI receiving HT have indexes of depression, anxiety, and stress similar to the population of women with preserved ovarian function (Menezes *et al.*, 2020). However, the cross-sectional design of these studies does not allow cause and effect conclusions. A systematic review of studies considering patient-reported outcomes for psychological and sexual wellbeing in surgically menopausal women and women after BSO, but not POI, showed that estradiol may beneficially affect psychological symptoms and testosterone might improve sexual desire and overall sexual functioning (Stuursma *et al.*, 2022).

Vasomotor symptoms could be implicated in a reduction of QoL for some women. In a cohort study, HT was reported to be associated with up to 80% reduction in the prevalence of hot flushes in POI (Vermeulen *et al.*, 2017). Non-hormonal drugs including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitor (SNRIs), clonidine, and gabapentin have produced moderate reductions in hot flush and night sweat frequency, averaging 37% across trials, although they

appear to have little effect on QoL measures (Rada *et al.*, 2010). Escitalopram and venlafaxine used as a non-hormonal therapy for vasomotor symptoms were associated with improvement in psychosocial QoL in peri-postmenopausal women, but effects have not been specifically assessed in POI (Diem *et al.*, 2020) (see also XII.1. Non-hormonal therapies). Back in 2005, Utian (Utian, 2005) stated that in women who need or wish to avoid HT, additional targeted therapies, validated by results from controlled clinical trials that are safe, efficacious, cost-effective, and well tolerated by symptomatic women are needed. At present, there is some hope from the possible use of a new class of drugs (NK3R antagonists) that target the hypothalamic neuroendocrine mechanisms generating vasomotor symptoms (Menown and Tello, 2021), but no data on their efficacy and safety are available in women with POI.

Psychological interventions

For some women diagnosed with POI, psychological wellbeing may be particularly compromised at specific time points, such as the time of diagnosis, when physical symptoms are most acute, when fertility treatments are being pursued, at the beginning or ending of an important relationship, or when a number of physical, psychosocial, and economic factors converge to exacerbate distress. The approach taken would depend on the presenting complaint, the therapeutic orientation of the HCP, and service constraints, bearing in mind that psychological interventions should be tailored to the specific needs of women with POI (McDonald *et al.*, 2022). To date however, there is no authoritative evaluative research of psychological interventions specific to a diagnosis of POI. This is partly because psychological interventions tend not to target medical diagnoses as such, but a psychological problem (e.g. health anxiety), which may be related to an aspect or multiple aspects of a condition (e.g. infertility) rather than to the diagnosis per se (e.g. POI). Singer stated that practicing sensibly may help women with POI to psychologically adjust to their situation. Even the involvement of the partner, when present, can help in understanding and communication (Singer, 2019).

Nonmedical interventions mostly comprise cognitive behavioural therapy (CBT) with a primary focus on vasomotor symptoms and indirect effects on QoL. A brief CBT (four to six sessions), theory- and evidence-based, is acceptable to women and was shown to have benefits to QoL (Hunter, 2021). A systematic review and meta-analysis including 14 RCTs comprising 1618 patients focussing on vasomotor symptoms reported a moderate effect of CBT on QoL (Ye *et al.*, 2022). Mindfulness-based interventions can improve overall QoL of menopausal women (Chen *et al.*, 2021). An Iranian randomized clinical study conducted in women with POI showed an improvement of QoL, but its methodology has been questioned (Pyri *et al.*, 2021).

Other approaches, including acupuncture, relaxation therapy, and exercise, have not been evaluated for effect on QoL. Studies focussing on vasomotor symptoms are discussed in section XII.2. Complementary therapies.

Where infertility is centrally implicated in a significant reduction of wellbeing, routine psychosocial care is mandatory according to recommendations formulated for infertile couples (Gameiro *et al.*, 2015, Romualdi *et al.*, 2023). However, fostering wellbeing in women with POI implies a stronger promotion of active coping and identity integration to manage stigmatisation that can predispose to poorer mental health independently of the infertility burden (McDonald *et al.*, 2022). Psychological distress in women with POI was negatively associated with goal re-engagement despite continued preoccupation with the loss (Davis *et al.*, 2010). Whilst supportive counselling could be first line psychological input, for some women there may be a need to extend such input to help patients to renegotiate life goals successfully.

A wide range of psychological approaches for infertility have been described that may be relevant in supporting adjustment to the diagnosis of POI. An early review (Boivin, 2003) identified three categories of intervention: i) counselling; ii) focussed education (including sex therapy, coping training, support and stress reduction, autogenic training, and preparatory information); and iii) comprehensive

educational programmes (including a mixed range of coping and relaxation techniques). Therapy offered was both short-term (1-2 weeks) and long-term (32 weeks) and formats varied including group, couple, and individual work. The author reported that on the whole, the interventions were more effective in reducing negative affect than in changing interpersonal functioning (e.g. social or marital relationships), and that group interventions, which had an emphasis on education and skills training, were more effective across a range of outcomes than those that required more emotional expression of thoughts and feelings in relation to infertility. None of these studies were specific to women with a definitive diagnosis of POI or QoL as an outcome. However, the review was useful in signposting a need for all psychological interventions to be more clearly specified and accountable, rather than referred to as 'counselling' as a catch-all concept. It is important to bear in mind that for many diagnosed women, POI is not the only challenge to their wellbeing, or even the most important one. The influence of past and (con)current psychosocial vulnerabilities should not be overlooked. Therefore, where psychological distress is significant and prolonged, a potential referral to specialist psychological or mental health care pathways should be discussed.

At present, care models for POI are under development taking into account six key themes: stakeholder engagement, supporting integrated care, evidence-based care, defined outcomes and evaluation, incorporating behaviour change methodology and adaptability (Jones *et al.*, 2020). Engagement of patients is central to improve clinical and process outcomes, translate evidence into practice, and use resources more efficiently to deliver a multidisciplinary care for POI.

Recommendation

Personalised care, including psychological support, should be accessible to women with POI	⊕◯◯◯	**STRONG**

Justification

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. An offer of intervention should be based on a thorough and holistic assessment of the presentation, and multi-disciplinary skills may be required. Once the hormone profile is adjusted, psychological interventions for problems that are associated with POI can lead to positive benefits on QoL, although validated, disease specific instruments to measure effectiveness are lacking. Contribution of patients is of paramount importance to fill the gaps still present in the POI process of care.

Research recommendation.

The role of medical and psychological interventions in improving QoL should be implemented with the aid of adequate instruments developed in collaboration with women with POI of different aetiologies.

IX. POI and sexuality

Sexual experiences and their interpretation and reporting are complex mind-body experiences. Observations within a purely biomedical knowledge framework are inevitably incomplete. POI may have direct or indirect effects on sexuality and the biopsychosocial model is essential to manage sexual consequences. Health-related quality of life (HRQoL), including sexual areas, is significantly impaired (Li *et al.*, 2020b). However, patient-centred primary research is sparse in the clinical literature and more efforts are necessary to explore the role of underlining POI aetiologies and life stages in QoL. Available data do not allow a confident answer to questions on female sexuality and POI in ways that are helpful to affected women and close others. Targeted-interventions (McDonald *et al.*, 2022) require detailed exploration of the potential sexuality effects of POI in a multidimensional perspective selecting relevant samples and using adequate instruments to assess and monitor bio-medical and/or psychosocial interventions.

IX.1. Impact of POI on sexuality

PICO Question: What are the consequences of POI for sexuality?

General aspects

Well-designed studies on sexuality in women with non-iatrogenic POI are limited and most data addressing sexual concerns are part of the general assessment of menopausal symptomatology following the standard approach used for usual age menopause (Nappi *et al.*, 2019). For instance, in a recent cross-sectional study involving 293 Chinese women with POI the use of the modified Kupperman Menopausal Index displays a high prevalence of menopausal symptoms, particularly related to psychological and sexual domains (Huang *et al.*, 2021). On the other hand, the adverse health consequences of early loss of ovarian function, including sexual consequences, are most studied in women experiencing iatrogenic POI [surgical treatment for benign gynaecologic disorders and risk reducing bilateral salpingo-oophorectomy (RRBSO) in women with BRCA mutations] (Kingsberg *et al.*, 2020). Less data on sexuality are available in survivors of childhood, adolescent, and young adult (AYA) cancer with POI (Lindau *et al.*, 2015) and even genitourinary symptoms have not been investigated yet according to a recent systematic review (Gargus *et al.*, 2018). However, despite many similarities, every clinical scenario displays its own biopsychosocial peculiarities that introduce confounding variables (e.g., variable endocrine milieu, anatomical modifications of the vaginal canal, loss of sensitivity and the emotional sequelae of the threat of the illness that had necessitated different types of surgery/treatments), rendering them at best partially comparable and generalizable to non-iatrogenic POI.

As reported, POI is a life-altering diagnosis with several psychosocial ramifications encompassing multiple dimensions of womanhood (Rafique *et al.*, 2012) which significantly influence sexuality along with the primary effect of the physiological changes associated with early hormonal deprivation (Panay *et al.*, 2020)(see also VIII. POI and psychological wellbeing). A qualitative focus on the perception and experience of women with POI regarding their sexual and reproductive health identifies four critical areas: endangerment of women's health, psychological agitation, disruption of social life and disturbance in sexual life (Moukhah *et al.*, 2021). However, the lack of difference between sexual function and distress in women who are unaware that they have POI and in age-matched women with normal gonadal function offers a fair example (Aydin *et al.*, 2017) that sexual effects of POI on women is far from straightforward. In reading the data on sexuality in women with POI, it is also important to consider that the hormonal challenge occurs at a younger age when distress associated with sexual complaints

is usually higher but age-dependent processes affecting the multi-systemic sexual response are less impaired in respect to women experiencing menopause at usual age.

Common clinical conditions associated with sexual problems.

The two most common clinical conditions associated with sexual problems in women with menopause at usual age are genitourinary syndrome of menopause (GSM) and low sexual desire with distress, named hypoactive sexual desire disorder (HSDD). Uncomfortable or painful intercourse from vaginal dryness is part of GSM, a chronic progressive condition associated with hormone- and age-dependent changes in urogenital tissues, which may influence all domains of the sexual response (desire, arousal, orgasm, satisfaction). HSDD is dependent on both hormonal changes, namely androgen decline, and other psychosocial aspects affecting intimacy and satisfaction with sex (Simon *et al.*, 2018a). HSDD has been well described in women with surgical menopause, who are deprived early of sex hormones, but it may be present in women of any age even in the absence of low testosterone levels, which cannot be used to diagnose poor sexual function. A certain amount of controversy exists concerning the separation of sexual desire domain from arousal domain and a single condition termed female sexual interest and arousal disorder (FSIAD) has been proposed in the last Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (Kingsberg and Simon, 2020).

Sexual function in women with POI

A study conducted in Turkey comparing surgically menopausal women with women undergoing menopause at usual age showed that surgery significantly affects sexual desire but not overall sexual performance (Bıldırcın *et al.*, 2020). Another Turkish cohort of non-iatrogenic and iatrogenic menopause reported no significant differences between the groups with respect to mean scores for desire, arousal, lubrication, orgasm, satisfaction, pain and sexual function measured by the Female Sexual Function Index (FSFI) (Gulbahar and Akgun Kavurmaci, 2022). Culture plays a crucial role in rebuilding individual feminine identity and sexual/marital relationship after surgical menopause, as shown by qualitative research conducted in Iran. Indeed, the main concern of women with surgical menopause is the emotional separation because of sexual changes after surgery (Abadi *et al.*, 2018).

Women with a BRCA1/2 mutation, who have undergone premenopausal RRBSO after completion of childbearing to reduce their risk of ovarian cancer, show a decline in sexual functioning following 3.5 years post-surgery (Hall *et al.*, 2019). However, a meta-analysis shows that decline of sexual function after RRBSO is independent of menopausal status (Kershaw *et al.*, 2021). Indeed, a recent large study demonstrated that the proportion of sexually active women (with premenopausal RRBSO more than 15 years ago is comparable with the proportion of sexually active women with a postmenopausal RRSO more than 15 years after premenopausal RRBSO. These same women with POI induced by risk reducing surgery experience more vaginal dryness and more often have substantial sexual discomfort during sexual intercourse without reporting less pleasure with sexual activity (Terra *et al.*, 2023). In a cross-sectional study of breast cancer survivors, similar sexual function scores and QoL are present in women with RRBSO or not with a rate of sexual dysfunction and HSDD already very high before the surgery (Tucker *et al.*, 2021). Recent systematic reviews and meta-analyses underline the importance of BSO in overall sexual function changes and the need of analysing predictors of sexual function change trajectories, especially different indications (Dedden *et al.*, 2023) and profiles of risk (Morgan *et al.*, 2023).

By using a general scale for menopausal symptomatology and QoL, a Chinese observational study of 215 women with POI after HSCT and 200 controls (menopausal women) showed no differences in scores related to sexual problems and vaginal dryness (Su *et al.*, 2020a). In young estrogen-replete women with spontaneous 46,XX POI, the Derogatis Interview for Sexual Function Self-Report (DISF-SR) indicated that sexual scores are lower, but still in the normal range, in comparison with regularly menstruating controls, and display a significant correlation with circulating testosterone levels. Women with POI with

lower circulating testosterone showed a non-significant trend to lower sexual function scores (Kalantaridou *et al.*, 2008). A case-control study evaluating sexual wellbeing concluded that women with POI have diminished general and sexual wellbeing and are less satisfied with their sexual lives than controls (van der Stege *et al.*, 2008). In addition, they have fewer sexual fantasies and masturbated less frequently. Sexual contacts were associated with less sexual arousal, reduced lubrication, and increased genital pain. However, the frequency of desire to have sexual contact and the frequency of actual sexual contact with the partner did not differ between women with POI and control women and was primarily affected by the wish to have (more) children. Women with POI had lower levels of total testosterone, which has only a weak influence on sexual functioning, and used HT in 59% of the cases, without any difference in sexual wellbeing or satisfaction between users and non-users (van der Stege *et al.*, 2008). A cross-sectional study comparing women with POI with an age-matched control group with normal ovarian function reported a diagnosis of sexual dysfunction (through cut-off score of the total FSFI) in 62.1% and 37.8% respectively. They calculated a 2.8-fold increased risk of sexual dysfunction in POI and commented that desire was the only FSFI domain showing no difference with controls (de Almeida *et al.*, 2011). In a subsequent study, the same research group reported that women with POI have impaired sexual function, mainly due to changes in arousal and desire (Benetti-Pinto *et al.*, 2015c). These data suggest an overall impact of POI on sexual function and point to the need to explore further the role of hormonal milieu and intimacy-based stimuli in sexual desire and arousal, and in their connection with poor lubrication and sexual pain. A narrative review on the long-term effects of POI indicated that urogenital atrophy interferes significantly with sexual functioning (Podfigurna-Stopa *et al.*, 2016). More recently, a case-control study of 66Iranian women (with POI and 66 age-matched fertile controls showed an in impairment in all areas of sexual function and QoL. Sexual desire, arousal, satisfaction, and pain had the most impact on QoL in women with POI (Javadpour *et al.*, 2021). A French cross-sectional observational study involving 88 women with POI showed a negative impact of GSM on QoL and sexual wellbeing by using validated questionnaires [Day-to-Day Impact of Vaginal Aging (DIVA) and FSFI] (Gosset *et al.*, 2023). An earlier study assessed the psychosexual wellness (as opposed to sexual function, a more performance-based construct) in a group of women aged 19 to 40 with POI interviewed by post (Liao *et al.*, 2000). Compared to normative data, women with POI reported lower scores on Sexual Esteem, Sexual Assertiveness, and Sexual Satisfaction, and higher on Sexual Anxiety and Sexual Depression.

In a cross-sectional observational study comparing 302 women with Turner Syndrome (TS) and 53 women with karyotypically normal POI, age at first relationship and sexual debut were significantly higher in women with TS, with no difference on whether estrogen replacement was started before or after 14 years of age. After adjusting for age and diagnosis, induction of puberty, as opposed to spontaneous puberty, was associated with a delay in the median age at first relationship and sexual debut, as well as with a reduced probability of having vaginal sexual intercourse (Cardona Attard *et al.*, 2020). Another cross-sectional study showed overall good sexual wellbeing and normal genital touch sensitivity in women born with differences of sex development or early loss of gonadal function (complete gonadal dysgenesis and POI) as compared to population-derived controls (Engberg *et al.*, 2022).

Recommendations

HCPs should be aware that a diagnosis of POI can have a significant impact on sexual wellbeing and function	⊕⊕◯◯	**STRONG**

The guideline group recommends that HCPs routinely enquire about sexual wellbeing and sexual function in women with POI.	**GPP**

Justification

Sexuality in women with POI may well be affected in the context of QoL aspects associated with the condition (see VIII. POI and psychological wellbeing) and its own aetiology. Despite the multidimensional aspects characterizing sexual experience, there is a lack of inter-disciplinary approach in current literature that limits interpretation of available data on the sexual consequences of POI. Whilst most studies acknowledge multiple factors, from hormonal to spiritual, there is a lack of commitment to collect quality information from socially diverse samples within a coherent inter-disciplinary framework. It is highly unlikely that any finding is generalizable to women across age groups and cultural and socio-economic conditions. Gender-equality issues and women's ability to sexually self-determine will profoundly shape their sexual outlook in relation to POI and generally.

There is an urgent need to develop a process of care based on the most recent model available for managing women's sexuality (Parish *et al.*, 2019), taking into account the number of mechanisms and factors able to characterize the relationship between POI and multiple aspects of sexuality. Basic counselling should be provided to uncover the topic and offer the basis for a multidimensional clinical interview that could be adapted to different categories of women with POI, stratified by age, diagnosis, partnership, and fulfilment of reproductive goals, general menopausal symptoms, attitudes and compliance to treatments, and any other relevant intra-personal and inter-personal variable. Core competences should include the identification of the most common sexual problems that cause distress, including low sexual desire, difficulty with sexual arousal and with orgasm, sexual pain/genito-pelvic pain, penetration dysfunction, medication-induced symptoms, and relationship conflicts. A diagnostic algorithm (see Figure 12) will provide guidance in the treatment and will help to understand when a referral to sexual medicine specialists for specific care is needed.

Research recommendation.

Studies conducted in a multidimensional perspective are needed to assess sexual changes in women with POI and the entity of distress.

A process of care specifically developed for women with POI presenting sexual symptoms is warranted.

IX.2. Management options

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

General aspects

A number of known and potential factors contribute to sexuality and sexual experiences, rendering sexual difficulties as much psychosocial as physical, hence the often-used description 'psychosexual'. The most recent standard process of care for management of sexual concerns and problems in women (Parish *et al.*, 2019), including HSDD (Clayton *et al.*, 2018), describes a therapeutic algorithm based on a multidisciplinary approach with pharmacologic and non-pharmacologic management. This separation is mainly for didactic purpose keeping in mind that, basically, acquired generalized sexual dysfunction firstly requires a biomedical approach, whereas lifelong or situational sexual dysfunction firstly needs a psychosexual approach. Brief counselling offers emotional relief, education, and empowerment, and provides very simple strategies to cope with sexual symptoms (Al-Azzawi *et al.*, 2010); therefore, it can

represent a first-line treatment in postmenopausal women, including those with POI. By replacing hormonal deficiencies, medical treatments aim to restore the neuroendocrine balance, which drives sexual desire, mental arousal, and satisfaction, and to maintain the urogenital response (genital arousal, lubrication, and orgasm) to sexual stimulatory clues (Nappi *et al.*, 2019). Non-pharmacological management includes multimodal physical therapies and cognitive behavioural and sexual therapies, alone or in combination for those women who may benefit from this approach (Nappi *et al.*, 2023a).

Systemic Estrogens

Estrogens are important for the health and function of the genitourinary system and preventing dyspareunia will affect sexual function and desire. The treatments for GSM are reviewed in IX.3. Treatment of genital-urinary symptoms. Systemic estrogens may also be relevant for other components that contribute to sexuality, possibly affecting peripheral as well as central neurotransmission and neurovascular modulators and should be the first choice in women with POI without contraindications (Nappi *et al.*, 2021). Women receiving estrogen therapy after oophorectomy reported better global sexual function but may require higher doses of estradiol replacement (Zilio Rech *et al.*, 2019). Even in women with POI, after RRBSO due to a BRCA mutation without personal history of breast cancer, the use of estrogen therapy for 1 year minimizes menopausal symptoms and sexual discomfort (Vermeulen *et al.*, 2017). Another prospective observational study of 73 premenopausal women at elevated risk of ovarian cancer planning RRBSO and 68 premenopausal controls at population risk of ovarian cancer confirmed the adverse impact of surgery on several aspects of sexual function (arousal, lubrication, orgasm, and pain), which may be mitigated by the use of estrogen therapy (Islam *et al.*, 2021). However, after 1-year, sexual desire and satisfaction were unchanged in the RRBSO group compared with controls. Indeed, according to another study investigating women with POI due to RRBSO, sexual symptoms profile (vaginal dryness and low sexual desire) does not always improve suggesting that HT may alleviate but not resolve sexual difficulties (Moss *et al.*, 2022). That being so, factors other than estrogens may influence sexuality in women with POI. A small Brazilian case-control study of 36 sexually active women with non-iatrogenic POI aged 18 to 40 years shows that following 12 months of systemic HT women with POI display significantly lower FSFI domain scores, in comparison with age-matched women with normal gonadal function, despite having similar vaginal tropism and vaginal flora (Pacello *et al.*, 2014). More sexual pain and poorer lubrication are present in treated POI women that score less on the vaginal health index (VHI), a clinical tool assessing vaginal mucosa elasticity, epithelial integrity, fluid secretion, pH, and hydration (Benetti-Pinto *et al.*, 2015b). The same group has recently compared the use of perineal electrotherapy sessions versus local estrogen therapy (LET) with low dose estriol vaginal cream in estrogen-replete women with POI showing an improvement in global sexual function, lubrication, and pain domains for both treatments. Of note, there was no pre-/posttreatment difference for the desire and arousal domains, whereas both orgasm and satisfaction improved with perineal stimulation (Benetti-Pinto *et al.*, 2020).

It is very important to underline that systemic HT has been mainly investigated in early menopausal women or in presence of menopausal symptoms with evidence of a small benefit on sexual function (Meziou *et al.*, 2023). Types of molecules and their metabolites, dose, and route of administration have to be considered to minimize the relative androgen insufficiency induced by exogenous estrogens, which may variably affect sex hormone binding globulin (SHBG) and free testosterone circulating levels (Nappi *et al.*, 2022b). When compared to oral formulations, transdermal estradiol improved lubrication and pain, measured by FSFI to a higher extent, with no significant difference in overall score of sexual function (Taylor *et al.*, 2017). The type and dose of combined progestogens add a further element of complexity due to the impact on SHBG. However, in absence of any evidence that the different androgenicity of progestogens plays a role in modulating sexual function, tolerability and safety should guide treatment choice (Nappi *et al.*, 2022b). It is important to underline also the lack of clear evidence

on the impact of combined hormonal contraception on sexuality of women with POI. In general, available evidence indicates that a minority of women experience a change in sexual functioning with regard to general sexual response, desire, lubrication, orgasm, and relationship satisfaction when assuming hormonal contraception (Both *et al.*, 2019). Natural estrogens in some oral contraceptives have a lesser effect on SHBG levels and, thus, exert a milder impact on androgen milieu (Nappi *et al.*, 2019). However, there is insufficient evidence to draw a clear algorithm for the management of hormonal contraception-induced sexual dysfunction in healthy women and, therefore, in women with POI.

Systemic Testosterone and other androgenic compounds

Clinical research has focused almost exclusively on the use of testosterone for low sexual desire, even though the relationship between the two is not certain. This is as true for women in general as for those diagnosed with POI. The rationale is rooted in the decline of androgens over time and under certain circumstances (iatrogenic or non-iatrogenic POI) (Davis *et al.*, 2019).

A series of randomised, placebo-controlled trials of testosterone patches have been carried out, using 300µg, daily for 24 weeks, in the form of a twice weekly patch worn on the abdomen (Shifren *et al.*, 2000, Braunstein *et al.*, 2005, Buster *et al.*, 2005, Simon *et al.*, 2005, Davis *et al.*, 2006, Shifren *et al.*, 2006, Davis *et al.*, 2008, Panay *et al.*, 2010). Some of these studies were part of the Phase III trial program that induced the European Medical Agency (EMA) to approve transdermal testosterone in surgically menopausal women with HSDD, whereas others were conducted in estrogen-replete and non-replete women with usual age menopause, and at premenopause. Overall, the effectiveness was clinically meaningful for improved sexual function as assessed by self-reports on psychometric scales and sexual activity logs alike, over and above a large placebo effect (Kingsberg *et al.*, 2007). A point of controversy is that all studies involved short-term treatment and follow-up. Moreover, the most intensively studied population was one of Caucasian (and presumably heterosexual) women, making the evidence not yet applicable to other populations. Adverse events of testosterone patches were reported as mild or minimal, rarely resulting in trial withdrawal, and no important changes in the safety or tolerability profile were revealed with long-term use for up to 4 years in a cohort of otherwise healthy women after BSO with HSDD on concomitant estrogens (Nachtigall *et al.*, 2011). However, long-term health and harm on a large scale remains unknown because testosterone patches prescribed in the trials are no longer available. A special consideration should be given to the occurrence of pregnancy in young POI women under testosterone treatment, even though the virilization risk to the foetus is minimal and occurs only in a very high hyperandrogenic state (Nappi *et al.*, 2019).A recent Global Consensus Position Statement provides clear clinical guidance on the use of testosterone therapy in women (Davis *et al.*, 2019), aiming to: (i) identify women that might benefit from testosterone therapy, (ii) to recognize symptoms, signs, and conditions without evidence for prescribing testosterone, (iii) to explore areas of uncertainty, and (iv) to avoid prescribing practices that have the potential to cause harm. Recommendations regarding the benefits and risks of testosterone therapy are based on findings of meta-analyses, which included blinded placebo/ comparator RCTs, of at least 12 weeks duration (Islam, *et al.*, 2019). Available data support a moderate therapeutic effect for HSDD, with insufficient data to support the use of testosterone for the treatment of any other symptom or clinical condition, or for disease prevention. The 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 further provides standards for safe prescription including identification of appropriate patients, dosing, and monitoring (Parish *et al.*, 2021). Shared decision-making involves comprehensive discussion of off-label use of one-tenth of a standard male dose of 1% transdermal testosterone or about 300 µg/day, as well as benefits and risks. Indeed, only in Australia is a transdermal 1% testosterone cream available by prescription, approved in

2020 by the Australian Register of Therapeutics Goods for treatment of HSDD in postmenopausal women.

In agreement with The Fourth International Consultation of Sexual Medicine conducting studies of testosterone therapy for women with POI presenting with desire and other sexual problems is desirable (Davis *et al.*, 2016) and will offer the possibility to explore also other effects on general health (see XI.5. Testosterone Therapy). A large number of exclusion criteria were deployed in previous research with testosterone patches, which may restrict the applicability of the findings within clinical practice, where women with POI may present with a range of issues that have been excluded. However, it seems reasonable to offer a trial of testosterone therapy for women with POI who experience HSDD despite adequate HT for at least 6 months, monitoring testosterone levels to avoid supra-physiological exposure (Davis, 2021).

Other androgenic compounds have been poorly investigated. Tibolone is a selective tissue estrogenic activity regulator, with some androgenic properties, approved in many countries for treatment of menopausal symptoms and for osteoporosis prevention (Baber *et al.*, 2016). A recent Cochrane review on synthetic steroids, including tibolone, did not show clear beneficial effects on sexual function advocating the need for high quality studies in the investigation of HT (Lara *et al.*, 2023). In a randomized crossover study involving women with iatrogenic POI (ovarian surgery), there were some signals that tibolone may improve sexual desire (in sexual subscale of the Greene Climacteric Scale) more than estrogen therapy alone (Somunkiran *et al.*, 2007). Whether this may translate in a larger sexual therapeutic effect of tibolone in women with natural POI is unknown.

In line with the Global Consensus Position Statement (Davis *et al.*, 2019), systemic dehydroepiandrosterone (DHEA) administration does not have consistent beneficial effects for menopausal symptoms, sexual function, cognition, or overall wellbeing in the general female population.

Psychosexual management

A range of dedicated professional services exists to provide assessment and treatment of sexual difficulties reported by men and women in the general population. This mirrors a broad acknowledgement of the role of complex interactions between the anatomical, physiological, psychological, and social factors in sexual preferences, activities, experiences, and their interpretations. Currently there is a significant amount of discussion on what type of intervention works best, for what, in what way, and for whom. The biopsychosocial lens suggests the need for combined therapy and a mix of approaches (Kingsberg *et al.*, 2017) keeping in mind that some women might respond better to one type of intervention over the others.

Knowledge needs to improve significantly to enable women with POI to make a truly informed choice. Indeed, sex therapy has received scanty scientific attention in women and couples affected by natural POI, whereas it often addresses psychosexual consequences of sexual pain and low distressing desire in usual age menopause (Simon *et al.*, 2018b). Psychosexual approaches aim to expand on patients' anatomical, physiological, and sexual knowledge and attitudes. Cognitive and behavioural strategies further assist sexually distressed patients to overcome unhelpful thoughts and feelings and encourage realistic goals to overcome problems or access preferred experiences (ter Kuile *et al.*, 2010).

Sexual counselling educational programs are effective in improving sexual dysfunction in postmenopausal women when compared to routine care (Santos Silva *et al.*, 2022). Evidence based techniques in sex therapy include sensate focus, cognitive behavioural therapy (CBT) and mindfulness, that may be useful to improve all domains of sexuality, including sexual pain and HSDD (Kingsberg *et al.*, 2017). A randomised controlled trial in 66 women carriers of the BRCA1/2 mutation who developed

at least two moderate-to-severe menopausal symptoms after RRBSO 8-week of mindfulness-based stress reduction improves menopause-related QoL, but not sexual functioning or distress (van Driel *et al.*, 2019a). Another randomized study with mindfulness versus education on sexuality and aging shows that women aged ≥45 years with low libido report a significant reduction of sexual distress with mindfulness and no significant changes in sexual function according to the type of sex therapy (Thomas *et al.*, 2023). A novel sexual health intervention, integrating elements of cognitive behavioural therapy with sexual health education, was tested in a single-arm trial in iatrogenic menopause (Bober *et al.*, 2015). Women with BRCA1/2 mutations who previously underwent RRBSO showed significant improvement in overall sexual functioning, as well as desire, arousal, satisfaction, and pain. Sexual self-efficacy and sexual knowledge also improved significantly from baseline to post intervention and women are highly satisfied with the intervention content and report utilizing new skills to manage sexual dysfunction. As in the gynaecological cancer population, both cognitive behavioural therapy and psychoeducation about sexuality and relationships can improve symptoms and sexual satisfaction in women with iatrogenic POI (Alexandre *et al.*, 2017).

Recommendation

The guideline group recommends personalised management using the biopsychosocial model for the effects of POI on sexuality.		**GPP**
Where available, transdermal testosterone therapy at physiological premenopausal levels can be considered as it may improve HSDD and sexual function.	⊕⊕◯◯	**CONDITIONAL**
HCPs should be aware that although short-term treatment with transdermal testosterone at physiological premenopausal levels is safe, longer term safety data are lacking.	⊕⊕◯◯	**STRONG**
HCPs should be aware that hormone therapy prescribed to women with POI for other indications may improve sexual function, although the effect is generally small.	⊕◯◯◯	**STRONG**

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 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. Adequate estrogen replacement, with additional local treatment if necessary for dyspareunia, is essential in women with POI and sexual dysfunction (see IX.3. Treatment of genital-urinary symptoms). 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.

For those who are refractory to hormone therapies and other women who have expressed a preference for non-medical interventions, which are so far under researched, low risk approaches such as psychosexual therapies may be of value and be more acceptable to a significant number of women with or without partners.

Research recommendation.

A better understanding on the effects of different type and dose of systemic estrogens alone or in combination with specific progestogens on sexuality of POI is warranted.

Studies should evaluate the safety of testosterone when applied for a longer period (more than 6 months) to improve sexual function in POI.

More research is needed to understand the difference between iatrogenic and non-iatrogenic POI in terms of testosterone levels and testosterone treatments.

IX.3. Treatment of genital-urinary symptoms

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

General aspects

Prolonged low levels of estrogens may lead to vulvovaginal atrophy (VVA), which is now part of genitourinary syndrome of menopause (GSM), a new definition encompassing a multitude of signs and symptoms related to genital, sexual and urinary health (Gandhi *et al.*, 2016). Even the decline of androgens plays a role given the presence of androgen receptors in the urogenital sinus and vaginal canal (Simon *et al.*, 2018b).

The real epidemiology of genitourinary symptoms in non-iatrogenic POI has not been reported. A recent systematic review (Mili *et al.*, 2021) on the prevalence of GSM symptoms (range 13%-87%) and its treatment (range 13-78%) included only one Spanish study out of 27 in which menopausal women were also under 40 years of age. This study reports up to 70% of postmenopausal women consulting the gynaecologist for GSM symptoms (vaginal dryness, irritation, itching, and dyspareunia) (Moral *et al.*, 2018). Iatrogenic POI seems especially associated with a significantly higher rate of VVA/GSM (Kingsberg *et al.*, 2020). A multitude of biopsychosocial factors is present in women after BSO, cancer survivors and in those undergoing risk reducing surgery. However, the endocrine insult deriving from surgery or chemotherapy, or radiotherapy plays a crucial role in the adverse effects on genitourinary health (Crean-Tate *et al.*, 2020). According to a recent systematic review, there is insufficient evidence to confirm that menopause is associated with urinary symptoms. The authors suggest that prospective studies of urinary symptoms after POI may help clarify the extent to which age or the endocrine changes of menopause contribute to urinary symptoms in this population (Christmas *et al.*, 2023).

A diagnosis of GSM combines the presence of subjective distressing symptoms with some objective signs that may be scored with validated scales to assess severity of the clinical condition and to monitor response to treatment. Despite available effective and safe treatments, research findings consistently show an unmet need in the management of VVA/GSM, requiring a proactive attitudes of health care providers (HCPs) to ensure compliance to chronic treatment (Shifren, 2018). More research is needed into the pathophysiology of VVA/GSM to explain variability of signs and symptoms across age groups and in dependence of specific risk factors that may affect the genitourinary environment (e.g., microbiota, immune system) (Stabile *et al.*, 2023).

Data about therapies specifically investigated in women with non-iatrogenic POI and VVA/GSM are lacking and evidence for practice derived from menopause at usual age (Nappi *et al.*, 2019) or from cancer survivors (Biglia *et al.*, 2015). Whenever possible, women with POI should start systemic HT but this may not be enough to relieve genitourinary symptoms (Panay *et al.*, 2020). In this case, vaginal non-hormonal and hormonal treatments, as well as other strategies may be added or selected with the specific purpose to alleviate symptoms and restore genitourinary tissues according to current international guidelines and local availability (Sturdee *et al.*, 2010, The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society, 2020, Hirschberg *et al.*, 2021).

Systemic therapy

Systemic hormone therapy (HT) relieves VVA/GSM symptoms in many postmenopausal women but not all. It has been calculated that in about 25% of them a combination of systemic and local therapy may be required initially to manage the condition (Sturdee *et al.*, 2010). In postmenopausal women with VVA/GSM on clinical examination, systemic HT reduced the incidence of urinary tract infections when compared with placebo (Marx *et al.*, 2004). However, systemic HT does not seem to improve urinary symptoms, including urinary (Christmas *et al.*, 2023) or faecal incontinence (Staller *et al.*, 2017).

A study including 149 patients with POI and 303 control women with similar age, BMI, and parity showed that the prevalence of stress urinary incontinence (SUI) is quite high among patients with POI, without an influence of duration of POI and use of systemic HT. Although data do not support an association between SUI and POI, the study points to the need to increase awareness about the importance of urinary system health in QoL of women with POI (Tan *et al.*, 2018). In a secondary analysis of a cross-sectional study that aimed to study the prevalence of pelvic floor disorders in women with POI, systemic HT did not modify pelvic floor muscle assessment scores but seems to improve some pelvic floor and urinary symptoms (Fante *et al.*, 2020).

POI is likely to occur in women following high dose chemotherapy and radiotherapy required for haematopoietic stem cell transplantation (HSCT). If medically stable, they are candidate to systemic HT and to regular gynaecological follow-up to prevent severe clinical signs and genital tract malignancies (Brennan and Hickey, 2017). Graft-versus-host disease (GVHD) is the main complication of allogeneic HSCT and can affect the genital tract causing vaginal bleeding, dyspareunia, synechia, and even complete vagina occlusion (Machado *et al.*, 2022), overlapping with VVA/GSM symptoms. An early study of 31 women with POI after HSCT showed that 54% of them have symptoms of VVA (vaginal dryness, burning sensation, and dyspareunia), 42% have urinary tract symptoms (dysuria, urinary frequency, mild urinary incontinence) and almost 100% display signs of genital atrophy. With systemic HT (various preparations were used), there is a rapid improvement of vulvovaginal atrophy and resolution of associated symptoms in half of the study sample (Piccioni *et al.*, 2004).

Ospemifene (SERM)

The use of a selective estrogen receptor modulators (SERMs), such as ospemifene, for relief of genito-urinary symptoms in women with POI has not been studied (Palacios *et al.*, 2023b). In view of the absence of data, there is no indication for this treatment in women with POI (Nappi *et al.*, 2021).

Local therapies

Vaginal lubricants, moisturizers, and other substances

Vaginal lubricants and moisturizers are available over the counter, but their chemical composition can vary significantly in pH, osmolality, and additives. They should be body similar to avoid irritation and minimize the risk of epithelial damage. 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. Lubricants can either be water, silicone or oil-based and are used prior to intercourse. They have been shown to relieve symptomatology of vaginal dryness and dyspareunia but also to enhance overall sexual satisfaction (Palacios *et al.*, 2023a). Moisturizers are longer lasting than lubricants and rehydrate tissues mimicking vaginal secretions (Cox and Panay, 2023). Hyaluronic acid-based moisturizers have been studied both in healthy and in high-risk women or survivors. Its strong water-binding properties provide lubricating and moisturizing effects, which contribute to maintaining a proper level of hydration and viscoelasticity in genitourinary tract. A review of available clinical data confirms its efficacy on signs and symptoms of VVA/GSM when regularly vaginally applied (Nappi *et al.*, 2022a). Other substances (oxytocin, polycarbophil, probiotics, herbal products, phytoestrogens, and vitamins) have been tested in local products for GSM symptoms, but more research is needed (Cox and Panay, 2023, Farahat *et al.*, 2023, Radnia *et al.*, 2023). The use of topical 4% aqueous lidocaine applied for 3 minutes before vaginal intercourse may be particularly effective for dyspareunia related to introital pain as compared to placebo (Faubion *et al.*, 2018).

Local estrogen therapy

Local estrogen therapy (LET) includes many vaginally administered products approved with the indication to treat symptomatic VVA because GSM is a novel heterogeneous clinical entity. Different formulations (tablets, rings, capsules, pessaries, creams, gels, and ovules) and molecules (estradiol [E2], estriol [E3], promestriene, conjugated equine estrogens [CEE] and estrone [E1]) are available displaying a class effect (Nappi *et al.*, 2023b). Indeed, the last Cochrane review in 2016 concluded that approved LET are all similarly effective in relieving vaginal dryness and dyspareunia, thus the choice should consider patient's preference (Lethaby *et al.*, 2016). Low-dose and ultra-low-dose LET is the gold standard due to its minimal systemic absorption and should be continued at the appropriate dose to relieve symptoms for as long as needed. When needed, LET can be used in association with systemic HT (Sturdee *et al.*, 2010). Long-term LET safety data show cardiovascular and oncological neutrality but special attention should be paid to women with iatrogenic POI due to hormone-sensitive malignancies. At present, in terms of recurrence risk, particularly in breast cancer survivors, who may present with severe symptoms associated with the use of anti-estrogenic therapies, especially aromatase inhibitors, a tailored counselling and a shared decision with the oncologist represent the standard of care (Faubion *et al.*, 2018). A recent systematic review and meta-analysis confirms caution related to cancer recurrence and points to the importance of keeping serum estradiol levels at the lowest possible concentration with the use of low dose LET (Comini *et al.*, 2023).

LET improves dysuria, frequency, urge incontinence, stress incontinence, and recurrent urinary tract infections in menopausal women (Christmas *et al.*, 2023). Even though LET is not a "universal fix" in the urologic setting, it is the first step in managing many of the effects of GSM in the urinary tract (Wasserman and Rubin, 2023).

In women with POI after allogeneic hematopoietic cell transplantation, early LET is effective in reducing in vaginal dryness, dyspareunia and prevent the occurrence of severe tissue consequences (Klasa *et al.*, 2020).

Local androgens

Intravaginal DHEA, also known as prasterone, is approved with the indication to relieve signs and symptoms of moderate-severe VVA with some benefits to sexual function and urinary function. Being a pro-hormone with an intracrine estro-androgenic intracellular action and only a minimal amount of steroid metabolites entering the circulation, it has a safety profile potentially suitable for women at high cancer risk or even for cancer survivors but well conducted studies are needed (Crean-Tate *et al.*, 2020) with validated assessment tools to better establish the efficacy, safety and cost effectiveness of intravaginal DHEA (Kearley-Shiers *et al.*, 2022). Use of local androgens are potential treatments in the

setting of concurrent aromatase inhibitors as aromatization to estradiol would be prevented In these patients, intravaginal testosterone cream shows efficacy to reduce dyspareunia and vaginal dryness and improve sexual function compared to placebo over a 24-week period, without significant changes in circulating sex steroids (Davis *et al.*, 2018).

Physical therapy

Physical therapy may be useful for several pelvic conditions, such as VVA/GSM, prolapse, vaginal laxity, incontinence, and may be combined with psychosexual education and other sex therapies. It ranges from use of vaginal dilators in women with severe dyspareunia (Faubion *et al.*, 2018) to vibrators that may increase sensation and engorgement, and to muscle exercises that may reduce pelvic floor dysfunctions and GSM, improving both perfusion and tonicity of pelvic tissues (Mercier *et al.*, 2023).

Lasers and other thermal energies

In recent years, energy-based therapies, including laser (micro ablative fractional CO_2 and non-ablative erbium laser) and radiofrequency technologies, have been proposed as an alternative to pharmacological treatment for GSM in healthy women and in women with contraindications to standard treatment, such as breast cancer survivors (Cucinella *et al.*, 2023). A recent pilot sham-controlled study with a novel home-use therapeutic ultrasound device for the treatment of vaginal dryness showed efficacy and safety, holding promise for postmenopausal women with VVA/GSM symptoms (Hickey *et al.*, 2023).

A systematic review and meta-analysis of RCTs found that vaginal laser treatment is associated with similar improvement in genitourinary symptoms as LET (Jang *et al.*, 2022b). A RCT comparing intravaginal laser therapy and hyaluronic acid suppositories showed that both options are effective for breast cancer women suffering from genitourinary symptoms with no differences between treatment regimens (Gold *et al.*, 2023). However, among women with postmenopausal vaginal symptoms, treatment with fractional CO_2 laser vs sham treatment did not significantly improve vaginal symptoms after 1 year (Li *et al.*, 2021b). In another prospective double-blind sham controlled RCT with 6 months of follow-up, CO_2 laser treatment was found to be safe, but no statistically significant differences in efficacy were observed between active therapy and sham laser therapy (Mension *et al.*, 2023). Therefore, caution and points of controversies still exist on efficacy versus less invasive measures, long-term effects and costs, and laser technology cannot be recommended as a standard of practice.

Other local approaches

In a small cohort bi-centric pilot study, multi-point vaginal intra-mucosal injections with a crosslinked hyaluronic acid may stimulate collagen formation improving VVA symptomatology and sexual function without modifying the vaginal mucosal thickness (Berreni *et al.*, 2021). Topical growth factors with the aim to activate collagen and elastin at a molecular level, and thus restore all vaginal functions such as secretion, absorption, elasticity, lubrication, and vaginal epithelium thickness deserve attention in well-designed studies (Isaza, 2019). In the meantime, HCPs and women are waiting for bioengineering techniques in regenerative medicine with stem cells tested in the preclinical model (Francés-Herrero *et al.*, 2022), all these approaches in female reproduction should still be considered experimental in the clinical setting.

Recommendation

HCPs should offer local estrogen therapy (LET) to improve genital, sexual and urinary GSM symptoms.	⊕◯◯◯	**STRONG**

Women with POI may be offered local estrogen therapy (LET) if GSM is not fully relieved by using systemic HT.	⊕◯◯◯	CONDITIONAL

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.	⊕◯◯◯	CONDITIONAL

The guideline group recommends that laser or thermal energy is not currently considered standard care for genitourinary syndrome of menopause (GSM) due to the lack of clear benefit in RCTs	**GPP**

Justification

Hypoestrogenism plays a crucial role in the clinical manifestation of genitourinary symptoms with a significant impact on QoL and sexual health. Symptoms are highly prevalent but the exact number of women with POI affected is not known. HCPs should be proactive in discussing genitourinary health because GSM is highly prevalent and undertreated, as women may not volunteer such symptoms. Vaginal lubricants, moisturizers, and menopause hormone therapy (both systemic and local) can be used to treat genitourinary symptoms. Vaginal lubricants and moisturizers may be used when there is a need for local treatment and systemic treatment is contra-indicated, or if women still experience genitourinary symptoms despite an appropriate dose of hormone therapy. Women with POI have not been considered in clinical trials for investigating the effects of local and systemic menopause hormone therapy on GSM.

Research recommendation.

More research conducted specifically in women with POI is needed on hormonal approaches for genitourinary symptoms.

Studies should explore the efficacy and safety of laser therapy and other non-hormonal approaches to relief genitourinary symptoms in women with POI, especially in those with contraindications to vaginal estrogen.

X. POI and neurological function

Neurological function was defined for the purpose of this review as cognitive impairment and dementia, parkinsonism and Parkinson's disease, and restless leg syndrome. By contrast, stroke was discussed as part of cardiovascular health following POI (see VII. POI and cardiometabolic health). A rapidly growing body of studies have directly investigated the long-term effects of both spontaneous and iatrogenic POI on neurological function. Many of these studies involved women who underwent premenopausal bilateral oophorectomy . Interestingly, bilateral salphingo-oophorectomy (BSO) was the most common cause of POI in a US study for the period 1988-2007 (Rocca *et al.*, 2023). The same pattern is expected to hold for many other countries; however, a decline in the frequency of oophorectomy over time has been reported in recent years (Erickson *et al.*, 2022).

This chapter is not addressing neurological function in women who experience POI in the context of a genetic disorder because it remains unclear whether the neurological manifestations observed are related to the premature deprivation of ovarian hormones (POI per se) or to the underlying chromosomal or genetic condition. In these genetic disorders, POI is only one of several manifestations of the disease. The neurological manifestations may precede, accompany, or follow the development of POI and generally do not respond well to estrogen treatment. For example, women with Turner Syndrome may have characteristic neurocognitive and psychosocial differences, including visuo-spatial and perceptual changes that are relatively estrogen-resistant, whereas other neurocognitive effects may respond at least in part to estrogen. In women who are carriers of the Fragile X premutation, there is a risk of developing Fragile X-associated tremor/ataxia syndrome (FTAS), which may affect about 16% of women. Readers are referred to specific literature and guidelines concerning neurological function and long-term sequelae in women affected by these genetic disorders (Ross *et al.*, 2000, Hutaff-Lee *et al.*, 2019, Cabal-Herrera *et al.*, 2020, Gravholt, 2024).

The focus of this chapter is on the long-term sequelae of the hormonal deprivation caused by POI rather than on acute changes in cognitive function (e.g., memory) caused by iatrogenic POI.

X.1. Impact of POI on neurological function

PICO Question: What are the consequences of POI on cognition/neurological function?

Cognitive impairment and dementia after non-iatrogenic POI

A number of authors have investigated the association between earlier age of menopause and risk of dementia or cognitive impairment (measured by cognitive tests). A 2016 systematic review and meta-analysis identified thirteen studies of adequate quality. (Georgakis *et al.*, 2016). Unfortunately, the studies showed a wide variability in study design (case-control studies, cross-sectional studies, and cohort studies), in the outcome measured (clinically defined dementia, dementia on death certificates, clinically defined Alzheimer's disease, Alzheimer's disease on death certificates, and severe cognitive impairment measured by cognitive tests), and in the number of confounding variables considered (level of adjustment). Finally, and important for this chapter, the cut-off point used to separate earlier onset menopause from later onset menopause varied greatly. Only one study used the cut-off of ≤40 year that would directly relate to POI (Ryan *et al.*, 2014). The authors contrasted later menopause to earlier menopause; therefore, the measures of association were reported in the opposite direction (decreased risk with later menopause rather than increased risk with younger menopause). Overall analyses did not show a significant decreased risk of dementia or of Alzheimer's disease in women who experienced a

later menopause. However, the analyses showed a significant decrease in cognitive impairment (Georgakis *et al.*, 2016).

A later systematic review focused on ten studies and used the cut-off of <45 vs. ≥45 years. The authors reported a decreased risk of all-cause dementia for menopause at age ≥45 years compared to <45 years. The association followed a linear trend by which the older the age of menopause, the lower was the risk of all-cause dementia. There was also a significant decrease in risk for Alzheimer's disease and vascular dementia considered separately. Finally, there was a decrease in risk of cognitive impairment (Fu *et al.*, 2022).

A 2022 study based on the UK Biobank reported an increased risk of all-cause dementia when comparing spontaneous menopause before age 47 years with spontaneous menopause at age 50 years (Gong *et al.*, 2022). A 2023 study based again on the UK Biobank provided more detailed analyses by age of menopause. The risk of all-cause dementia was increased both for premature spontaneous menopause (HR 1.4; 95% CI 1.0 to 1.8; age ≤40 years) and for early spontaneous menopause (HR 1.2; 95% CI 1.0 to 1.4; age 41-45 years) compared to women with menopause at ages 46-50 years (Hao *et al.*, 2023).

In addition, a 2023 study from the Wisconsin Registry for Alzheimer Prevention reported imaging analyses suggesting that younger age of menopause compared with later age of menopause may be associated with higher regional tau deposition in the brains of women with elevated $_{\beta}$-amyloid deposition. The affected brain regions included medial and lateral regions of the temporal and occipital lobes. Women with both non-iatrogenic and iatrogenic menopause were included in that study (Coughlan *et al.*, 2023).

In summary, because of the age cut-off used in most studies, the relevance of these results to the question addressed in this chapter is limited. Only two studies used the age cut-off of ≤40 years which is approximately equivalent to the definition of POI (<40 years) (Ryan *et al.*, 2014, Hao *et al.*, 2023).

Cognitive impairment and dementia after iatrogenic POI

A 2019 systematic review and meta-analysis on cognitive outcomes after bilateral oophorectomy identified eleven studies of adequate quality (Georgakis *et al.*, 2019). The studies showed wide variability in the outcome measure used. Some studies considered dementia as an overall clinical diagnosis; other studies measured cognitive performance on one or several cognitive tests cross-sectionally (at only one point in time during follow-up). Other studies followed women for a number of years and measured cognitive decline over time. Finally, one study considered neuropathologic lesions in women who died during the follow-up (senile plaques and global pathology score)(Bove *et al.*, 2014). In addition, major heterogeneity across studies related to the timing of oophorectomy. When oophorectomy was considered at any age, there was no association with dementia; however, oophorectomy was associated with a decline in verbal memory, semantic memory, and processing speed. When analyses were restricted to women who underwent BSO at age 45 years or younger (corresponding to POI or early menopause), oophorectomy was associated with a 70% increased risk of dementia (HR 1.7; 95% CI 1.1 to 2.7; based on two studies). In addition, oophorectomy was associated with a decline in global cognition and semantic memory (based on one study)(Georgakis *et al.*, 2019). Several studies were published after the systematic review.

In 2021, a case-control study showed an increased risk of mild cognitive impairment (MCI) associated with bilateral oophorectomy performed at age 45 years or younger (OR 2.2; 95% CI 1.4 to 3.5)(Rocca *et al.*, 2021a). The association varied by surgical indication (stronger in women with a benign ovarian indication). In 2021, the same Mayo Clinic group also reported a cross-sectional study of bilateral oophorectomy and cognitive performance measured using nine cognitive tests in four cognitive domains. Bilateral oophorectomy at age 45 years or younger was associated with lower performance in

global cognition, attention, and executive function, and on a short test of mental status. The association was particularly strong for women who had the oophorectomy before age 40 years (corresponding to POI) (Rocca *et al.*, 2021a).

In 2022, another study was published from the Danish Nurse Cohort Study. However, the study had limited power to test the association, and the relative risk for dementia was not statistically significant (Uldbjerg *et al.*, 2022). A second case-control study of MCI was reported in 2022 from a collaboration of six countries in Latin America. Bilateral oophorectomy at any age was associated with increased risk of MCI (OR 1.6; 95% CI 1.1 to 2.2) (Blümel *et al.*, 2022). A 2023 study based on the UK Biobank confirmed the increased risk of all-cause dementia and of Alzheimer's disease following bilateral oophorectomy at age ≤40 years compared to age 46-50 years (Hao *et al.*, 2023). Finally, a 2023 systematic review confirmed the association of bilateral oophorectomy before age 45 years with increased risk of dementia (Hassan *et al.*, 2024).

In summary, bilateral oophorectomy performed before menopause at age 45 years or younger is associated with an increased risk of cognitive decline (measured by cognitive tests), MCI, and dementia. However, the timing of oophorectomy is crucial in predicting the risk.

Parkinsonism and Parkinson's disease after iatrogenic POI

Because Parkinson's disease is relatively uncommon, several studies have considered the broader group of patients with parkinsonism (the syndrome including Parkinson's disease). We do not have a systematic review of the literature for premature or early bilateral oophorectomy and parkinsonism. However, a recent paper by Rocca and colleagues included a review of nine studies (Rocca *et al.*, 2022). The studies used different methods and different definitions of the outcome. Five studies used the case-control design whereas the remaining four studies used a cohort study design. Five of the nine studies provided evidence in favour of an association but four did not. The reasons for the discrepant findings remain partly unclear (Rocca *et al.*, 2022). A 2017 meta-analysis of reproductive risk factors for Parkinson's disease did not focus on premature and early oophorectomy but rather on surgical menopause at any age (including both hysterectomy and BSO). The authors suggested that surgical menopause may be associated with a decreased risk of Parkinson's disease after adjusting for coffee intake or for smoking. However, the authors reported an increased risk of Parkinson's disease in studies that did not adjust for smoking (Lv *et al.*, 2017). The timing of oophorectomy is crucial in predicting the risk. Not surprisingly, some studies that lumped hysterectomy and oophorectomy at all ages reported contradictory results.

The 2022 study by Rocca and colleagues was a cohort study of 2,750 women with oophorectomy and 2749 referent women. In women who were age 43 years or younger at oophorectomy (first tertile) the risk was increased for both parkinsonism (HR 7.7; 95% CI 1.8 to 33.3) and Parkinson's disease (HR 5.0; 95% CI 1.1 to 22.7). The number needed to harm was 27 women for parkinsonism and 48 women for Parkinson's disease. In addition, there was a significant trend of increasing risk with younger age at oophorectomy for parkinsonism (Rocca *et al.*, 2022).

Two studies were published after the review in the Rocca and colleagues' paper. In 2022, another case-control study from Egypt confirmed the association (Ibrahim *et al.*, 2022). Finally, in 2023, another cohort study from France confirmed the association (Pesce *et al.*, 2023).

In summary, the evidence from a total of eleven studies is reasonably strong to support an association between premature or early oophorectomy and the risk of parkinsonism or Parkinson's disease. Out of a total of eleven studies, seven provided supporting evidence. However, some studies that grouped hysterectomy and oophorectomy at all ages, reported contradictory results.

Other neurological diseases after iatrogenic POI

In 2021, Huo and colleagues reported a significant association between bilateral oophorectomy before usual age menopause and restless leg syndrome (HR 1.4; 95% CI 1.1 to 1.9)(Huo *et al.*, 2021). As of today, this association has not been replicated. Several studies investigated the long-term risk of stroke after POI or bilateral oophorectomy (Hassan *et al.*, 2024). However, the studies are discussed in chapter VII. POI and cardiometabolic health.

Recommendation

HCPs should be aware that earlier age of menopause is associated with an increased risk of dementia.	⊕◯◯◯	**STRONG**

The guideline group recommends that HCPs implement appropriate preventive actions for the consequences of POI on neurological function	**GPP**

The possible detrimental effect on cognition and the increased risk of dementia, parkinsonism, and other neurologic diseases should be discussed when planning a bilateral oophorectomy under the age of 45 years, especially for women at average risk of ovarian cancer.	⊕◯◯◯	**STRONG**

Justification

Although the cut-off age used to separate early menopause from late menopause varied across studies, there is adequate evidence that younger age of 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.

X.2. Management options

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

Long-term estrogen replacement therapy for cognitive impairment and dementia after POI

There are no clinical trials examining the long-term effects of estrogen replacement therapy (ERT) on neurological function after spontaneous or iatrogenic POI. The evidence available comes primarily from observational studies of women who underwent premenopausal bilateral oophorectomy. The systematic review by Georgakis and colleagues did not consider the effect of hormonal treatment. (Georgakis *et al.*, 2019). In 2007, the Mayo Clinic Cohort Study of Oophorectomy and Aging showed a lower risk of cognitive impairment or dementia in women who underwent oophorectomy and received ERT (HR 0.8; 95% CI 0.3 to 2.5) compared to women who did not receive ERT (HR 1.9; 95% CI 1.3 to 2.8). Even though the difference was not statistically significant, it was clinically important (Rocca *et al.*, 2007). This protective effect of ERT was confirmed seven years later by another US study. Longer duration of hormone use was associated with slower decline in global cognition when ERT was administered within the 5-year perimenopausal window (Bove *et al.*, 2014). In 2014, the French Three-City Study showed a beneficial effect of ERT in women who underwent POI (defined as age ≤40 years). In that study, both

spontaneous and iatrogenic POI were considered separately (Ryan *et al.*, 2014). Finally, in a 2023 study based on the UK Biobank, the women with spontaneous menopause at age ≤45 years who did not receive ERT had a higher risk of all-cause dementia and Alzheimer's disease compared to women who received therapy. The difference was significant for Alzheimer's disease (Hao *et al.*, 2023).

Some more recent studies focused on MCI. A 2021 case-control study of bilateral oophorectomy and risk of MCI did not show a significant effect of ERT therapy (Rocca *et al.*, 2021a). By contrast, ERT was beneficial for preventing MCI in the Latin America case-control study published in 2022 (Blümel *et al.*, 2022).

The beneficial effect of ERT in women who experienced POI or early menopause is consistent with the timing hypothesis. The timing hypothesis is supported by observational clinical data, some clinical trial data, and by animal research data. The hypothesis suggests that the effects of estrogens are most beneficial when initiated around the usual age of menopause but may become neutral or detrimental if initiated further away from menopause (Rocca *et al.*, 2014). The timing hypothesis was introduced to explain the contradictory findings from the Women's Health Initiative randomized clinical trials as compared to findings from previous observational studies (Gleason *et al.*, 2015, Henderson *et al.*, 2016). However, the focus of the Women's Health Initiative trials was on the majority of women who underwent spontaneous menopause within the normal age range (approximately 45-54 years). For women who experienced POI or early menopause, both spontaneous and iatrogenic, the age at onset of ERT is shifted farther to younger ages (age <40 years or 40-44 years), and the protective effect is expected to be more pronounced (Rocca *et al.*, 2021b).

Long-term estrogen replacement therapy for other neurologic diseases after POI

The studies of the association between oophorectomy and parkinsonism or Parkinson's disease reviewed above did not have adequate power to test for differences in strata with and without ERT. The study by Rocca and colleagues reported a lower risk in women who underwent oophorectomy at age 45 years or younger and received ERT compared to women who did not for both parkinsonism and Parkinson's disease. However, the differences were not statistically significant (Rocca *et al.*, 2022). The analyses for restless leg syndrome did not suggest a beneficial effect of ERT (Huo *et al.*, 2021). In summary, the evidence for the effect of ERT on the long-term risk of other neurological diseases remains inconclusive.

Recommendations

Hormone replacement therapy to reduce the possible risk of cognitive impairment and the risk of dementia, parkinsonism and other neurologic diseases is recommended in women with POI at least until the usual age of menopause.	⊕⊕◯◯	**STRONG**
Hormone replacement therapy may be recommended for neurological function even in the absence of menopausal symptoms, as HRT is for cardiovascular and bone health.	⊕⊕◯◯	**STRONG**
The guideline group recommends that women with POI should be advised to maintain a healthy lifestyle, involving exercise, healthy diet, avoidance of smoking, and maintenance of normal body weight to reduce possible risks for cognitive impairment.		**GPP**

Justification

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. 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.

The majority of these observational studies suggest that ERT until the approximate average age of spontaneous menopause may be beneficial for cognitive function and other neurologic outcomes in women who have undergone a premature or early menopause. By contrast, hormone treatment initiated at an older age (>60 years of age) may confer added risk for dementia and vascular disease (2022). Because the intention of treatment is to replace the hormones that have become prematurely insufficient, the treatment should be independent from the development of menopausal symptoms. Both women with and without menopausal symptoms should be treated.

There is no evidence of adverse effects on brain function of ERT therapy before the usual age of menopause, but this may not be true after the average age of spontaneous menopause. 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).

Research recommendation.

Research is needed to further clarify the pathogenetic mechanisms mediating the effects of POI, both non-iatrogenic and iatrogenic, on adverse neurological outcomes including cognitive decline and dementia. In addition, further research is needed to confirm the beneficial effects of ERT in women who underwent POI, both with and without menopausal symptoms.

XI. POI Treatment: Hormone Therapy

This chapter focuses on treatment with sex steroids such as Hormone Replacement Therapy (HRT) and the Combined Oral Contraceptive Pill (COC) for women with POI.

A summary of the principles and indications for use of HT in POI is provided, with reference to other chapters where relevant. A review of possible risks and adverse effects of HT use in women with POI then follows. The next section reviews the options for existing preparations including details about regimens, routes of administration, dosage, and recommendations of treatment duration. The final parts of the chapter cover the role of testosterone therapy in POI, and specific considerations for hormone therapy in iatrogenic POI.

XI.1. Hormone therapy in POI – Principles and indications

Principles of HT

- The aim of HT is to approximate physiological replacement.
- If the uterus is present, combined therapy with estrogen with a progestogen is required.
- Non oral delivery of estrogen avoids first pass hepatic effects e.g., thrombotic effects.
- Estrogen doses required are usually higher than those for women at usual age of menopause, reflecting the physiological environment in younger women and dose response effect on bone mineral density (BMD)

Pragmatic aspects

- There are few prospective RCT data for specific HT regimens regarding symptom relief, QOL and prevention of bone loss.
- Doses of estrogen and progestogen (including progesterone) are usually decided based on the basis of the principles of HT [as above] rather than good quality evidence.
- The availability and cost of HT regimens vary immensely from region to region and country to country.
- The choice of regimen often varies according to patient preference e.g., desire for pregnancy versus contraception, to optimise adherence and peer friendliness rather than evidence for effectiveness and safety.

Indications for HT in POI

The sequelae of POI and the possible benefit of HT for each of them has been outlined in the respective chapters and summarised in Table III Summary of Indications for HT in women with POI.

Recommendations

Women with POI should be advised that hormone therapy is recommended for the preservation of bone, cardiovascular and brain health.	⊕⊕◯◯	**STRONG**

Women with POI should be advised that hormone therapy is recommended for the treatment of symptoms due to low estrogen.	⊕⊕◯◯	**STRONG**

Hormone therapy should be continued until at least the usual age of menopause	⊕⊕◯◯	**STRONG**

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3942 **TABLE VI SUMMARY OF INDICATIONS FOR HORMONE THERAPY (HT) IN WOMEN WITH POI**

Symptoms or Sequelae of POI	Indication for HT	Supporting recommendation
Vasomotor symptoms	**YES**	HT is indicated for the treatment of vasomotor symptoms in women with POI.
Genito-urinary symptoms	**YES**	Offer local estrogen therapy (LET) to improve genital, sexual and urinary symptoms. Women with POI may be offered LET if genitourinary syndrome of menopause (GSM)is not fully relieved by using systemic HT.
Life expectancy	**YES**	Women with POI should be offered HT at least until the usual age of menopause as primary prevention to reduce risk of overall morbidity and mortality
Skeletal health	**YES**	Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.
Muscle health	**Uncertain**	The effect of HRT on muscle parameters in women with POI is uncertain but may be of benefit.
Cardiovascular health	**YES**	Despite lack of data from randomised controlled trials, hormone therapy with early initiation is recommended in women with POI to control future risk of cardiovascular disease. HT should be continued at least until the usual age of menopause.
Quality of life	**Uncertain**	HT has a positive impact on quality of life in women at usual age of menopause. There are minimal data regarding women with POI, but HT may be of benefit
Sexual function	**YES**	Where HT has been prescribed for other indications to women with POI, it may ameliorate sexual function, acknowledging the effect is generally small.
Neurological function	**YES**	Hormone replacement therapy to reduce the possible risk of cognitive impairment and the risk of dementia, parkinsonism and other neurologic diseases should be recommended in women with POI at least until the usual age of menopause.
Fertility treatment	**YES**	HRT in higher doses creates a favourable hormonal environment for fertility intervention such as replacement of embryos in oocyte donation IVF.
Puberty Induction	**YES**	HT is indicated for normal pubertal development and skeletal maturation

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XI.2. Risks of hormone therapy

In this section, the evidence for risks of HT in women with POI is summarized and supplemented with applicable data from women at usual age menopause (UAM) where evidence was scarce.

PICO QUESTION: WHAT ARE THE RISKS OF HORMONE THERAPY?

Risk of breast cancer

The incidence of breast cancer in women with POI has been poorly investigated. Modulating risk factors for breast cancer such as pregnancy and breast-feeding may not apply to women with POI. It has been reported that breast cancer risk increases with increasing age of menopause, and this risk seems lowest in women experiencing menopause before the age of 40 years.

From a theoretical standpoint, women with POI taking HT with estradiol in physiological doses should not have a higher risk of breast cancer than women with normal ovarian estrogen production (Wu *et al.*, 2014).

Possible impact of HT on breast density

Higher breast density, as assessed by mammography, is associated with increased breast cancer risk (Boyd *et al.*, 2007) . However, increased breast density due to HT is not thought to be as significant as familial/genetically pre-determined breast density.

A report on 62 women with Turner syndrome described the effect of prolonged (> 25 years) use of combined HRT, commencing at the age of 11-19 years. Mammography was initiated from the age of 35-40 years. While high breast density was associated with increased breast cancer risk, none of these women had an increase in breast density. Furthermore, none of these women were diagnosed with breast cancer or a benign breast disorder (Bosze *et al.*, 2006).

A study compared mammographic density between women with POI taking HRT and those with POI not taking HRT over a 5-year period (Benetti-Pinto *et al.*, 2014). They observed no significant difference in mammographic density between the groups and concluded that breast density in women with POI decreases across a period of 5 years, regardless of HRT use.

The effect of different HRT types on breast density was compared in women with a high risk of breast cancer (familial risk +/- BRCA1/2 mutation). Women aged 30-50 years who had undergone risk reducing salpingo-oophorectomy were randomised to tibolone or conjugated estrogens with medroxyprogesterone acetate; there was also an untreated comparison group. 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) (van Barele *et al.*, 2021). If increase in breast density with HRT is regarded as a risk factor for breast cancer it could be argued that tibolone was the safer option in this study.

Risk of breast cancer in women with POI

It has been demonstrated that the risk of breast cancer is lower in women with untreated POI who have less estrogen exposure (RR 0.67; 95% CI 0.62 to 0.73) (Collaborative Group on Hormonal Factors in Breast Cancer., 2012), however the risks of many other conditions are increased if estrogen is not replaced.

Wu and colleagues found a decreased incidence of breast cancer in Chinese women with POI due to diverse causes compared with women with usual age menopause (OR 0.59; 95% CI 0.38 to 0.91) after adjustment for confounding factors (Wu *et al.*, 2014).

A Danish study identified no increased breast cancer risk in a cohort of 15,631 women using any form of HRT (non-systemic HRT not included), compared with 62,749 unexposed women. During a mean

follow-up of 10 years, they found that 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) (Ewertz *et al.*, 2005).

Observational data of breast cancer in women in early menopause demonstrate an 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. However, the comparator group were never users of HRT, rather than age matched women with normal ovarian function (Collaborative Group on Hormonal Factors in Breast Cancer., 2019).

Risk of breast cancer in women with iatrogenic POI and a BRCA mutation

In iatrogenic POI due to surgery, breast cancer risk is decreased by at least 50% in BRCA1/2 carriers as well as in genetically uncharacterized women (Rebbeck *et al.*, 2009).

In a cohort study, 178 379 women were recruited in 2006-2010. Self-reported data showed that 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) (Xu *et al.*, 2022). 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 usual age 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).

A recent expert narrative review (Rozenberg *et al.*, 2021) advised that carriers of BRCA 1/2 mutation after risk reducing bilateral salpingo-oophorectomy (RRBSO), without a personal history of cancer, may be treated with HRT till the age of 50 based on the results of two systematic reviews and meta-analyses (Marchetti *et al.*, 2018, Gordhandas *et al.*, 2019). The data included both women with POI and with early menopause. Another systematic review and meta-analysis demonstrated similar findings, indicating the evidence is more favourable for estrogen alone therapy (Vermeulen *et al.*, 2019). These observations are repeated in recent review articles (Loizzi *et al.*, 2023a, Loizzi *et al.*, 2023b).

Women who have had irradiation to the breast (e.g. mediastinal or total body irradiation) are at an increased risk of breast cancer. In theory, this risk may be reduced by the hypoestrogenic state of POI, but returned to the same level as those without POI by HT.

HT Regimens and breast cancer risk

A higher risk of breast cancer has been demonstrated with continuous combined estrogen-progestogen regimens compared with the sequential, in several large cohort studies of postmenopausal women (Lambrinoudaki, 2014, Collaborative Group on Hormonal Factors in Breast Cancer., 2019). However, since the risk of breast cancer for women with POI may be reduced compared to normal and, given that the little published data regarding the risks of various HRT regimens in the POI group is conflicting, extrapolation of evidence based on postmenopausal women may not be appropriate.

There has been considerable debate on the effect of different progestogens on the risk of breast cancer (Stahlberg *et al.*, 2004, Seeger and Mueck, 2008). In theory, progesterone has a less proliferative and a more apoptotic effect than androgenic progestogens. However, the evidence is largely observational and relates to women with UAM; there are no data specific to POI (Vinogradova *et al.*, 2020).

With regards to the combined oral contraceptive pill, there is a lack of data in the POI population but in those with normal ovarian function, a large, nested case-control study and meta-analysis indicates a small increase in breast cancer risk (OR 1.23; 95% CI 1.14 to1.32) (Fitzpatrick *et al.*, 2023).

Recommendations

It is suggested that women with POI be informed that hormone therapy does not appear to increase the risk of breast cancer before the usual age of menopause compared to women without POI in the same age group.	⊕⊕◯◯	CONDITIONAL

Women with POI should be informed that hormone therapy is generally contra-indicated in breast cancer survivors.	⊕⊕⊕◯	**STRONG**

Women with BRCA1/2 mutations without a personal history of breast cancer should be advised that hormone therapy is an option after risk reducing bilateral salpingo-oophorectomy.	⊕⊕◯◯	**STRONG**

Justification

The evidence in terms of risks of HT in relation to breast cancer are reassuring for all women apart from breast cancer survivors. As such, recommendations on reassuring women with POI and women with BRCA1/2 mutations without a personal history of breast cancer were formulated, as in these women the benefits of HT outweigh the risks. This is not the case for breast cancer survivors and a recommendation against HT was formulated for these women.

Risk of endometrial cancer and endometrial hyperplasia

Estrogen-only HT is associated with increased risk for endometrial hyperplasia and endometrial cancer in postmenopausal women . The effect of estrogen-only HRT on the endometrium of women with POI with an intact uterus has not been studied. However, because the association has been well-proven in postmenopausal women , only combined estrogen-progestogen therapy should be used in women with POI and an intact uterus.

According to the Cochrane Library review on oral HRT and endometrial hyperplasia, all doses of unopposed estrogen therapy led to a significant increase of approximately 50% for endometrial hyperplasia within three years. Regimens combining estrogens with continuous progestogens are not significantly different from placebo at two years (Furness *et al.*, 2012). Continuous progestogen HRT regimens appear to be safer that sequential HRT regimens for protecting the endometrium (Weiderpass *et al.*, 1999).

The combined oral contraceptive pill reduces the risk of endometrial hyperplasia and endometrial cancer in women with normally functioning ovaries, especially if administered continuously, and so it is reasonable to expect that it will have the same effect in women with POI (Michels *et al.*, 2018).

Recommendations

Women with POI should be advised that progestogen should be given in combination with estrogen therapy to protect the endometrium in all women with an intact uterus.	⊕⊕◯◯	**STRONG**

It is suggested that the dose of progestogen is increased when higher doses of estrogen therapy are used.	⊕◯◯◯ CONDITIONAL

Justification

The dose of progestogen required for adequate endometrial protection is related to the dose of estrogen used. Given that the dose of estrogen used in HRT for POI is higher than used conventionally in postmenopausal women , it is important that adequate progestogen doses are used for endometrial protection (unless the woman has progestogen intolerance) (Hamoda, 2022).

Risk of stroke

No evidence was identified regarding the risk of stroke for women with POI treated with HT. The increased risk of stroke in women with POI or early menopause due to surgical menopause, was found to be reduced by HRT, suggesting that estrogen deprivation is involved in the association (Rocca *et al.*, 2012b).

Studies on the use of HRT in women with UAM have identified an increased risk of thrombotic stroke with HRT (maximum RR 1.47, increasing from 6 per 1000 in the control group to 8 per 1000 in the HRT group) (Marjoribanks *et al.*, 2012, Gu *et al.*, 2014) although this risk is not evident in women using standard or low dose transdermal estradiol (Renoux *et al.*, 2010).

In young women using the combined oral contraceptive pill (i.e. menstruating women requiring contraception), the risk of stroke is roughly doubled although the absolute risk is extremely low (21.4 per 100,000 person-years) (Lidegaard *et al.*, 2012).

Recent studies suggest that an individual's genomic profile may modify the COC associated risk of ischaemic stroke (Lin *et al.*, 2023).

Risk of thromboembolic disease

Only one study on the risks of thromboembolism and HRT use for women with POI has been identified, and that was of a minority sub-group within the WHI clinical trials.

This looked at venous thromboembolism (VTE) occurring in women on HRT (CEE+MPA) who had no history of VTE. Overall, the authors did not identify any significant relation between occurrence of first VTE event in relation to HRT use compared with placebo. Analyses restricted to non-procedure related VTE showed a U-shaped relationship between age of menopause: after adjustment for potential confounders, women who experienced menopause at 39 years or younger, or at 56 years or older had increased thrombotic risk as compared with women with age of menopause between 40 and 49 years (adjusted HR 1.8; 95% CI 1.2 to 2.8) while using HRT (Canonico *et al.*, 2014).

Evidence on VTE risk in women at UAM using oral HRT has shown 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 (Marjoribanks *et al.*, 2017). However, most observational and case-controlled data in women with menopause at usual age have shown that the risk of VTE can be reduced or negated through the use of transdermal estradiol and micronized progesterone or dydrogesterone (Canonico *et al.*, 2006, Canonico *et al.*, 2007, Canonico *et al.*, 2008, Vinogradova *et al.*, 2020).

A recent real-world survey data in women with UAM, showed a lower VTE risk of an oral combined estradiol / progesterone formulation compared to conjugated equine estrogen / medroxyprogesterone acetate formulations (Panay *et al.*, 2023).

The risk of VTE in women (age 15-49) using an oral contraceptive pill is increased compared to non-users: adjusted rate ratio (95% CI 2.65 to 3.01) (Lidegaard *et al.*, 2012).

The evidence on VTE risk in COC users is relevant to women with POI using COC because they are in the same age group, albeit with exogenously suppressed ovarian function. The mechanism of VTE does not appear to be any different between women with normal ovarian function and those with POI.

Known risk factors for VTE in COC users such as smoking, and obesity therefore can be applied to women with POI using the COC.

It is possible that estradiol or estetrol delivering COCs are associated with a similar or even lower cardiovascular and VTE risk but there is very little clinical experience using these pills in POI, and no published data on safety issues in this population (Dinger *et al.*, 2016, Reed *et al.*, 2021)

POI patients with potential higher risks of HT linked to comorbidities.

Women with POI and endometriosis

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus. Medical or surgical ovarian suppression in women with endometriosis is effective in improving pain symptoms. Medical treatments prescribed for women with endometriosis (GnRH agonists) induce a temporary state of hypoestrogenism that is restored after discontinuation of treatment. Hysterectomy with bilateral oophorectomy should only be considered in women who no longer wish to conceive and failed to respond to more conservative treatments (Becker *et al.*, 2022) (Iancu *et al.*, 2022). (

As endometriosis is an estrogen-dependent disease, the use of estrogen therapy in women with endometriosis and POI (for instance after hysterectomy and BSO) could theoretically reactivate residual disease. A systematic review reported a small association between the treatment with HT and recurrence of endometriosis, but this conclusion was based on limited available data (Gemmell *et al.*, 2017). Malignant transformation was reported in only a few reports, and mostly related to unopposed estrogen treatment (Gemmell *et al.*, 2017).

Despite a lack of good evidence, most experts recommend the use of continuous progestogen with estrogen in women thought to have residual disease after hysterectomy and BSO (Gemmell *et al.*, 2017).

The question on how to treat vasomotor symptoms in women with endometriosis has also been discussed in the "ESHRE guideline: Endometriosis" (Becker *et al.*, 2022) and similar recommendations were formulated.

Recommendation[11]

The guideline group recommends that HCPs treat women with a history of endometriosis after surgical menopause with combined estrogen-progestogen at least until the usual age of menopause	**GPP**

Further recommendations on treatment of women with endometriosis, including women after surgical menopause, is available in the "ESHRE guideline: Endometriosis" (Becker *et al.*, 2022).

[11] These recommendations were derived from the ESHRE Guideline Endometriosis, with minor changes to the formulation for consistency with the terminology used in this document.

Women with POI and Migraine

The main issues to consider regarding HT use in women with POI and migraine are the potential risk of ischaemic stroke and whether HT might affect the occurrence of migraine.

A recent comprehensive review of the subject indicated that data on hormonal treatments in migraine are scarce and heterogeneous but suggest a good safety profile in women with menstrual migraine, especially if used with reduced or absent hormone free intervals (Nappi *et al.*, 2022c).

Good quality data on the effect of migraine and COC use on risk of ischaemic stroke are lacking although caution should be exercised in prescribing the COC in this group of women (Ornello *et al.*, 2020).

No studies were identified for the dose, type, or route of administration of HRT in women with POI and migraine. Data for women at UAM, with migraine is also minimal and conflicting. Migraine with aura remains a contraindication for combined oral contraceptive pill use in women, including those with POI. 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.

Given that some migraine is provoked by estrogen (by high, low, or even changing levels), a migraine history should be sought and documented when commencing HRT in women with POI. Should migraines become more frequent whilst taking HRT, consideration should be given to whether the potentiating factor could be over- or under-replacement.

Other causes should be considered as well as HRT if new migraine occurs during HT.

Transdermal estrogen may have the advantage of providing a constant level of estrogen and may be associated with a lower risk of thrombosis (MacGregor, 2018, Nappi *et al.*, 2022c).

Recommendation (1)

Migraine should not be seen as a contraindication to hormone therapy use by women with POI.	⊕⊕◯◯	**STRONG**
HCPS should consider changing dose, route of administration or regimen if migraine worsens during hormone therapy.	⊕⊕◯◯	**STRONG**
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**

Women with POI and other comorbidities

An overview of the most common comorbidities in women with POI, the specific risks of HT in these women and the probability are listed in Table VIII. Where possible, the table also provides a suggested HT options for each comorbidity.

TABLE VII SUMMARY OF RECOMMENDATIONS FOR HT IN WOMEN WITH POI WITH POTENTIAL HIGHER (RISKS LINKED TO COMORBIDITIES

Comorbidity	HT	Type of risk	Probability	Proposed HT
Breast cancer survivor	Contra-indicated	Recurrence	High	n/a
BRCA1/2 mutations after RRBSO, without a personal history of breast cancer	Can be considered	Developing BC	Low	TE/MP[1]
Migraine	Can be considered	Ischaemic stroke	Unclear	Dose/regimen/administration can be adapted in line with migraine symptoms
Migraine with Aura	Can be considered	Ischaemic stroke	Unclear	Transdermal estrogen (COC contraindicated[2])
Hypertension	Can be considered	CVD/VTE	Low	TE/MP[1]
Diabetes mellitus	Can be considered	CVD/VTE	Low	TE/MP[1]
Obesity	Can be considered	CVD/VTE	Low	TE/MP[1]
Endometriosis	Can be considered	Disease reactivation / malignancy	Low	combined estrogen-progestogen
Prior VTE	Can be considered after haematologist review.	VTE/PE	High	TE/MP[1] (COC contraindicated[2])
Malabsorption	Recommended	Inadequate absorption of oral therapy	Unclear	Non-oral HT
Known CVD	Relatively Contra-indicated	CVD	Unclear	TE/MP[1]
Abnormal liver function	Can be considered	Worsening of liver function	Unclear	Transdermal estrogen

[1] TE/MP: Transdermal estrogen, Micronized progestogen

[2] See https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html

XI.3. HT – treatment options

PICO Question: What are the options for hormone therapy?

In contrast to women with UAM, the need for hormone therapy (HT) in younger women with POI extends beyond the need for symptom relief (the primary indication for HT in women with UAM.

As reviewed in the other chapters evidence suggests that HT is justified in women with POI to protect against serious morbidity and earlier mortality related to prolonged estrogen deficiency but should at the same time be prescribed safely to avoid or minimize potential risks (see also Table III Summary of Indications for HT in women with POI),

In a retrospective chart review the authors stated that treatment should be initiated rapidly after confirmation of diagnosis, for the physical as well as emotional components of the condition, especially to preserve bone mineral density (Kanj *et al.*, 2018).

This section reviews the HT options for women with POI: types of preparation, regimens and route of administration, doses, duration, monitoring, and adherence to therapy.

Research on the optimal HT for women with POI is limited. On the other hand, there are numerous studies on the effect of regimens, route of administration, doses, and management of HRT in women at UAM, above the ages of 45-50 years. As a consequence of the sparse evidence, recommendations for HT in POI must necessarily be based on theoretical knowledge about physiology and endocrinology and extrapolated from the evidence of HRT in women with UAM.

Thus, recommendations in this chapter are primarily based on "best clinical practice" supplemented by evidence where it exists. Patient preference and individualisation of regimens is important for adherence and must therefore be taken into consideration when prescribing.

Type of preparations: Estrogens and progestogens

Estrogens

There are four types of estrogen that are available for hormone replacement: estradiol (the main ovarian estrogen 17β-estradiol), ethinylestradiol (a synthetic estrogen) and conjugated equine estrogens (CEE - derived from pregnant mare's urine) and the new estetrol products. At the time of writing only the estetrol/drospirenone COC was available but research was progressing to bring to market an HRT option.

The main goal of hormone therapy for women with POI is to reproduce the normal physiological endocrinological environment to achieve estrogen replacement. Given current evidence, experts in management of POI recommend that the choice of hormone therapy should closely mimic normal ovarian steroid hormone production and provide sufficient levels of estradiol to reduce menopausal symptoms, maintain bone density, minimize psychological impacts of estrogen deficiency, and protect against early progression of cardiovascular disease and dementia. Hormone therapy is long-term in women with POI, and therefore it is essential that the risk benefit ratio is optimal to maximise longer term health (Sassarini *et al.*, 2015, Sullivan *et al.*, 2016).

In a recent publication the authors proposed an "integrated and patient-based hormonal approach for women with POI, from puberty to late reproductive age" (Fruzzetti *et al.*, 2020). However, there is still lack of consistency in terms of what precisely is advised for hormone replacement in POI and largely depends on what is available in each country at any particular time.

COC versus HRT

In many countries the COC is free of charge and perceived as more "peer friendly" hence its popularity for HT in this group of young women if they do not wish to achieve a pregnancy (approx. 5% chance in non-iatrogenic POI). In an online survey of Australian health care providers, the combined oral contraceptive pill was reported as the first-line treatment for women with premature menopause (52% of respondents), (Yeganeh *et al.*, 2017)

Most oral contraceptives contain the potent synthetic estrogen ethinylestradiol (EE), which in effect provides more steroid hormone than is needed for physiological replacement, with unfavourable effects on the lipid profile, on haemostatic factors and with an increased risk of thromboembolic events related to both the EE and progestogen, and the first pass hepatic effects.

Some newer oral contraceptives now deliver estradiol and estetrol, but there is some concern as to whether the estrogen levels achieved are sufficient in women with POI.

Bone: Evidence regarding HT and bone suggest that prompt initiation, continued use, adherence, and higher doses of estrogen are needed to optimise bone mineral density. Data regarding COC are conflicting with continuous use associated with better preserved BMD, versus conventional discontinuous use (Fine *et al.*, 2022). This is covered comprehensively in the bone chapter *(see* VI. POI and musculoskeletal health*)*.

Cardiovascular: With regards to metabolic effects, Langrish and colleagues found that a "physiological" HRT regimen led to lower mean blood pressure, reduced plasma angiotensin II and reduced serum-creatinine without altering plasma aldosterone concentrations, compared with women with POI treated with COCs (Langrish *et al.*, 2009).

A well conducted systematic review found that HRT reduced plasma cholesterol concentrations, avoided uterine atrophy and increased adult height in prepubertal girls with Turner Syndrome (Gonçalves *et al.*, 2022).

There are no comparative studies on the risks of VTE with the estradiol and estetrol COC preparations and so the indications for their use in women with POI should remain contraception, although more research is warranted to determine if these could provide the ideal balance between contraception and hormone therapy. These findings may have major implications for the future cardiovascular and bone health of young women with POI, who require long-term sex steroid replacement therapy.

The need for better comparative data has been highlighted by the authors of a recent paper in which they described the POISE study (Premature Ovarian Insufficiency Study of Effectiveness of hormonal therapy) which has been designed to determine whether hormone therapy is superior to combined oral contraceptives on important clinical outcomes such a bone mineral density and cardiovascular risk markers, and patient-reported symptoms, based on the hypothesis that hormone therapy provides more physiological continuous hormone supplementation with natural estrogens (Upton *et al.*, 2021). The study is ongoing in the UK at the time of update of this guideline.

Estrogen Choice in Turner Syndrome

Most experts now prefer transdermal estradiol for puberty induction in Turner syndrome and advise against the use of conjugated estrogens or ethinylestradiol for metabolic reasons and to achieve good uterine growth (Klein *et al.*, 2018, Klein and Phillips, 2019) (see XIII. Puberty Induction for more details).

Progestogens

Progestogens protect the endometrium from the mitogenic effect of estrogen. However, there is a lack of evidence on the effect and role of various progestogen preparations in HT for women with POI. Although all progestogens are progesterone receptor agonists, thus enabling their endometrial

protective effect, binding to other steroid receptors also occurs which varies with the progestogen. These differing agonist and antagonist effects contribute to the variable adverse effects profile (for example, breast cancer or VTE as discussed below) and this should be considered when deciding on the HT regimen (Stanczyk *et al.*, 2013).

Synthetic progestogens provide effective endometrial protection and cycle control but should not be used for endometrial preparation for embryo transfer (Fatemi *et al.*, 2007).

Evidence from women with UAM, appears to favour micronized progesterone or dydrogesterone. These appear to have favourable cardiovascular and breast safety profiles when compared to androgenic progestogens (Mueck, 2012).

Compounded "bio-identical" preparations of estrogen and progesterone are not recommended due to lack of data on efficacy and safety unless no alternative regimens are available.

However, recently published data indicate that if the estrogen is delivered transdermally in HRT then haemostatic biomarkers do not differ significantly between micronized progesterone and androgenic progestogen (MPA) users (Mittal *et al.*, 2022).

Also, as previously described, micronized progesterone and dydrogesterone may be preferred over other progestogens with regard to breast cancer risk (Davey, 2013, Vinogradova *et al.*, 2020).

A randomised controlled trial demonstrated that in women with UAM, micronized progesterone given in an oral dose of 200mg/day for 12 days per 28-day cycle was as effective as the same regimen using 10mg/day medroxyprogesterone acetate (MPA), or 2.5mg MPA every day, for protecting the endometrium from hyperplasia caused by 0.625mg/day conjugated equine estrogens (CEE) (The Writing Group for the PEPI, 1996).

These data on the safety of progesterone on the endometrium were supported by a subsequent meta-analysis (Stute *et al.*, 2016) assuming the dose and duration of use is adequate.

An RCT in women with UAM also demonstrated endometrial safety in a continuous combined oral estradiol and progesterone formulation (Mirkin *et al.*, 2020).

A recent national French case control study found a significant increase in risk of meningioma with the progestogens, depot MPA, cyproterone acetate, nomegestrol, promegestone, medrogestone and chlormadinone acetate which are not usually used for endometrial protection in HT – no link was found with progesterone, dydrogesterone and the levonorgestrel intrauterine device and excess risk of meningioma (Roland *et al.*, 2024).

HT Regimens

Continuous estrogen replacement is required to avoid symptoms of estrogen deficiency and minimise risk of co-morbidities. Some women using the combined oral contraceptive pill for hormone therapy will be symptomatic during the pill-free (or inactive pill) week.

Studies of women with UAM, have shown that use of sequential progestogen (progestogen for 10 days or more per month or 14 days up to every 12 weeks) lowers (but not eliminates) the risk of endometrial hyperplasia/cancer risk and is associated with a regular withdrawal bleed. Whereas, continuous combined estrogen-progestogen therapy, designed to omit the withdrawal bleed, may even prevent endometrial hyperplasia and cancer (see section *XI.2.b Risk of endometrial cancer and endometrial hyperplasia*)

Long cycle HT (continuous estrogen combined with 14 days of progestogen every 12 weeks) is an option for some women with progestogen intolerance but is associated with an increased risk of endometrial

hyperplasia. In this case, endometrial surveillance should be instituted with ultrasonography and hysteroscopy and endometrial biopsy where indicated.

As per women with UAM, unscheduled breakthrough bleeding should be investigated even on conventional HT regimens.

The incidence of endometrioid cancer of the ovary was increased in women with sequential but not with continuous combined estrogen-progestogen HRT in a Danish study (Mørch *et al.*, 2012).

The atrophic effect on the endometrium of the contraceptive pill may also be a reason to avoid its use for HT in women with POI desiring of pregnancy, at least until after a period of treatment with a sequential combined HRT regimen (see V.1. Fertility and fertility treatments).

Younger women are more likely to experience breakthrough bleeding with continuous combined HRT than women with UAM and should probably use sequential therapy for at least two years.

Women with POI who desire bleed-free HRT (and contraception) may benefit from using the 52mg levonorgestrel intrauterine device with appropriate estrogen replacement which is licensed in many countries for endometrial protection and/or contraception.

Route of administration

Estrogens

Systemic estrogen can be administered orally or through transdermal patches, spray, gels, and implants. However, the availability of these different preparations varies within and between countries.

Local estrogen treatment for treatment of vulvovaginal atrophy (VVA)/genitourinary syndrome of menopause can be administered in the form of an estrogen-releasing vaginal ring and estrogen-based vaginal creams and pessaries. Locally administered estrogen (Suckling *et al.*, 2006) is not believed to carry a risk of endometrial hyperplasia if used in the licensed dosage (Lethaby *et al.*, 2016) and a progestogen is not required.

There is also a locally (vaginally) active selective estrogen receptor modulator (ospemifene) although there is little experience of using this in women with POI.

The major advantage of transdermal estrogen is avoidance of first-pass metabolism in the liver and effect on VTE risk as previously discussed (Chetkowski *et al.*, 1986). A recent clinical trial in women with POI using transdermal estradiol (and either sequential oral micronized progesterone or medroxyprogesterone acetate for endometrial protection) confirmed absence of statistically significant changes in thrombin generation (Mittal *et al.*, 2022).

Compared to oral administration, the transdermal route does not increase SHBG and can achieve higher plasma levels of circulating estradiol with a lower treatment dose and therefore fewer circulating estrogen metabolites than oral estradiol (which is metabolised to estrone), thereby more closely matching the normal premenopausal state (Goodman, 2012).

There are now a large amount of data regarding the route-dependent effect of the metabolic actions of estrogen. However, most studies were conducted in women with UAM. A more general review of the cardiovascular impact of estrogen route is included in the CV chapter (VII. POI and cardiometabolic health).

Practical aspects

Transdermal patches may result in local skin irritation, although the smaller dot matrix patches are better tolerated, and some individuals find them difficult to keep in place. Advice on correct application and

rotation of application sites may help. Younger women with POI may be reluctant to use a patch because of concerns that others might see it.

Estradiol gel and sprays are available, but younger women may still prefer oral HRT (Davies and Cartwright, 2012).

Estradiol implants are not widely available in many countries. These have often been used for surgical menopause; a pellet can be inserted subcutaneously at the time of hysterectomy to prevent consequent severe vasomotor symptoms. Panay and colleagues found little clinical difference between 25mg and 50mg implants in a randomized double-blind trial in women after total abdominal hysterectomy and bilateral salpingo-oophorectomy although there is a dose response effect on bone density (Panay *et al.*, 2000).

Given the paucity of evidence regarding the optimum route of administration for estrogen in women with POI, compliance with HRT is the main issue and patient preference is therefore currently the most important consideration (Stevenson *et al.*, 2021).

Progestogens

Progestogens can be administered via the oral, transdermal (as a patch), or intra-uterine routes for HRT. No studies have been identified comparing route of administration for synthetic progestogens as a component of combined HRT for women with POI. However, there is no reason to believe that their safety and effectiveness for endometrial protection would be any different to that for women with UAM, for which there are a considerable amount of safety data. Subdermal implants and intramuscular depot preparations are also available, but these are licensed as contraceptive devices, and no data exist for their use in HRT for endometrial protection.

If the woman prefers a bleed-free regimen, local treatment with a 52mg progestogen-releasing intra-uterine system (IUD) will provide sufficient protection from endometrial hyperplasia (Ewies and Alfhaily, 2012), usually with fewer side effects compared to systemic progestogen treatment (Pirimoglu *et al.*, 2011). This is also licensed for contraception in many countries, in those that require it. (NB: Not licensed for endometrial protection in some countries e.g. US)

Micronized progesterone preparations are available to use orally, vaginally, and as transdermal (cream) preparations. Only the oral route of administration is licensed for endometrial protection. Vaginal progesterone may have the benefit of achieving adequate endometrial protection whilst avoiding side effects such as drowsiness and low mood due to the absence of conversion to allopregnanolone. On the other hand, some women notice sleep and calming benefit with oral usage.

Cyclical vaginal progesterone 100mg/day or 200mg/day had no significant effect on endometrial thickness as assessed by ultrasound scan and was associated with better compliance and therefore cycle control, than equivalent oral doses in an RCT of postmenopausal women using 50 µg estradiol patches (Di Carlo *et al.*, 2010). However, the trial did not assess the endometrium histologically and follow up was only for 1 year.

Recent data in women with UAM, indicated that a 4% formulation of micronized progesterone gel administered intravaginally for 10 days with a low dose of estrogen (1mg estradiol) was insufficient to fully protect against endometrial hyperplasia (Sriprasert *et al.*, 2021). Caution should therefore be exercised in assuming that vaginal progesterone will always provide adequate endometrial protection and endometrial surveillance should be instituted when lower dose / reduced duration regimens are prescribed (Hamoda and Sharma, 2023).

The evidence for oral and vaginal micronized progesterone usage is well summarised in a meta-analysis. (Stute *et al.*, 2016).

In a study of 54 women with UAM, Vashisht and colleagues found that compounded transdermal natural progesterone cream in a continuous regimen was insufficient to fully attenuate the mitogenic effect of estrogen on the endometrium (Vashisht *et al.*, 2005) and should therefore not be used for this purpose.

Dose

Estrogen

Evidence indicates that a dose of at least 2 mg oral estradiol or 100 µg transdermal estradiol per day or equivalent is required to reliably prevent bone loss (Costa *et al.*, 2023) (also see VI. POI and musculoskeletal health). Low dose HT suitable for older postmenopausal women is not sufficient for women with POI to preserve bone mass.

Titrating the dose against vasomotor symptoms may be helpful, although some women with POI have minimal symptoms despite being estrogen deficient. The dose required to treat vasomotor symptoms may not be the same as that required for bone protection or to achieve peak bone mass, for example.

It is reasonable to aim for physiological estradiol levels as found in the serum of women with normal menstrual cycles of approximately 200-400pmol/l (Panay et al 2020 #2804). These levels can be achieved with 100µg estradiol patches or 2-4 pumps (or 2-3mg) of estrogen gel, or 2-3 estradiol sprays when given transdermally to women with POI (Steingold *et al.*, 1991, Popat *et al.*, 2008).

Similar levels can be provided by oral estradiol in doses of 2 to 4 mg, but serum levels of estrone become supra-physiological, which is of uncertain clinical significance (Steingold *et al.*, 1991). No data were identified to support the use of any particular dose for symptom relief in women with POI, although opinion was expressed that a transdermal dose of 100µg/day was usually sufficient (Nelson, 2009).

In women who are minimally symptomatic or asymptomatic it is reasonable to start with lower doses to avoid adverse effects and then to increase the dose according to tolerance, estradiol levels and bone mineral density (Panay *et al.*, 2020).

Progestogens

Women with POI and an intact uterus taking estrogen replacement require progestogen therapy to protect against endometrial hyperplasia/ cancer as discussed previously.

The dose of progestogen required depends on the dose of estrogen and the regimen (i.e. continuous combined or sequential). Continuous regimens require a minimum dose of 1mg of oral norethisterone (NETA) daily, 2.5mg medroxyprogesterone acetate (MPA), 5mg dydrogesterone or 100mg of micronized progesterone. The dose may need to be doubled with higher doses of estrogen. Sequential regimens require 2.5-5.0mg NETA, 5-10mg MPA, 10-20mg dydrogesterone for a minimum of 10 to 12 days per month, or 200-300mg micronized oral progesterone (Furness *et al.*, 2012, Hamoda, 2022).

These regimens have been largely determined in women with UAM, on HRT based on pharmacokinetics and endometrial safety (see Table IX)

XI.3.e Duration

There is some evidence that the longer estrogen is used in POI the lower the risk of CVD although long term prospective randomised trial data are absent (Zhu *et al.*, 2019).

In order to prevent the long-term health consequences of the loss of ovarian function, the consensus of the guideline group was that HT should be continued at least until the usual age of menopause (although this varies globally). This is in line with the recommendation of other organizations (Pitkin *et al.*, 2007, Vujovic *et al.*, 2010, Zhu *et al.*, 2019, Panay *et al.*).

Subsequently, recommendations regarding the use of HT in women with UAM, can be followed, considering factors such as symptoms, bone density, cardiovascular and cognitive risks.

Commencing HT as early as possible is particularly important for young women with POI in order to maximize peak bone mass (see VI. POI and musculoskeletal health). Similarly, cardiovascular risk factors may be minimized by early use of estrogen replacement (see VII. POI and cardiometabolic health).

XI.3. Adherence to therapy

It is not possible or realistic to achieve 100% adherence with hormone therapy in POI although desirable unless there are contraindications. In a commercial database study, the cumulative rate of estrogen use at 36 months after surgical menopause was found to be only 79.1% (95% CI 76.9 to 81.1) in those aged 18-29 years, 75.9% (95% CI 74.5 to 77.3%) in those aged 30-34 years, 70.2% (95% CI 69.1 to 71.2%) in those aged 35-39 years (Suzuki *et al.*, 2022).

Adherence with HT is crucial if the benefits are to be maintained and optimised. Very few studies have followed up the long-term use of HT. A cross sectional study demonstrated poor adherence to HRT in which 42.6% withdrew from treatment due to "lack of interest" or fears about breast cancer risks.

In multivariate analysis, after adjustment by stepwise model selection on age (p=0.05), BMI (p=0.48), smoking use (p=0.22) and vitamin D deficiency (p = 0.69), and duration of POI (p=0.003); discontinuation of HRT over one year was always associated with significant loss of femoral BMD: -17 mg/cm² versus -52 mg/cm² (p=0.022)(Bachelot *et al.*, 2016). At the vertebral level, they also found this non-significant trend -37 mg/cm² versus -45 mg/cm² (p=0.80).

In a study of women with POI due to Fragile X premutation, 52% of women never took hormone therapy, started it years after POI diagnosis, or stopped it before 45 years of age (Hipp *et al.*, 2016).

Recommendation

The guideline group recommends that women are advised that compounded "bio-identical" preparations of estrogen and progesterone are not recommended due to lack of data on efficacy and safety unless no alternative regimens are available.		**GPP**
Women with POI should be advised that estradiol has advantages over ethinylestradiol and conjugated equine estrogens when used for hormone therapy.	⊕⊕⊕◯	**STRONG**
The guideline group recommends shared decision making when prescribing each component of hormone therapy with consideration of patient preference, contraceptive needs, and presence of co-morbidities.		**GPP**
Women with POI should be advised that adherence to hormone therapy is important to minimise long term health risks and therefore long term follow up is needed.	⊕⊕◯◯	**STRONG**

Justification

There have been very few studies comparing different types and regimens of estrogen replacement for women with POI.

The little evidence there is suggests physiological sex steroid replacement regimens may be more beneficial than the combined oral contraceptive pill (COC) and 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 *et al.*, 2024).

If adherence is improved with the use of the COC, then this is a reasonable alternative, or if contraception is required.

Conclusion

As with women at UAM 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.

4455 **TABLE VIII SUMMARY OF HORMONE THERAPY (HT) OPTIONS: STANDARD AND 'PREMATURE OVARIAN**
4456 **INSUFFICIENCY (POI)' REGIMENS (ADAPTED FROM (PANAY *ET AL.*, 2020), PERMISSION REQUESTED)**

HT type	***Sequential combined HT***		***Continuous combined HT***	
Per 24 hours or day	*Low/standard doses*	*Higher 'POI' doses*	*Low/standard doses*	*Higher 'POI' doses*
Estradiol type				
Patch (transdermal, µg/24h	**25–50**	**75–100**	**25–50**	**75–100**
Gel sachet (transdermal, mg)	**0.5–1.0**	**1.5–2.0**	**0.5–1.0**	**1.5–2.0**
Gel pump (1 metered dose = 0.75 mg)	**1–2**	**3–4**	**1–2**	**3–4**
Spray (1.53mg per spray)	**1-2**	**3-4**	**1-2**	**3-4**
Oral (mg)	**1.0–2.0**	**3.0–4.0**	**1.0–2.0**	**3.0–4.0**
Progesterone/progestogen				
Micronized progesterone (oral/per vagina, mg)	**100–200**	**≥ 200 (e.g. 300–400)**	**100**	**≥ 200**
Dydrogesterone (oral, mg)	**10**	**20**	**5.0**	**10**
Medroxyprogesterone acetate (oral, mg)	**5.0**	**10**	**2.5**	**5.0**
Norethisterone acetate (oral, mg)	**2.5–5.0**	**2.5–10**	**1.25–2.5***	**5.0**
E2/progesterone combined regimens				
E2/micronized progesterone (oral, mg)	**1.0–2.0/100–200**	**> 2.0/> 200**	**1.0–2.0/100–200**	**3.0–4.0/300–400**
E2/norethisterone acetate (transdermal) (µg)	**25–50/85–170**	**75–100/255–340**	**25–50/85–170**	**75–100/255–340**
E2/dydrogesterone (oral, mg)	**1.0–2.0/10**	**3.0–4.0/20**	**0.5–1.0/2.5–5.0**	**3.0–4.0/7.5–10**
E2/norethisterone acetate (oral, mg)	**1.0–2.0/1.0**	**3.0–4.0/2.0–4.0**	**0.1–2.0/0.5–1.0**	**3.0–4.0/1.5–2.0**
Levonorgestrel intrauterine system	**n/a**	**n/a**	**20 µg/day sufficient for higher POI doses (52mg LNG IUD)**	

4457 The table does not show all available options globally. Licensed (in at least one country) types/doses/regimens of
4458 HT shown in bold; other regimens are achieved off-label by halving/doubling/combining regimens.

4459 • Higher doses of estradiol usually required in POI but, to assess tolerance or in case of adverse effects, lower
4460 doses may be used initially.
4461 • Variation globally as to what doses perceived as low, medium, and high, e.g. North America 0.5 mg E2 is low
4462 dose, 1 mg E2 is standard dose, and 2 mg E2 is high dose.
4463 • Sequential regimens require 12-14 days progesterone/progestogen per cycle for endometrial protection –
4464 this may need modification depending on tolerance.
4465 • Endometrial safety is less assured with micronized progesterone used for > 5 years[1].
4466 • Progesterone/progestogen doses shown are the minimum effective for endometrial protection given current
4467 data[2].
4468 • Endometrial safety data lacking for the minimum effective dose of progestogen/progesterone with higher
4469 estrogen doses.

4470 *A 1 mg dose of norethisterone acetate is adequate for standard-dose continuous combined HT, but not available
4471 separately from E2, hence 1.25–2.5 mg doses (¼ to ½ of a 5 mg tablet).

XI.4.Monitoring HT

Currently, there is no good evidence regarding the optimum HT monitoring strategy. Estrogen dosage should be titrated to achieve symptom control and adequate bone density. Although acknowledging limitations of estradiol assays, measurement of serum estradiol may be helpful in clinical practice where there is inadequate symptom relief, failure to achieve adequate bone protection or where there are adverse effects. Women being treated with hormone implants should have their estrogen levels checked to minimise the risk of tachyphylaxis.

Estradiol assays do not measure ethinylestradiol (in COCs) or estrone (the predominant estrogen produced by some oral HRT). There is no value in monitoring FSH levels, since they may not normalize due to dependence on inhibin as well as estradiol levels (Davies and Cartwright, 2012). Regular reviews are recommended, with the aim to assess adherence, satisfaction, side effects, and possible need for change of regimen or administration form. Adherence is improved with shared decision making, empowering and involving the woman in the discussion of treatment choice (Cartwright *et al.*, 2012, Panay *et al.*, 2020).

Mammography

As described previously, there is no evidence to suggest an increased risk of breast cancer in young women on HRT compared with age-matched normally menstruating/ovulating women. It is therefore appropriate to commence mammographic screening as per national screening programme at the age of 45 to 50 years in unless there are specific risk factors e.g. BRCA 1/2 mutation, previous chest irradiation.

Bone density assessment

The importance of monitoring bone health in women with POI has been described in detail in Section VI. POI and musculoskeletal health. Measurement of bone mineral density (BMD) with Dual-Energy X-ray Absorptiometry (DXA) should be performed at diagnosis of POI in all individuals where available, especially where other risk factors for osteoporosis are present. Optimal timing of repeat bone density measurement is unclear.

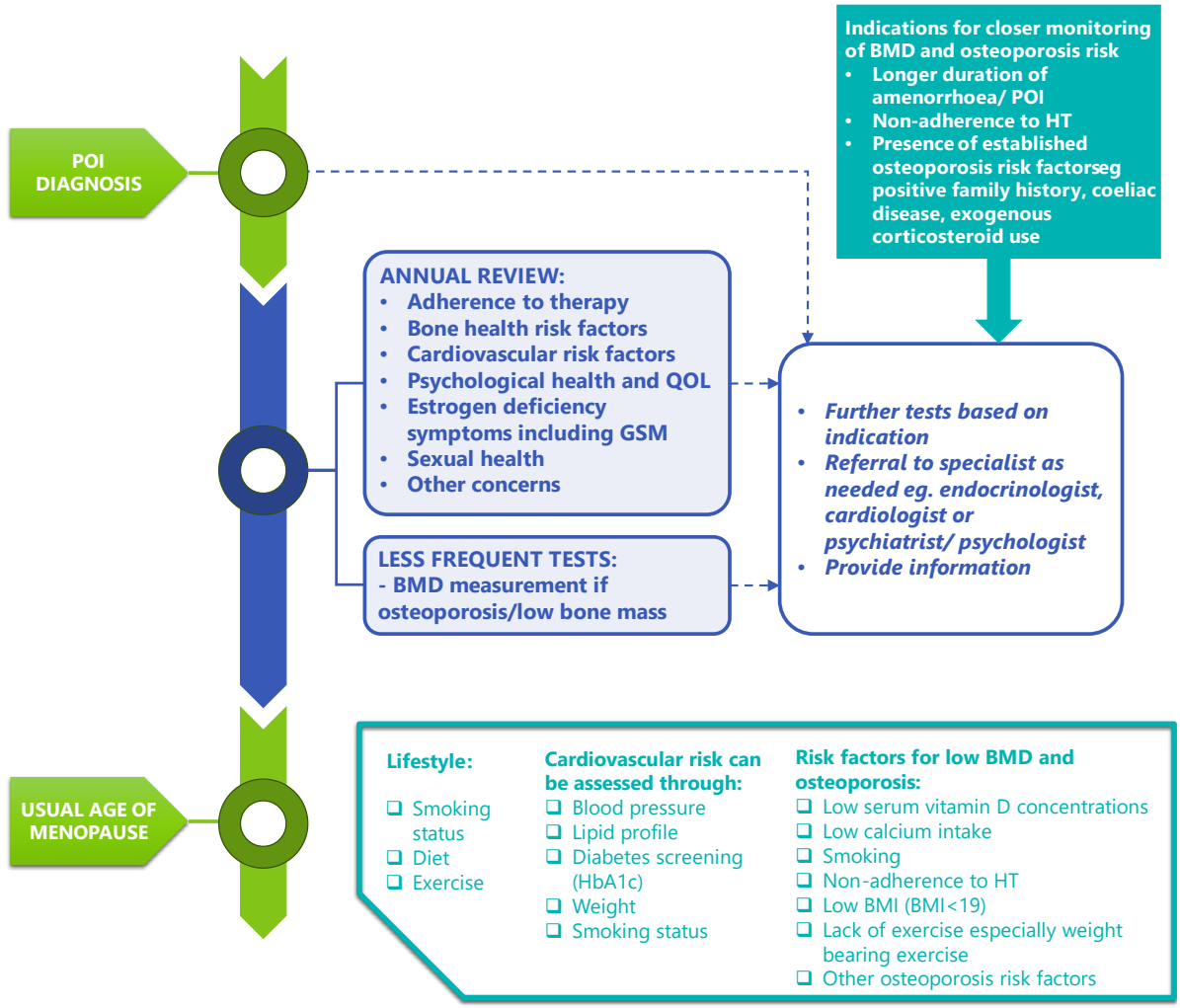
Cardiovascular health

Women with POI (spontaneous and iatrogenic) are at increased risk of cardiovascular disease, including coronary artery disease, heart failure and stroke. As such assessment of cardiovascular risk factors is recommended in women with POI, with a suggestion for screening of blood pressure, lipid profile, diabetes screening (HbA1c), weight and smoking status at least annually, and more frequently or additional risk factors where indicated. Further information on Monitoring of Cardiovascular health is discussed in section VII.3. Monitoring of cardiovascular risk factors

Recommendation

Women with POI should be advised to have a clinical review at least annually, addressing individualised risk review (specifically cardiovascular and bone health) and adherence to therapy.	⊕⊕◯◯	**STRONG**

4508 **FIGURE 14. SUMMARY OF MONITORING OF WOMEN WITH POI FROM DIAGNOSIS TO USUAL AGE OF MENOPAUSE**



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XI.5. Testosterone Therapy

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

The decision to treat with androgens in women with POI should be made as in women with UAM using a biopsychosocial approach (Davis *et al.*, 2019). The currently accepted indication is for hypoactive sexual desire disorder (HSDD) which is distressing low libido in women who are replete of systemic and local estrogen. Not all women with POI require androgens but all should be counselled about the possibility of using androgens if they have distressing symptoms not alleviated by conventional HRT.

Androgen concentrations fall with advancing age (Davison *et al.*, 2005). There is much debate whether the cessation of ovarian function (at any age) leads to a more rapid decline in androgen concentration. A systematic review and meta-analysis have shown that women with POI are at risk for decreased concentrations of androgens such as testosterone, dehydroepiandrosterone sulphate and androstenedione (Soman *et al.*, 2019).

A major pitfall in this research area is the lack of reliable testosterone assays. Although liquid chromatography-tandem mass spectrometry (LCMS) seems most precise and sensitive for measuring the relatively low testosterone levels in women compared to men, most available studies on the incidence of androgen deficiency and the efficacy of androgen replacement therapy have applied less reliable assays such as direct radioimmunoassay (Stanczyk, 2006, Janse *et al.*, 2011). Moreover, there is large between-women variability, thereby making the diagnosis of hypoandrogenemia even more challenging (Shiraishi *et al.*, 2008, Labrie *et al.*, 2011). In women with non-iatrogenic POI, there is still debate whether androgen concentrations are different from those in age-matched cycling women (Janse *et al.*, 2012). In contrast, women who underwent oophorectomy at a young age are probably hypo-androgenic due to the lack of ovarian androgen production, which makes up for 25% of the total production in premenopausal women (Longcope, 1986, Sluijmer *et al.*, 1995, Burger, 2002, Fogle *et al.*, 2007, Janse *et al.*, 2012) and around 50% in postmenopausal women (Simon, 2002, Stanczyk *et al.*, 2019).

Despite all the uncertainties, it has become clear from previous chapters that women with POI, either spontaneous or iatrogenic, may suffer from long-term health consequences such as diminished sexual function, neurological complaints, and decreased bone density. It has been suggested that androgen replacement therapy may be used for these indications. This section provides an overview of the available evidence on indications for androgen replacement therapy, possible risks, and routes of administration.

Indications

Sexual function

As was noted in IX. POI and sexuality, it is important to realize that not all women identified by medical researchers as presenting with hypoactive sexual desire disorder (HSDD) or female sexual disorder, actually have low testosterone levels, and no single testosterone level predicts low female sexual function (Schwenkhagen and Studd, 2009). However, according to the International Society for the Study of Women's Sexual Health clinical practice guideline for the use of systemic testosterone for HSDD in women, total testosterone and SHBG (to calculate the free androgen index) should be measured before initiating therapy and during testosterone therapy to avoid supra-physiological levels (Parish *et al.*, 2021). A series of randomised, placebo-controlled trials of testosterone patches in women after BSO have been carried out over the past years, using 300µg testosterone patches daily for 24 weeks, in the form of a twice weekly patch worn on the abdomen (Shifren *et al.*, 2000, Braunstein *et al.*, 2005, Buster *et al.*, 2005, Simon *et al.*, 2005, Davis *et al.*, 2006). Overall effectiveness is reported for improved sexual function as assessed by self-reports on psychometric scales and sexual activity logs alike, over and above

a large placebo effect. All of the studies involved short-term treatment and follow-up and reported mild or minimal short-term adverse effects of treatment. The efficacy of transdermal testosterone replacement for sexual dysfunction seems to be similar in surgically and spontaneously postmenopausal women with and without estrogen therapy (Davis *et al.*, 2006, Panay *et al.*, 2010). The recent global consensus position statement on the use of testosterone therapy for women clearly stated that total testosterone level should not be used to diagnose HSDD, and testosterone treatment should only use formulations (transdermal) that achieve blood concentrations of testosterone that approximate premenopausal physiological concentrations (Davis *et al.*, 2019). Systemic DHEA cannot be recommended for women with HSDD (Davis *et al.*, 2019).

Neurological function

Studies on neurological function and the use of androgen replacement therapy in women with spontaneous or iatrogenic POI are scarce. An older study in women who underwent surgical menopause and received either a combined estrogen-androgen preparation, estrogen alone, or androgen alone indicated a protective role of these treatments on two tests of short-term memory, a test of long-term memory and a test of logical reasoning that were significantly impaired with placebo use (Sherwin, 1988). Another study focussed on girls with Turner syndrome between 10 and 14 years old and not using estrogen replacement. In this study, the effect of androgen replacement therapy on neurological function, including verbal abilities, spatial cognition, executive function and working memory, was investigated. Oxandrolone-treated girls showed improved performance on the working memory domain score only after 2 years of treatment as compared to girls receiving placebo (Ross *et al.*, 2003). Studies in the elderly (postmenopausal women and elderly men) have shown conflicting results, and only involved small samples, inducing supraphysiological levels of androgens and without control for confounders (Wisniewski *et al.*, 2002, Davison *et al.*, 2011, Kocoska-Maras *et al.*, 2011). More recent systematic reviews on the impact of testosterone on cognitive function in postmenopausal women have not shown a benefit ((Sultana *et al.*, 2023a); more data are required in both POI and usual age menopause. Similarly, a systematic review did not support a beneficial effect of DHEA therapy on cognitive performance in postmenopausal women (Sultana *et al.*, 2023b).

Bone health

The effect of testosterone on bone health has been discussed elsewhere (see Testosterone) showing mixed results in terms of benefit.

Risks of androgen therapy

Masculinising effects

Supraphysiological androgen concentrations may lead to acne, hirsutism, deepening of the voice and androgenic alopecia. However, these have not been described often in studies in which women receive physiological levels of testosterone of up to 5mg of testosterone per day. A study by Buster *et al,* also including 54 (10%) women with surgical POI, reported a non-significant increase of alopecia, acne, and voice deepening (5.3 vs 2.6%, 7.5 vs 4.1%, 3.0 vs 1.5%, respectively)(Buster *et al.*, 2005). The most reported side effect of transdermal testosterone therapy was unwanted (non-scalp) hair growth (9% in the treatment group vs. 5.3% in the placebo group) (Simon *et al.*, 2005). In the recent systematic review and meta-analysis of studies using physiological doses of testosterone replacement only the incidence of acne and excess hair growth were increased with no significant effect on alopecia, voice changes or clitoromegaly (Islam *et al.*, 2019b).

Endometrial effect

Theoretically, androgen therapy could lead to endometrial hypertrophy by peripheral aromatization of androgens to estrogen. However, the endometrium is thought to be devoid of aromatase and androgens are now believed to be associated with endometrial atrophy. In one large clinical study

(APHRODITE) on transdermal testosterone therapy in postmenopausal women aged 20-70 years (of whom one quarter had surgical menopause) not using estrogen replacement, similar endometrial biopsy findings were identified between baseline and after 1-year use. The frequency of endometrial bleeding was increased in the group with higher dosage (300 compared to 150µg), along with an increased occurrence of endometrial atrophy on biopsy (Davis *et al.*, 2008).

When using estrogen replacement along with testosterone treatment, it is advisable to also add progestogen therapy for endometrial safety, as was discussed in XI.2. Risks of hormone therapy. Long-term follow-up data of the effect of androgen therapy on the endometrium is not available.

Breast cancer risk

None of the studies conducted to date showed an increased risk of breast cancer associated with the use of testosterone, but conclusive data on long-term safety are not yet available (Davis *et al.*, 2012). The APHRODITE study, mentioned in the previous section on endometrial effects, observed no differences in breast density between transdermal testosterone and placebo use (Davis *et al.*, 2008). After using testosterone patches for over 1 year on average, no increase in breast cancer incidence compared with that of the Australian reference population was identified during a follow-up of six years (Davis *et al.*, 2009). The combination of methyltestosterone with estrogen was associated with an increased risk of breast cancer (RR 2.48; 95% CI 1.53 to 4.0) in women included in the Nurses' Health Study with a follow-up of 24 years (Tamimi *et al.*, 2006) but this was not physiological replacement, and the estrogen could have had an effect. The data from the large meta-analysis by Islam et al showed no increase in risk of breast cancer but there were no RCT data for longer than 24 months (Islam *et al.*, 2019b).

Routes of administration, dose, duration, monitoring

Testosterone may be administered transdermally (gel/patch/cream), orally or through an implant. The patches are not commercially available and currently only a 1% testosterone cream is licensed for use in women with HSDD in Australia. A search for women with menopause at the usual age identified that oral administration may be associated with decreased high-density lipoprotein (HDL) cholesterol and other less-favourable lipid changes (Chiuve *et al.*, 2004), while in transdermal administration this is not observed (Braunstein *et al.*, 2005). Moreover, the transdermal route is the most investigated in women. The major complaint in transdermal use of testosterone is application site effects such as excess hair growth and skin irritation with patches, leading to a discontinuation of the transdermal patches in 4% in a surgically postmenopausal group (Simon *et al.*, 2005). Similar to estrogen and progestogen replacement, women's preferences need to be considered when deciding on the route of administration of androgen replacement.

Androgen replacement should not be given in the dosages prescribed for men, since these will lead to supraphysiological levels in women for which there are no data on safety and efficacy. One study in 447 women aged 24-70 years after BSO identified a 67%, statistically significant increase of sexual desire with a 300µg/day patch compared to placebo and 150 µg/day. The higher dosage of 450µg/day did not lead to a further increase of sexual desire.

The optimal duration of treatment is unclear. Most studies have only prescribed androgen replacement for the duration of the trial, 6 to 12 months on average, and no RCT evidence on efficacy and safety is available after 24 months. No studies have been performed on the monitoring of androgen treatment. In the recent global consensus statement (Davis *et al.*, 2019) it was agreed that the baseline total testosterone concentration should be evaluated before treatment is started and continue to be measured every 3 to 6 months to avoid overdose, particularly with off label use of male gels. 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.

Recommendations

Testosterone treatment should be considered in women with POI to manage hypoactive sexual desire disorder (HSDD)when other biopsychosocial aetiologies are excluded.	⊕⊕◯◯	**STRONG**

The guideline group recommends that women with POI are informed that there is limited data for androgen treatment for indications other than hypoactive sexual desire disorder (HSDD), and that long-term health effects are unknown.	**GPP**

Justification

Androgens decline with age and women with POI display lower circulating levels of androgens. The methodological difficulties in accurately measuring testosterone in women in routine practice with reliable sensitive assays at low levels, coupled with the paucity of safe treatments, have significantly delayed clinical research on significant endpoints such as symptoms and conditions that may be androgen dependent. Current knowledge is based on clinical trials, often with small sample sizes, short duration and follow-up, and conducted with a variety of products. These methodological limitations indicate the need for a conservative approach to testosterone therapy. 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. 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). Other health benefits, especially bone measures and cognitive function, should be evaluated in long-term well-designed trials.

XI.6. HT in women with Iatrogenic POI

PICO QUESTION: What are the specific considerations for hormone replacement therapy in iatrogenic POI ?

In contrast to HT regimens for women with UAM, HRT regimen for women with iatrogenic POI need to consider the impact of hormones on the primary disease. Different primary diseases convey different risks of HRT. There is a lack of data specific to the POI population in many instances and evidence in relation to older women is cited below.

Breast Cancer

In women with breast cancer, POI may occur secondary to chemotherapy or bilateral oophorectomy (discussed in section XI.2. Risks of hormone therapy). RCT studies of breast cancer survivors, predominately aged over 50 years, have shown that HRT may increase the risk of breast cancer recurrence (Kenemans *et al.*, 2009, Bundred *et al.*, 2012, Fahlen *et al.*, 2013). The recurrence of breast cancer is related to many factors, including family history, heredity, pathological type, stage, differentiation, extent of surgery, radiotherapy, chemotherapy, and endocrine therapy. The expression of hormone receptor (ER/PR) (Poggio *et al.*, 2022) and BMI (Cui *et al.*, 2014) are also important factors for recurrence. Among non-breast cancer survivors, a retrospective study of Hodgkin lymphoma survivors showed that breast cancer risk increased linearly with radiation dose (Krul *et al.*, 2017). However, HRT did not appear to increase breast cancer risk in Hodgkin survivors with premature menopause (Krul *et al.*, 2017).

Gynaecological Cancers

In terms of reproductive system cancers, vulvar, vaginal, and cervical squamous cell carcinoma are not hormone-dependent and can be treated with systemic or local HRT (Rees *et al.*, 2020) .

Cervical Cancer

Cervical cancer is more common in women under 40 years of age. Although most cervical cancer survivors might need to consider HRT to relieve menopausal symptoms (Lee *et al.*, 2022b), less than half of patients might be willing to use (Cotangco *et al.*, 2020), counselled or prescribed HRT (Rauh *et al.*, 2017), or continue HRT beyond 5 years (Everhov Å *et al.*, 2015). Women were more likely to be prescribed HRT if younger age, fewer co-morbidities, earlier stage disease and longer follow-up duration (Rauh *et al.*, 2017). HRT does not increase the risk of cervical squamous cell carcinoma (Vargiu *et al.*, 2021). However, in addition to squamous cell carcinoma, cervical cancer also includes adenocarcinoma, adenosquamous carcinoma and other types. Meta-analysis showed that HRT may slightly increase the risk of recurrence in patients with cervical adenocarcinoma (Standardised incidence ratio 1.83; 95% CI 1.24 to 2.59, 1 study, > 5 years of HRT) (Vargiu *et al.*, 2021).

Endometrial Cancer

The overall 5-year survival rate of endometrial cancer is approximately 86%, increasing to 97% if the disease is confined to the uterus (Edey *et al.*, 2018). Retrospective studies have shown that postoperative HRT does not increase the risk of recurrence in patients with early-stage, low-risk endometrial cancer (Suriano *et al.*, 2001). A randomized double-blind study in women, median age 57 years (<10% with POI), showed that the absolute recurrence rate was low (2.3% in ERT patients versus 1.9% in placebo group) with stage I or II endometrial cancer at median 36 months follow-up with no significant increased risk of recurrence or death versus placebo (Barakat *et al.*, 2006). A 2014 systematic review including one RCT and five observational studies (n=896 HRT users and 1079 nonusers) concluded that there was no

evidence of an increased risk of endometrial cancer recurrence with HRT use (Shim *et al.*, 2014). Given that the positive effect of HRT on quality of life in surgically postmenopausal patients may outweigh the risk of recurrence, systemic or vaginal estrogen may be considered in patients with low-grade, early detected endometrial cancer with low risk of recurrence, but the regimen needs to be individualized and discussed in full detail with the patient (Rees *et al.*, 2020).

Ovarian cancer

There is limited evidence regarding the risk of recurrence in patients with ovarian cancer treated with HRT after surgery. A retrospective study of patients with papillary serous ovarian cancer (SOC) showed that progression-free survival (PFS) in patients with SOC was mainly related to FIGO stage and whether cytoreductive surgery was adequate. HRT is not a prognostic factor for PFS in SOC patients (Zhang *et al.*, 2016). Meta-analysis showed that 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) in epithelial ovarian cancer patients, with very low rates of breast cancer, transient ischemic attack, cerebrovascular accident, and myocardial infarction (Saeaib *et al.*, 2020).

In general, malignant tumours with hormone dependence, such as uterine sarcoma, endometrioid carcinoma, ovarian clear cell carcinoma, ovarian granulosa cell tumour, sex cord-stromal tumours, require caution when considering hormone replacement therapy. Estrogen or progesterone receptor status is an important factor when considering the safety of HRT (O'Donnell *et al.*, 2016).

Surgical Menopause

In patients who undergo surgical menopause, menopausal symptoms tend to be more severe than in spontaneously menopausal women due to sudden decline in hormone levels (O and Manyonda, 2022). HRT relieves symptoms associated with estrogen deficiency, and decreases risk of death, CVD, osteoporosis, and cognitive decline (refer to respective chapters) (Techatraisak *et al.*, 2021). In recent years, androgen deficiency in surgical postmenopausal patients has also attracted attention. Meta-analysis found that androgen supplementation in surgically menopausal patients might improve sexual desire, function, and satisfaction, but not mood (Stuursma *et al.*, 2022).

Risk reducing bilateral oophorectomy.

A large population-based retrospective study has shown that BRCA mutation positivity is an important reason to choose risk reducing bilateral salpingo-oophorectomy (RRBSO). However, compared with other patients undergoing premature surgical menopause for medical reasons (such as endometriosis, or benign ovarian tumours), BRCA mutation-positive patients are more likely to opt for HRT after risk reducing surgery (Jang *et al.*, 2020). These women chose RRBSO because of a family history of cancer, positive BRCA mutations, or other cancer risk. Prospective, multicentre, age-matched cohort studies show that most of these women experienced menopausal symptoms after surgery (Hickey *et al.*, 2017), decreased bone density and strength (Jiang et al. 2021), depression and anxiety (Hickey *et al.*, 2021b), increased cardiovascular and metabolic risk (Hickey *et al.*, 2021d), and decreased quality of life (Hickey *et al.*, 2021c).

HRT should be considered as early as possible after RRBSO in women under 50 years old, especially under 46 years old, to reduce the incidence of estrogen deficiency related symptoms and co-morbidities. In a large prospective study (n=872), estrogen-only therapy use is associated with reduced breast cancer risk in BRCA-1 mutation carriers undergoing RRBSO before 45 years of age (HR 0.24; 95% CI 0.06 to 0.98 for over 5 years of ERT use) (Kotsopoulos *et al.*, 2018). In contrast, addition of a progestin is associated with increased risk of breast cancer (HR 1.78; 95% CI 1.17 to 9.73 for over 5 years of HRT) (Kotsopoulos *et al.*, 2018). Consistent with this, a 2018 meta-analysis (three studies, n=1100) indicated no increased risk of breast cancer in BRCA1/2 mutation carriers receiving HRT post RRBSO (HR 0.98;

95% CI 0.63 to 1.52) with possible greater benefit with estrogen-only therapy (Marchetti *et al.*, 2018). The cumulative incidence of breast cancer among BRCA-mutation carriers was 12% with estrogen-only therapy. In contrast, the incidence of breast cancer was 22% with combined estrogen+progestogen therapy (Kotsopoulos, 2018). A systematic review concluded that HRT mitigates risks of premenopausal RRBSO with evidence of safety for short term use in BRCA mutation carriers without breast cancer and recommends use after RRBSO until AUM (Gaba and Manchanda, 2020). Thus, BRCA mutation carriers undergoing hysterectomy with RRBSO can choose estrogen-only replacement therapy post-surgery. However, for BRCA mutation carriers who retain their uterus, counselling with consideration of alternative treatment options may be needed (Gordhandas *et al.*, 2019). Available studies suggest that HRT may not increase ovarian cancer risk in BRCA mutation carriers (Huber *et al.*, 2021).

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is an important method for the treatment of haematological diseases, especially haematological malignancies, and some congenital or hereditary diseases. However, the myeloablative conditioning regimen (MAC) before transplantation will cause irreversible damage to the patient's ovaries. The resulting POI affects the health of multiple systems such as skeletal, cardiovascular, urogenital, and neurological systems, quality of life, and even reducing life expectancy (Gargus *et al.*, 2018). Prospective observational studies suggest that HRT is safe for patients with POI after HSCT. HRT can relieve menopausal symptoms and correct bone loss after HSCT (Ha *et al.*, 2020), and does not increase the risk of recurrence of the primary disease (Yang *et al.*, 2017).

Recommendations

The guideline group recommends a personalised approach to risks and benefits of hormone therapy in women with iatrogenic POI after gynaecological/breast cancer		**GPP**
Hormone therapy does not increase the risk of recurrence of squamous cell carcinoma of the cervix and is recommended for women with iatrogenic POI due to treatment of squamous cell carcinoma.	⊕⊕⊕◯	**STRONG**
Hormone therapy may be associated with a low risk of recurrence of cervical adenocarcinoma and a personalised approach considering individualised hormone therapy risk and benefits is recommended.	⊕⊕◯◯	**STRONG**
HCPs could consider use of hormone therapy in women with early-stage low-risk endometrioid adenocarcinoma, as there is a low risk of cancer recurrence with hormone therapy use	⊕⊕◯◯	**CONDITIONAL**
HCPs could consider hormone therapy in women with iatrogenic POI due to epithelial ovarian cancer.	⊕⊕⊕◯	**CONDITIONAL**
The effect of hormone therapy on the risk of recurrence of non-epithelial ovarian cancer is unclear and it is suggested that HCPs use	⊕◯◯◯	**CONDITIONAL**

an individualised approach to prescribing hormone therapy including consideration of tumour hormone receptor status.		
Hormone therapy 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.	⊕⊕⊕◯	**STRONG**
Women should be informed of the risks of iatrogenic POI and risks and benefits of hormone therapy before risk reducing bilateral salpingo-oophorectomy.	⊕◯◯◯	**STRONG**
Women with POI should be informed that hormone therapy is generally contra-indicated in breast cancer survivors.	⊕⊕⊕◯	**STRONG**
Women with BRCA1/2 mutations without a personal history of breast cancer should be advised that hormone therapy is an option after risk reducing bilateral salpingo-oophorectomy	⊕◯◯◯	**STRONG**
It is recommended that individualised hormone therapy or pubertal induction be commenced in girls/women with POI following hematopoietic stem cell transplantation.	⊕⊕◯◯	**STRONG**

Justification

While in general, HT is recommended in women with POI, for women with iatrogenic POI after cancer treatment, risks may outweigh the treatment benefits. Different recommendations were formulated for iatrogenic POI after gynaecological/breast cancer taking into consideration the possible risks of recurrence or reactivation of cancer, and other risk factors (see also Table X Summary of recommendations for POI linked to gynaecological/breast cancer.

4792 **TABLE IX SUMMARY OF RECOMMENDATIONS FOR POI LINKED TO GYNECOLOGICAL/BREAST CANCER**

Cancer/previous diagnosis	HT	Risk of recurrence with HT use	Other considerations
Squamous cell carcinoma	✓ Recommended	Not increased	
Cervical adenocarcinoma	💬 Consider after risk assessment	Low risk	
Early-stage low-risk endometrioid adenocarcinoma	💬 Consider after risk assessment	Low risk	
Epithelial ovarian cancer	💬 Consider after risk assessment		
Non-epithelial ovarian cancer	💬 Consider after risk assessment	Moderate risk	Tumour hormone receptor status.
Hormone dependent ovarian or uterine tumours (uterine sarcoma, endometrioid carcinoma, ovarian clear cell carcinoma, ovarian granulosa cell tumour, sex cord-stromal tumours)	⊘ Contra-indicated	High risk	
Breast cancer survivors.	⊘ Contra-indicated	High risk	
BRCA1/2 mutation carrier after RRBO, without a personal history of breast cancer	💬 Can be considered	NA	Estrogen-only HRT has lower risk compared to combined estrogen/progestogen
POI following hematopoietic stem cell transplantation	✓ Recommended	Not increased	Individualised HT / pubertal induction

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XII. POI Treatment: Non-hormonal treatments, complementary treatments, and lifestyle interventions

Hormone therapy (HT) is preferentially used in women with POI to prevent or treat sequelae as detailed in previous chapters. However, some women with POI may choose against HT, while for other women, including those with hormone-sensitive malignancies, studies have shown severe adverse events and HT may not be appropriate.

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.

XII.1. Non-hormonal therapies

In this section the evidence regarding non-hormonal therapies for symptom management in POI is presented. Indirect evidence from studies of peri- or postmenopausal women is also included. The 2023 nonhormone therapy position statement of The North American Menopause Society provides a useful overview of this topic in the non-POI population (2023). Non-hormonal therapies for urogenital symptoms are discussed in Section IX.3. Treatment of genital-urinary symptoms .

PICO Question: What non-hormonal therapies are available for POI?

The systematic search of non-hormonal therapies included the following: antidepressants, clonidine, gabapentin, pregabalin, neurokinin receptor antagonists, oxybutynin, cognitive behavioural therapy (CBT), stellate ganglion blockade and hypnosis. Clinical outcomes included vasomotor symptoms and other menopause related symptoms, e.g. sleep, and quality of life.

Women with POI

We did not identify any RCTs, cohort or case-control studies evaluating non-hormonal treatments in women with POI specifically, as defined in chapter 2. Several RCTs (Hummel *et al.*, 2017) included women with iatrogenic menopause aged over 18 years or aged under 50 years with menopause following risk reducing BSO (Bober *et al.*, 2015), but did not specify POI. The following summary of the evidence relates to perimenopausal or postmenopausal women, including breast cancer survivors, and may be of relevance to women with POI (Table). It is important to remember that many nonhormonal pharmacological therapies for vasomotor symptoms are not government approved for this indication in many countries and their use is considered "off label".

Pharmacologic therapies for vasomotor symptoms

Antidepressants

A 2022 systematic review of Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) which included 36 RCTs (27 acceptable and nine low quality) involving 7347 healthy peri-/postmenopausal (studies involving women with cancer were excluded), concluded that the SSRIs escitalopram, paroxetine, and fluoxetine, and SNRIs, venlafaxine and desvenlafaxine, are effective in reducing vasomotor symptom frequency and severity (Azizi *et al.*, 2022). Studies on the effectiveness of sertraline, citalopram, fluvoxamine, and duloxetine were limited in number or showed inconsistent results.

Data from the MS FLASH RCTs involving 899 peri-/postmenopausal women aged 40-62 years with prevalent hot flushes, reported 18-37% reductions in vasomotor symptom frequency with 10-20mg escitalopram, 75 mg venlafaxine and 0.5 mg oral estradiol at 8-12 weeks versus placebo (Joffe *et al.*, 2014, Guthrie *et al.*, 2015). Estradiol was associated with the greatest reduction in vasomotor symptoms.

Two previous meta-analysis of 5 RCTs (1482 postmenopausal women) with significant heterogeneity (Wei *et al.*, 2016, Riemma *et al.*, 2019), reported a significant reduction in hot flush frequency with paroxetine versus placebo at 12 weeks (mean difference 7.36 per week; 95% CI 4.25 to 10.46; P< 0.00001) (Wei *et al.*, 2016). Efficacy was observed with low dose paroxetine and in women with either natural or surgical menopause (Wei *et al.*, 2016).

A recent RCT involving 91 symptomatic postmenopausal Mexican women, average age 54 years, comparing 20mg fluoxetine and 20mg citalopram observed 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 (Rios-Espinosa *et al.*, 2022).

A pharma sponsored RCT involving 1888 postmenopausal women aged 40-65 years reported decreased hot flush frequency and severity at 4 and 12 weeks with esmirtazepine compared to placebo (Birkhaeuser *et al.*, 2019).

Gabapentanoids

Gabapentanoids are used for the management of seizures and neuropathic pain. A 2020 meta-analysis of gabapentin and pregabalin (19 RCTs and 2 randomized crossover trials, n= 3519 participants) reported a reduction in hot flush frequency with gabapentin (mainly 900mg/day dosing) versus comparator with moderate quality evidence at four weeks and low-quality evidence at 12- and 24-weeks follow-up (Shan *et al.*, 2020). A similar response was seen in women with and without breast cancer. Two crossover studies showed no difference between gabapentin and fluoxetine or venlafaxine in reducing hot flush severity. Gabapentin was less effective than estrogen therapy (2 RCTs) and was associated with a higher rate of dizziness and drowsiness (Shan *et al.*, 2020). Similar findings were reported in another meta-analysis (Yoon *et al.*, 2020). Pregabalin was superior to placebo for hot flush frequency and severity (1 RCT) but inferior to Stellate ganglion block (1 RCT) (Shan *et al.*, 2020). However, pregabalin is a controlled substance in many countries due to the potential for abuse (North American Menopause Society)

Oxybutynin

Oxybutynin, an antimuscarinic, anticholinergic agent, is used for the management of overactive bladder and urinary urge incontinence. A RCT of 148 healthy postmenopausal women (surgical menopause excluded) aged 40-65 years with moderate- severe vasomotor symptoms reported significant reduction in hot flush frequency with 15 mg daily extended-release oxybutynin versus placebo (mean change -9.48 and -4.69 hot flushes/day respectively) at 12 weeks follow up (Simon *et al.*, 2016). A significant reduction in severity of hot flushes with oxybutynin versus placebo was also observed.

Clonidine

Clonidine, a centrally acting alpha2 adrenergic antagonist, is used to treat hypertension. A 2010 Cochrane review (Rada *et al.*) reported (on the basis of two RCTs using transdermal patch or oral clonidine; n=252) that clonidine significantly reduced the number and severity of hot flushes by approximately 20% compared with placebo. A subsequent RCT involving 102 women with breast cancer (Boekhout *et al.*, 2011) compared venlafaxine, clonidine and placebo and reported significantly lower hot flush scores in the clonidine versus placebo groups at 12 weeks follow-up. Clonidine is less effective compared to other pharmacological agents and is associated with adverse effects including dry mouth,

hypotension, headache, and dizziness with sudden cessation resulting in elevation of blood pressure (NAMS 2023 position statement)

Neurokinin B receptor antagonists

Fezolinetant, a neurokinin B3 receptor antagonist postulated to act on the hypothalamic KNDy neuron thermoregulatory system, was recently approved in Europe, North America, and Australia for the management of vasomotor symptoms in postmenopausal women (Morga *et al.*, 2024). Phase 2 studies of elinzanetant (a dual neurokinin B 1 and 3 receptor antagonist) and phase 3/ 4 studies of fezolinetant in other populations are ongoing (Koysombat *et al.*, 2024). The SKYLIGHT 1,2 and 4 RCTs involving ~1000 postmenopausal women, average age 54 years, demonstrated efficacy of fezolinetant at 12 and 52 weeks versus placebo in reducing vasomotor symptoms(mean difference in hot flush frequency at 12 weeks versus placebo −2.51 (95% CI −3.20 to −1.82) (Johnson *et al.*, 2023, Lederman *et al.*, 2023) (Santoro *et al.*, 2024). Pooled 12-week data from Skylight 1 and 2 indicated efficacy across a range of intrinsic (age, BMI, ethnicity, baseline vasomotor symptom duration or severity) and extrinsic (lifestyle, geographic region, previous HT use) factors indicating efficacy in diverse populations (Santoro *et al.*). A recent systematic review of neurokinin B antagonists (fezolinetant, elinzanetant) included 6 RCTs and reported > 50% reduction in moderate-severe hot flush frequency by 12 weeks versus placebo with favourable safety profiles and low incidence of liver enzyme elevations (Cieri-Hutcherson *et al.*, 2024). A 2024 Bayesian network meta-analysis (Morga *et al.*, 2024) involving 2 fezolinetant RCTs and 23 comparator studies reported that 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 (Morga *et al.*, 2024). Fezolinetant significantly reduced vasomotor symptom severity compared with placebo or 50mg desvenlafaxine but was less effective compared to tibolone or conjugated estrogen/ bazedoxifene.

Other

A phase 2 study of oral Q122 in 131 women aged 18-70 years with estrogen- receptor positive breast cancer demonstrated a significant reduction in vasomotor symptom severity compared to placebo (Vrselja *et al.*, 2022). The effect of sulpiride, a neuroleptic which acts on dopaminergic and serotoninergic receptors, was investigated in a small RCT involving 29 postmenopausal Brazilian women (Borba *et al.*, 2020). Reduction in hot flush severity and frequency at four- and eight-weeks follow-up was observed with sulpiride compared with placebo. Suvorexant, a dual orexin receptor antagonist, reduced nighttime vasomotor symptoms and insomnia indices in a small RCT of 56 postmenopausal women (Rahman *et al.*, 2022)

Non-pharmacological therapies for vasomotor symptoms

Cognitive behavioural therapy (CBT)

A 2022 meta-analysis including 14 RCTs comprising 1618 women with and without breast cancer (six and eight studies respectively) investigated CBT in managing menopausal symptoms. In most studies, interventions were delivered face to face (both individual and group) with the remaining studies using web-based interventions (Ye *et al.*, 2022). CBT intervention groups were compared to waitlist (n = 9), usual care (n = 3), or menopause education (n = 2) control groups and involved various settings including the workplace. CBT was associated with reductions in vasomotor symptom problem rating and frequency compared to controls which extended to a mean 23-week follow-up. However, women with treatment induced menopause displayed a smaller response to CBT compared to those with usual age menopause. Secondary analysis (Atema *et al.*, 2020) of a RCT (Atema *et al.*, 2019, Ye *et al.*, 2022) indicated that breast cancer survivors with a high school/vocational training degree benefited most from an internet based CBT program for treatment-induced vasomotor symptoms and that the positive effects of the CBT program on vasomotor and overall menopausal symptom burden were mediated by

the development of healthier beliefs regarding the ability to cope with and control vasomotor symptoms. Secondary analysis (Donegan *et al.*, 2022) of a RCT (Green *et al.*, 2019, Ye *et al.*, 2022) included 51 peri-/postmenopausal women aged 40-65 who received weekly group CBT for 12 weeks or a wait-list control group. CBT participants reported greater improvements compared to controls in menopause-specific beliefs, dysfunctional attitudes, and menopause-specific behaviours (assessed using validated scales) at 12 weeks treatment and then at a further three-month follow-up. Economic analyses concluded that CBT was cost effective for menopausal symptoms in women with breast cancer (Mewes *et al.*, 2015, Verbeek *et al.*, 2019).

Hypnosis

Hypnosis, a mind-body therapy, uses mental imagery for coolness, deep hypnosis, and dissociation from hot flushes and positive imagery to alleviate vasomotor symptoms. RCTs in women with and without breast cancer have shown reduction in vasomotor symptoms (subjective and objective measures) with hypnosis compared with wait list or sham hypnosis controls (Elkins *et al.*, 2008, Elkins *et al.*, 2013b, Barton *et al.*, 2017). Hypnosis was similarly effective in reducing vasomotor symptoms to comparators 900mg/ day gabapentin or 75 mg venlafaxine in two small RCTs of breast cancer survivors (Maclaughlan David *et al.*, 2013, Barton *et al.*, 2017). A pilot study of thirteen women suggests that self-guided hypnosis may also be helpful (Elkins *et al.*, 2013a).

Other

No benefit was observed with non-aerobic yoga, aerobic exercise, or 1.8 g/day omega-3 fatty acid supplementation in the MS-FLASH RCT (Guthrie *et al.*, 2015).

A review of stellate ganglion blockade RCTs concluded that vasomotor symptom frequency was reduced with stellate ganglion blockade compared with sham in one American RCT (Lee *et al.*, 2022c). Similar findings were reported in a recent RCT of stellate ganglion blockade versus saline sham in 40 symptomatic perimenopausal Chinese women with a significant reduction in hot flush frequency and severity versus control at 4-, 8- and 12-weeks follow-up (Li *et al.*, 2023c). No difference was observed in two RCTs comparing paroxetine or pregabalin to stellate ganglion blockade in women with breast cancer (Lee *et al.*, 2022c).

A systematic review and meta-analysis of 12 studies (including 6 studies of breast cancer survivors) with high heterogeneity involving 1019 postmenopausal women examined the effect of psychological interventions including CBT (5 studies), behavioural therapy (4 studies) and mindfulness-based therapies (3 studies) on menopausal symptoms compared to controls (predominately wait list or usual care) (van Driel *et al.*, 2019b). Web-based psychological interventions or RCTs involving yoga, hypnosis, exercise, meditation, awareness training breathing techniques as stand-alone therapies were excluded. Reduction in hot flush bother was observed with psychological interventions versus comparator but no difference was seen regarding hot flush frequency. Sub-group analysis showed similar benefits in women with natural or iatrogenic menopause. A recent Iranian study of 40 postmenopausal women indicated that an intervention involving predominately phone based cognitive behavioural counselling achieved similar vasomotor symptom benefits to an in-person intervention (Sadeghijoola *et al.*, 2022).

TABLE X NONHORMONAL OPTIONS FOR MANAGEMENT OF VASOMOTOR SYMPTOMS (ADAPTED FROM (NORTH AMERICAN MENOPAUSE SOCIETY., 2023), PERMISSION REQUESTED)

Agent	Dose	Comments
Pharmacological		
SNRIs		
Venlafaxine	37.5-150 mg/day	Commence with lowest dose then titrate upwards
Desvenlafaxine	100-150 mg/day	Commence with 50mg/day and titrate upwards
SSRIs		
Paroxetine	7.5 mg/day*	Single dose, no nitration needed
	10-25 mg/day	Commence with 5-10mg dose then titrate upwards
Escitalopram	10-20 mg/day	
Citalopram	10-20 mg/day	
Other		
Gabapentin	900-2400 mg/day in three divided doses.	Commence with 100-300 mg nighttime dose.
Fezolinetant	45 mg/day*	Single dose no titration needed
Oxybutynin	2.5-5 mg twice daily	Commence with lowest dose then titrate upwards
Clonidine	50-150 µg/day in twice daily dosing*	Commence with 25 µg twice daily and titrate upwards.
Non-Pharmacological		
Cognitive behavioural therapy		
Hypnosis		

*Government approved in some countries for use for vasomotor symptoms

Non-hormonal therapies and the effect on other symptoms or quality of life

A 2020 meta-analysis of seven RCTs (n=1949 peri-/postmenopausal women) investigating the effect of serotoninergic antidepressants on sleep indicated that these agents improved sleep quality compared with placebo but with small effect sizes (Cheng *et al.*, 2020). Only 3/7 RCTs involving escitalopram, citalopram, or venlafaxine, reported significant differences to the placebo groups. A sub-study of the MS-FLASH RCT (n=399) reported a small significant improvement in subjective sleep quality with low dose estradiol but not venlafaxine versus placebo in peri-/postmenopausal women with vasomotor symptoms (Caan *et al.*, 2015, Ensrud *et al.*, 2015). Modest improvement in the insomnia index was observed with venlafaxine versus placebo but did not reach significance with low dose estradiol. Addition of 5mg melatonin to fluoxetine resulted in greater improvements in sleep quality compared with fluoxetine alone in a Polish study of 64 postmenopausal women (Chojnacki *et al.*, 2015).

Although sleep quality indices improved in both groups, a RCT comparing 900mg/ day gabapentin to electroacupuncture administered as ten treatments over eight weeks in 58 predominately postmenopausal breast cancer survivors (age range 31-75 years) reported a significant between group difference in favour of electroacupuncture at eight weeks (Garland *et al.*, 2017). In contrast, 900mg/day gabapentin was associated with greater improvement in sleep quality index at 12 weeks follow-up compared with 60mg isoflavones in a RCT involving 50 Indian peri-/postmenopausal women, mean age 50 years (Singhal and Shullai, 2016).

Analysis of secondary outcomes indicated that stellate ganglion blockade was associated with a significant reduction in Kupperman index and sleep quality scores compared to sham (Li *et al.*, 2023c).

Improvement in sleep indices was reported in 2/3 RCTs of 45mg fezolinetant which assessed sleep and two RCTs involving elinzanetant at doses>120 mg was reported in a systematic review of neurokinin B antagonists (Cieri-Hutcherson *et al.*, 2024). This review also reported improved quality of life scores with both agents.

Sleep quality index, a secondary outcome, was significantly improved by hypnosis compared to structured attention controls in addition to vasomotor symptoms in a RCT of postmenopausal women (Elkins *et al.*, 2013b).

The MS Flash study reported improved menopause related quality of life (MENQOL scale) with 75mg venlafaxine or 0.5mg estradiol versus placebo in women with prevalent vasomotor symptoms (Caan *et al.*, 2015, Azizi *et al.*, 2022).

Evidence (RCTs and a 2022 meta-analysis) indicate that CBT is associated with improvement in depression, anxiety, stress, sleep, fatigue, and quality of life indices with small to medium effect sizes, compared to comparator (Abdelaziz *et al.*, 2021, Ye *et al.*, 2022). A RCT of 169 breast cancer survivors aged 18-65 years with sexual function problems demonstrated that weekly therapist guided internet-based CBT for 24 weeks was associated with improvements in sexual function parameters, menopausal symptoms, body image and marital sexual satisfaction compared to wait-list controls (Hummel *et al.*, 2017).

A 2022 meta-analysis of 13 studies with significant heterogeneity, investigated the effect of mindfulness-based interventions including mindfulness, meditation, and yoga (n=1138 menopausal women without psychiatric disorder aged 40-70 years) (Liu *et al.*, 2022a). The authors reported reduced stress but no effect on anxiety or depression with a mindfulness intervention versus comparator (wait list, usual care, or education).

Recommendation

Non-hormonal pharmacologic and non-pharmacologic therapies effective in peri-/postmenopausal women are likely to be helpful in women with POI although POI specific data is lacking	⊕◯◯◯ CONDITIONAL

Justification

There is a lack of evidence specific to women with POI regarding the use of non-hormonal therapies. This is of particular concern regarding the large number of women with iatrogenic POI associated with breast cancer treatment where HT is usually contra-indicated. Research to address this gap is needed. 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.

XII.2. Complementary therapies

The prevalence of use of complementary therapies in women in POI has not been reported. Use of natural products for menopause is around 13% (Gartoulla *et al.*, 2015, Vanden Noven *et al.*, 2023). Use of complementary therapies in breast cancer survivors is high, with research showing 45.5% of women with breast cancer use mind-body therapies, and 31.8% use natural health products and dietary therapies (Balneaves *et al.*, 2016). Breast cancer survivors report inadequate access to information on the safety and efficacy of complementary therapies and have called for concise and credible information about complementary therapies in order to support them in making informed and safe decisions about using complementary therapies for menopausal symptom management (Balneaves *et al.*, 2016). In one study, almost one third (29%) of Chinese breast cancer survivors were using traditional Chinese medicine (Yeo *et al.*, 2020).

The presence of menopausal symptoms such as vasomotor symptoms is associated with higher use of complementary therapies, both in natural and chemotherapy-induced menopause (Yeo *et al.*, 2020, Vanden Noven *et al.*, 2023).

In this section the evidence on complementary therapies for relief of symptoms in POI is summarized. Indirect evidence on women after usual age menopause is added, where evidence in POI is absent.

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

Chinese herbal medicine (CHM)

CHM + HT versus HT alone

A 2016 meta-analysis of Chinese herbal medicine (CHM) + HT compared to HT alone reported a mean difference of -1.19 (95% CI -1.77 to -0.61; 3 trials; n=152; I^2 63%; p<0.0001; low certainty evidence) in the Kupperman index (KI)[12] at end of treatment, favouring CHM + HT (Kou *et al.*, 2016). The included trials used a variety of CHM formulae including *Peikun* pills, *Yishenkangshuai* decoction, and *Taijingkangshuai* decoction. Treatment duration ranged from 3 to 5 months and HT used in the control groups included conjugated estrogen and medroxyprogesterone acetate, estradiol valerate and cyproterone, and estradiol valerate and dydrogesterone. We note that KI scores were low at end of treatment, ranging from 5 to 9 in the experimental and 10 to 12 in the control groups (i.e. scoring in the mild range). Adverse events were not reported in the review. CHM + HT was reported to be more efficacious than HT alone for reducing FSH levels (MD -7.08; 95% CI -9.8 to -4.37; 17 trials; n=1352; I^2 78%; p<0.00001) and increasing E2 levels (MD 3.45; 95% CI 2.11 to 4.79; 17 trials; n=1352; I^2 72%; p<0.00001) but not for LH (15 trials; n=1246).

A more recent network meta-analysis examined patent CHM + HT v HT alone (64 RCTs examining 12 oral patent medicines; n=5675) (Zhong *et al.*, 2022). For FSH, three patent medicines (*Kuntai* capsule, *Fuke Yangrong* capsule, *Liu Wei Di Huang Wan* capsule) + HT were more efficacious than HT alone (59 RCTs; n=5415). For LH, four patent medicines (*Guishen* pill, *Liu Wei Di Huang Wan* capsule, *Kuntai* capsule and *Fuke Yangrong* capsule) and for E2, three patent medicines (*Ziheche* capsule, *Fuke Yangrong* capsule and *Zuogui* pills) + HT were more efficacious than HT alone. Thirteen studies reported adverse effects. Only *Kuntai* capsule + HT resulted in fewer adverse effects compared to HT alone.

[12] Reflecting perimenopausal syndrome and symptoms

Two meta-analyses examined a Chinese herbal medicine formula known as *Kuntai* capsule[13] + HT v HT alone (Liu *et al.*, 2019, Ma *et al.*, 2020). The analysis by Liu *et al* reported that *Kuntai* capsule + HT was more effective than HT alone for some lipid parameters including triglycerides (WMD -0.55; 95% CI -0.67 to -0.43; 3 studies; n=290; I^2 0%; p<0.00001; low certainty evidence), total cholesterol (-0.63; 95% CI -0.74 to -0.52; 3 studies; I^2 0%; P<0.00001; low certainty evidence), LDL cholesterol (WMD -0.62; 95% CI -0.75 to -0.49; 3 studies; I^2 0%; p<0.00001; low certainty evidence) but not for HDL (very low certainty evidence). The reviewers also report on findings from one RCT that found a mean difference of -5.99 in the KI between intervention and control (95% CI -8.04 to -3.94; n=100; p<0.00001). *Kuntai* capsule + HT was more efficacious than HT alone for LH (MD -3.47; 95% CI -5.68 to -1.26; 11 trials; n=1100; I^2 92%; p=0.002), FSH (MD -8.15; 95% CI -10.44 to -5.86; 11 trials; n=1100; I^2 83%; p<0.00001) and E2 (MD 17.21; 95% CI 10.16 to 24.26; 11 trials; n=1100; I^2 98%; p<0.00001)(Liu *et al.*, 2019).

Ma *et al* reported that *Kuntai* capsule + Climen was more effective than Climen alone for menopausal symptoms (KI) (MD -3.86; 95% CI -4.92 to -2.8; 5 trials; n=606; I^2 83%; p<0.00001, very low certainty evidence). Mean endpoint scores in both groups for the KI ranged from 6 to 13 (i.e. in the mild range). *Kuntai* capsule + HT was more effective than HT alone for FSH (MD -8.987; 95% CI -11.94 to -6.12; 10 trials; n=990; I^2 74%; p<0.00001), LH (MD -7.01; 95% CI -10.77 to -3.24; 5 trials; n=460; I^2 92%; p=0.0008) and E2 (MD 11.38; 95% CI 7.11 to 15.64; 10 trials; n=990; I^2 87%; p<0.00001) (Ma *et al.*, 2020).

CHM versus HT

One meta-analysis examined Chinese herbal medicine formulae that are designed for the Chinese medicine functions of tonifying the kidney (bushen) and activating blood (huoxue) compared directly with HT (Li *et al.*, 2020a). CHM was more effective than HT for KI (SMD -0.78; 95% CI -1.24 to -0.31; 7 trials; n=452; I^2 81%; p=0.001; very low certainty evidence). KI scores ranged from 7.2 to 18.24. CHM was more efficacious than HT for E2 levels (SMD 0.70; 95% CI 0.14 to 1.26; 19 trials; n=1345; I^2 95%; p < 0.05)), and FSH (SMD −0.50; 95% CI −0.81 to −0.18; 19 trials; n=1345; I^2 95%; p < 0.05) but not for LH.

CHM versus placebo

A double-blind placebo controlled RCT (n=146) compared a Chinese herbal formula *Yangyin Shugan* formula against matched placebo. The study reported significant reductions in the intervention group compared to placebo at 12 weeks for the total score of the Chinese MENQOL[14] (38.64±5.69 vs 65.04±4.40) and for the different domains including the vasomotor, psychosocial, physical, and sexual domain (p<0.01 for all comparisons) (Cao *et al.*, 2018). CHM was more efficacious than placebo for reducing FSH (10.11±4.63 vs 32.66±13.81), increasing AMH (1.76±2.11 vs 0.73±1.61) and AFC (6.97±3.35 vs 4.43±3.06), but not for E2 at endpoint. There were no differences between groups for whole blood counts, renal and liver function. No serious adverse events were reported in either group. One participant in the placebo group reported abdominal pain. One participant in the placebo group withdrew from the study. Compliance was excellent with all participants taking at least 95% of scheduled doses based on medication count (Cao *et al.*, 2018)

CHM + acupuncture versus HT alone

A meta-analysis examined the effectiveness of the combination of CHM and acupuncture compared with HT, placebo, or no treatment (Li *et al.*, 2020c). Only one trial reported on the outcomes of interest to this guideline. This trial (n=56) reported a lower KI in the acupuncture + CHM (*Bushen Nuan Chong Tang)* group compared to HT (EV + cycloprogesterone) after three months of treatment (KI 14.41 $\pm$ 2.97 vs 25.69 $\pm$ 3.25; p<0.05). The meta-analysis reported no difference between acupuncture + CHM and

[13] *Kuntai* capsule is a formula containing *Rhizoma coptidis, Radix Paeoniae alba, Poria cocos, Radix scutellariae,* and *Rehmannia glutinosa.*

[14] Chinese version Menopause-Specific Quality of Life questionnaire

control for adverse events (RR 0.31; 95% CI 0.04 to 2.54; 5 trials; n=387; I^2 42%; p=0.28). Acupuncture + CHM was more efficacious than HT for reducing FSH (MD -2.88; 95% CI -5.00 to -0.76; 12 trials; n=778; I^2 0%; p=0.008), and normalisation of menstrual cycles (RR 2.06; 95% CI 1.62 to 2.61; 14 trials; n=1030; I^2 26%; p<0.00001) but not for LH.

An RCT examined the effectiveness of acupuncture (*Tiaobu Chongren* style) and CHM (*Wenjing* decoction) compared with HT (Climen) (n=119) (Yi *et al.*, 2021). Participants were asked to rate how "hot and sweaty" they felt based on a 4-point Likert scale from 0-3 representing no symptoms, mild, moderate, and severe symptoms. Acupuncture + CHM resulted in lower scores at 3 months compared to the HT group (0.7 ± 0.08 vs 1.45 ± 0.12, p<0.05).

Acupuncture and moxibustion.

Acupuncture + HT (or CHM) versus HT alone.

A 2015 meta-analysis included 3 RCTs comparing acupuncture + HT versus HT alone, and one RCT comparing acupuncture + CHM versus HT alone. (Jo *et al.*, 2015). Two RCTs (n=125) used the KI as an outcome measure, but neither reported any difference in the KI at end of treatment between acupuncture + HT and HT alone however there was a difference between groups at 6 months post end of treatment in one study. Acupuncture as an adjunct to HT/CHM was efficacious for lowering FSH (MD -11.40; 95% CI -19.61 to -3.2; 3 trials; n=161; I^2 0%; p=0.006), resumption of menstruation (RR 1.20; 95% CI 1.03 to 1.39; 4 trials; n=233; I^2 37%; p=0.02), lowering LH (MD -19.81; 95% CI -34.14 to -5.48; 2 trials; n=80; I^2 0%; p=0.007) but not for improving E2 (3 trials, n=161).

Acupuncture versus HT

The same 2015 meta-analysis included 4 trials comparing acupuncture with HT and found that acupuncture was more efficacious than HT for reducing FSH (MD -8.60; 95% CI -13.58 to -3.62; 3 trials, n=360; I^2 23%; p=0.007), resumption of menstruation (RR 1.32; 95% CI 1.10 to 1.59; 4 trials; n=381; I^2 62%; p=0.003), raising E2 (MD 42.61; 95% CI 6.4 to 78.83; 3 trials; n=318; I^2 97%; p=0.02), but not for improving LH (2 trials; n=198) (Jo *et al.*, 2015).

A 2017 RCT randomised 80 women to receive either electroacupuncture and moxibustion or HT (Climen) for 6 months and reported a lower night sweat score in the intervention group at end of treatment (1.17 ± 0.82 vs 1.53 ± 0.65, p<0.05) where the night sweat score ranged from 0 to 4 with 0 being occasional fever and slight sweatiness, and 4 being intermittent fever with sweatiness and red face, interfering with attention and affecting sleep (Wxu and Tian, 2017).

A 2014 case series reported on 31 women who received acupuncture for 3 months (Chen *et al.*, 2014). At the end of the 3-month period, there was a reduction in anxiety (Self-Rating Anxiety scale) from 54±6 to 41±7 and in the KI from 18±4 to 12±2 (p=0.00 for both).

A 2022 umbrella review (Cao *et al.*, 2022) included two systematic reviews already described above (Jo *et al.*, 2015, Li *et al.*, 2020c).

It should be noted that the total effective rate or effectiveness rate, a commonly used outcome measure in Chinese medicine trials, has not been considered as a relevant outcome measure for this guideline as it is aims to assess efficacy of treatment according to resolution of symptoms that are relevant in Chinese medicine only.

Moxibustion + HT versus HT alone

Moxibustion is an acupuncture-related technique that involves burning of mugwort leaves near acupuncture points. One RCT (n=66) compared moxibustion with HT versus HT alone for 3 months and reported a higher AFC (3.06±1.2 vs 2.33±0.96), E2 (77.57±9.21 vs 67.16±9.95 pmol/L) and lower FSH

(50.31±6.19 vs 59.12±6.82 IU/L) in the intervention group compared to control (p<0.05) (Wang *et al.*, 2021)

Korean medicine

One case series reported on three women with POI (age range 26-39) treated with Korean herbal medicine, electroacupuncture and moxibustion, and placental acupuncture for at least 3 months (Jang *et al.*, 2022a). 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.

Nutrients

Evidence on nutrient supplementation for POI is very limited due to lack of randomised controlled trials. We found only one RCT and one case report. The RCT (n=67) evaluated the efficacy of three months of a selenium and Vitamin E supplement against matched placebo. Improvements in AMH (MD 0.59; 95% CI 0.48 to 0.71; p<0.001), AFC (MD 5.08; 95% CI 4.36 to 5.08; p<0.001) and mean ovarian volume (MD 2.17; 95% CI 1.87 to 2.47; P<0.001) were reported in the intervention group compared with placebo at 12 months (Safiyeh *et al.*, 2021).

A case report on the use of methylfolate in a 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, reported natural conception after 3 months of methylfolate 800 mg daily with a B vitamin supplement (dose and ingredients unspecified). This was complicated by vanishing twin at 9 weeks and oligohydramnios and preeclampsia at 36 weeks. Delivery was by Caesarean section at 37 weeks due to oligohydramnios, preeclampsia, and breech presentation. A healthy male baby was delivered weighing 2.69 kg (Goyco Ortiz *et al.*, 2019). Methylation is proposed to be an important process in DNA repair, gene expression regulation and epigenesis, with an impact on early and late embryogenesis, trophoblast development and implantation. Synthetic folic acid has poor capacity to form tetrahydrofolate and 5 MTHF which is required for recycling of homocysteine.

Phytoestrogens: soy, red clover, and flaxseed

Phytoestrogens are plant substances that have similar effects to estrogen. Two groups of phytoestrogens, isoflavones and lignans, can be found in soybeans-red clover, and flaxseed, respectively.

We did not identify studies evaluating phytoestrogens in women with POI. We report on data from RCTs of postmenopausal women.

Cardiovascular health

A 2022 meta-analysis of RCTs in postmenopausal women reported benefits from phytoestrogens (flaxseed, red clover, and soy) on lipid profiles. Flaxseed was associated with reductions in total cholesterol (TC) (weighted-mean difference (WMD) -0.26; 95% CI -0.38 to -0.13; 7 RCTs; n=452; I^2 6%; p=0.0001) and low-density lipoprotein cholesterol (LDL-C) (WMD -0.19; 95% CI -0.30 to -0.08; 7 RCTs; n=417; I^2 0%; p=0.0006). However, flaxseed also resulted in an increase in high-density lipoprotein cholesterol (HDL-C) (WMD -0.06; 95% CI -0.11 to -0.01; 7 RCTs; n= 418; I^2 0%; p=0.0150). Soy protein resulted in reductions in TC levels (WMD -0.15; 95% CI -0.25 to 0.05; 18 RCTs, n=1322; I^2 26%; p=0.0048), LDL-C levels (WMD -0.15; 95% CI -0.25 to 0.05; 16 RCTs; n=1234; I^2 17%; p=0.0067), as well as an increase in HDL-C levels (WMD 0.05; 95% CI 0.02 to 0.08; 18 RCTs; n=1322; I^2 0%; p=0.0034). Red clover reduced TC levels (WMD -0.11; 95% CI -0.18to-0.04; 8 RCTs; n=884; I^2 0%; p=0.0017) and increased HDL-C levels (WMD 0.04; 95% CI 0.01 to 0.07; 8 RCTs; n=884; I^2 0%; p=0.0165) (Błaszczuk *et al.*, 2022).

Vasomotor symptoms

A meta-analysis of eight trials (ten comparisons) in postmenopausal women demonstrated a statistically significant reduction in hot flush frequency in women receiving red clover compared to those receiving placebo (WMD -1.73 ; 95% CI -3.28 to -0.18; 8 RCTs; n=751; I^2 87%; p=0.0292). The greatest benefit appears to be in women with ≥5 hot flushes per day, a duration of >12 weeks, with an isoflavone dose of ≥80 mg/day, and when the formulations contained a higher proportion of biochanin A (Kanadys *et al.*, 2021).

Sexual function

A 2021 systematic review and meta-analysis reported no benefit of soy, red clover, or flaxseed on sexual function, however soy improved dyspareunia (1 RCT, n=37) (Najaf Najafi and Ghazanfarpour, 2018) .

Black cohosh

Black Cohosh is a plant native to North America widely used for the relief of vasomotor symptoms. A 2012 Cochrane review reported no benefit from using black cohosh for vasomotor symptoms compared to placebo in postmenopausal women (Leach Matthew and Moore, 2012). No updated meta-analyses have been published.

Other supplements

Single trials have not demonstrated benefits from wild yam (*Dioscorea villosa*), dong quai (*Angelica sinensis*), or evening primrose oil (*Oenothera biennis*) for vasomotor symptoms (North American Menopause Society., 2023).

A 2022 review on ginseng reported a reduction in menopausal symptoms, hot flushes, and quality of life but no benefit for sexual function (Lee *et al.*, 2022a). A 2021 review reported improvements in menopausal symptoms with fennel (Foeniculum vulgare Miller) compared to placebo, but no benefit for quality of life, psychological health, or sexual function. No serious adverse events were reported (Lee *et al.*, 2021).

Recommendations

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		**GPP**
Complementary treatments do not prevent the long-term sequalae of POI and should therefore not be used to replace hormone therapy.	⊕◯◯◯	**STRONG**
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.	⊕◯◯◯	**STRONG**
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 hormone therapy.	⊕◯◯◯	**STRONG**

Women who are considering using nutrient supplements for improving reproductive parameters in POI should be informed that the evidence is very limited with only one intervention (Vitamin E and selenium) studied in randomised controlled trials.	⊕◯◯◯	**STRONG**

Women who are considering using other nutrient supplements and herbal medicines should be informed that there is insufficient evidence to support their use.	⊕◯◯◯	**STRONG**

Justification

In general, evidence on the different complementary treatments is limited, both in terms of efficacy for relief of vasomotor symptoms and improving of fertility, as well as for possible side effects.

Acknowledging that women with POI may seek complementary interventions to relief their symptoms or improve their fertility, emphasis was put on informing them that there is too little evidence of benefit to recommend the different treatments, as well as, for some interventions, too little evidence to consider them to be safe.

Considering the data on efficacy and the different long-term consequences of estrogen deprivation in POI, the guideline group strongly recommends not to replace the recommended HT treatment with complementary therapies solely aimed to relief short term vasomotor symptoms. In women with vasomotor symptoms while taking HT, a revision of the HT regimen should be prioritised over complementary treatments.

XII.3. Lifestyle management options

Given both the shorter-term symptoms and quality of life (QoL) impact of POI and the potential long-term health implications, there is growing interest in identifying effective interventions to mitigate the adverse effects, improve the overall wellbeing and prevent long-term complications for women with this condition. Healthy lifestyle is routinely advocated for healthy ageing and mitigation of common preventable illnesses. This includes cardiovascular disease and osteoporosis. Prevention of these conditions is even more relevant in POI.

In this section, the evidence regarding lifestyle interventions in menopausal women is summarized.

PICO QUESTION: WHAT ARE THE LIFESTYLE MANAGEMENT OPTIONS FOR POI?

The systematic literature search included lifestyle intervention, diet, and physical activity/ exercise. The outcomes include relief of menopause symptoms, quality of life and cardiovascular outcomes. Osteoporosis and bone health outcomes are covered elsewhere in this guideline (VI. POI and musculoskeletal health).

Menopause symptoms

There is a lack of evidence specifically investigating the effects of lifestyle interventions on the relief of menopause symptoms in women with POI.

A systematic review conducted by Noll et al. found inconclusive evidence regarding the association between dietary intake and the intensity of menopausal symptoms. Nevertheless, some studies have suggested that postmenopausal women who adhere to a high-quality diet, including consumption of vegetables, fruits, and whole grains, may experience lower intensity of menopausal symptoms (Noll *et al.*, 2021). Conversely, diets rich in processed foods, saturated fat, refined grains, fried foods, fatty meats, sweets, and sugar-sweetened beverages were associated with more severe psychological, vasomotor, and somatic symptoms (Noll *et al.*, 2021).

Regarding exercise interventions, in a Cochrane review and meta-analysis, no significant difference was found between exercise and control groups in frequency or intensity of vasomotor symptoms in symptomatic peri- and postmenopausal women (SMD -0.10; 95% CI -0.33 to 0.13; 3 studies; 454 women). Also, no significant differences were observed between exercise and yoga when two studies were pooled (SMD -0.03; 95% CI -0.45 to 0.38; 279 women). Also, one small trial found fewer frequency of hot flashes in hormone therapy group compared to the exercise group. Women involved in these studies were aged 40-63 years. All studies were of low quality (Daley *et al.*, 2014). However, Liu (2022) found in a systematic review that exercise interventions significantly improved the severity of vasomotor symptoms compared to no-treatment control group (SMD 0.25; 95% CI 0.04 to 0.47, 10 studies), but no significant changes in vasomotor frequency were observed (SMD 0.14; 95% CI -0.03 to 0.31). Authors reported that further exploration is required to understand the potential impact of exercise on menopause symptoms based on the intensity and type of exercise (Liu *et al.*, 2022b).

Quality of life

Several systematic reviews have examined the impact of exercise interventions on the QoL in menopausal women. However, there is no study assessing the effect of lifestyle interventions on the QoL of women with POI.

A systematic review of 11 studies including 1548 peri- and post-menopausal women aimed to explore the impact of various exercise programs on sexual function and quality of sexual life related to

menopausal symptoms. Mind-body exercises such as yoga showed the potential to improve menopausal symptoms, whereas the effectiveness of aerobic training was inconclusive and resistance training did not exhibit any significant improvements in this context (Carcelén-Fraile *et al.*, 2020).

A systematic review of 23 studies focusing on perimenopausal women (n=1812) revealed that exercise-based interventions and mind-body therapies have the potential to enhance QoL (SMD −0.67; 95% CI −1.29 to −0.05; 5 studies/6 interventions) and alleviate menopausal symptoms (SMD −1.32; 95% CI −1.72 to −0.91;10 studies) and depression (SMD −1.10; 95% CI: −1.73 to −0.47; 7 studies). However, the analysis did not find a significant intervention effect for mitigating hot flashes. The meta-analysis results showed high levels of heterogeneity among studies (Shorey *et al.*, 2020).

Additionally, a systematic review of nine RCTs, explored the impact of exercise interventions including yoga, pelvic floor muscle training, aerobic training, walking and self-directed exercise programs (such as swimming, running, and cycling) on the QoL in 882 women experiencing menopausal symptoms. The meta-analysis revealed some positive effects of exercise on physical and psychological QoL scores, although the results were not statistically significant [(SMD 0.89; 95% CI −0.11 to 1.89; p=0.08; 5 studies; I^2 97%) and (SMD 0.56; 95% CI −0.04 to 1.15; p=0.07; 7 studies; I^2 93%), respectively]. However, there was no conclusive evidence to indicate that exercise interventions had a significant effect on overall, social, and menopause specific QoL scores when compared to no active interventions. Among the interventions studied, yoga and pelvic floor muscle training were the most commonly used interventions for women experiencing menopausal and urinary symptoms, respectively. Yoga significantly improved physical QoL, but its effects on overall, psychological, sexual, and vasomotor symptom QoL scores were not significant. Similarly, pelvic floor muscle training did not yield a significant effect on overall QoL (Nguyen *et al.*, 2020).

A meta-analysis of five RCTs including 268 post-menopausal women (mean age 53-67 years) revealed that pelvic floor muscle training, commonly known as Kegel's exercise, significantly enhanced health-related QoL (HRQoL) in those experiencing urinary symptoms compared to non-Kegel's exercise or regular activity (SMD −0.95; 95% CI −1.35 to −0.54; 3 studies; I^2 0%). However, there was no significant impact on HRQoL related to sexual symptoms (SMD 1.11; 95% CI −0.25 to 2.47; 2 studies; I^2 94%). The Kegel's exercise programs in the included studies consisted of 8-12 sessions lasting 20-40 minutes, twice weekly. Most studies exhibited a low risk of bias (Nguyen *et al.*, 2024).

A systematic review of 12 studies involving 925 menopausal women highlighted the effectiveness of exercise, phytoestrogen and isoflavone products and participating in educational programs in improving the QoL in menopausal women (Taebi *et al.*, 2018).

The impact of aquatic exercises on postmenopausal women (n=594) was assessed in a systematic review and meta-analysis comprising 16 RCTs predominantly of moderate quality. The findings revealed 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) among women engaging in aquatic exercises compared to those with no exercise. Furthermore, within the range of aquatic exercises, 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 (Zhou *et al.*, 2023).

Cardiovascular health

Two RCTs assessed the effect of a lifestyle intervention on cardiovascular fitness among cancer survivors. In a small trial involving 35 BRCA1/2+ breast cancer survivors (with a mean age of 46 years) who

underwent risk reducing oophorectomy, a 12- month web-based lifestyle modification program improved body composition and bone health and successfully prevented a decline in cardiovascular fitness (Sturgeon *et al.*, 2017). In another study on 154 female cancer survivors (with a mean age of 52 years), a 12-month aerobic-resistance exercise intervention at a fitness centre yielded significantly better results in terms of cardiovascular fitness and metabolic risk factors compared to a home-based physical activity group (Knobf *et al.*, 2017).

In a systematic review of 14 RCTs, most studies highlighted the significant benefits of physical activity/ exercise interventions on cardiorespiratory fitness and cardiovascular risk factors including lipid and glycemic metabolism, body composition, blood pressure, inflammatory index, and autonomic responses in both premenopausal and postmenopausal women. These interventions have been shown to increase maximum oxygen uptake or decrease inflammatory factors in women. It is worth noting that women of different ages (ranging from 18 to 77 years) participated in these studies (Ruiz-Rios and Maldonado-Martin, 2022).

A systematic review encompassing 129 studies, including 7141 post-menopausal women with the mean age of 53-90 years indicates that exercise training 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). However, there was a significant heterogeneity among studies for all outcomes. Sub-group analysis shows a significant enhancement in cardiorespiratory fitness and muscle strength among both middle-aged and older individuals and women engaged in medium- and long-term interventions. Various types of exercise-such as aerobic, resistance, combined aerobic-resistance and water-based training were associated with significant increases in cardiorespiratory fitness levels and lower-body strength. Resistance exercise notably increased upper-body strength, while both resistance and combined training enhanced handgrip strength. However, aerobic training alone did not affect handgrip strength (Khalafi *et al.*, 2023b).

Exercise training was also found effective for improving body composition, leading to increased muscle mass (SMD 0.26; 95% CI 0.13 to 0.39; I^2 0%) and decreased fat mass (WMD -1.27 kg; 95% CI -1.93 to -0.62; I^2 56%) in post-menopausal women, as revealed in a meta-analysis on 101 RCTs (n=5697 women, mean age 51-89 years). Specifically, aerobic training was found effective for fat loss, while resistance training contributed to muscle gain. Sub-group analysis further indicates that these favourable outcomes are observed predominantly among middle aged and older women, engaged in medium- and long-term interventions. Consequently, this study suggests incorporating a combination of aerobic and resistance exercises to promote overall health in postmenopausal women (Khalafi *et al.*, 2023a).

The effect of resistance training was assessed through a systematic review and meta-analysis including 20 RCTs with a total of 742 overweight/ obese postmenopausal and older women. The findings demonstrate improvements in body composition and metabolic health, as well as reductions in inflammation, in both low-volume and high-volume resistance training interventions. However, high-volume resistance training reveals superior efficacy in mitigating metabolic risk factors and inflammation than low-volume training when compared to the control group. This study suggests the potential benefits of incorporating resistance training, particularly high-volume, into interventions targeting obesity and related metabolic disorders in this demographic (Nunes *et al.*, 2023).

In a systematic review of 13 studies (12 RCTs and one retrospective cohort, mostly with fair quality) involving 700 postmenopausal women, aerobic training and a combined aerobic-resistance training were found to enhance cardiorespiratory fitness and decrease arterial stiffness while also lowering pulse waive velocity. Of these approaches, the combined exercise program exhibited the greatest

effectiveness. Notably, the study included participants aged 47 to 88 years, reflecting a diverse range of postmenopausal women (Ferreira *et al.*, 2024).

A meta-analysis of 17 small RCTs (n=792 women) highlighted the significant benefits of exercise on body fat (SMD −0.34; 95% CI −0.60 to −0.08; 8 studies), waist circumference (SMD −0.39; 95% CI −0.68 to −0.09; 5 studies), triglyceride levels (SMD −0.37; 95% CI −0.62 to −0.11; 7 studies), and bone mineral density (SMD 0.38; 95% CI 0.08 to 0.68; 5 studies) in menopausal women. The exercise interventions encompassed various modalities, such as aerobic exercise, resistance training, strength training, tai chi, high-impact training, and yoga (Yeh *et al.*, 2018).

Resistance training was found effective in reducing lipid profile including total cholesterol (WMD -11.47 mg/dl, 95% CI -18.55 to -4.39, n=686 women), triglyceride (WMD -6.61 mg/dl; 95% CI -13.03 to -0.19; n=741 women) and low-density lipoprotein cholesterol (WMD -8.48 mg/dl; 95% CI -15.05 to -1.91; n=721 women) compared with placebo, as revealed by a meta-analysis encompassing 19 RCTs (mostly with a good quality). However, significant heterogeneity was observed among studies. Although the impact of resistance training on reducing high-density lipoprotein was minimal overall, it was discernible in women with obesity. Notable, the 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 (He *et al.*, 2023).

A meta-analysis of 63 RCTs revealed that exercise training (including aerobic, resistance or combined training) resulted in small but clinically relevant reductions in systolic blood pressure (MD –3.43 mm Hg; 95% CI -5.16 to -1.71), diastolic blood pressure (MD –2.25 mm Hg; 95% CI -3.40 to -1.11) and mean arterial pressure (MD –3.48 mm Hg; 95% CI -5.84 to -1.11) in menopausal women. Combined training showed the highest reductions in blood pressure and mean arterial pressure. The included studies encompassed women aged between 50 and 85 years (Loaiza-Betancur *et al.*, 2021).

Considering the menopause transition stage, a systematic review noted limited research on exercise and/or dietary interventions on women's body weight and composition. Out of 3 included studies in this review, one high quality RCT suggested that exercise combined with dietary interventions could potentially mitigate the increase in body adiposity. Additionally, two other studies with higher risk of bias indicated that exercise, including walking programs or circuit training, might help reduce weight gain and modify abdominal adiposity patterns during the menopause transition (Jull *et al.*, 2014).

Recommendation

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**

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.	**GPP**

Justification

While there is limited research specifically assessing lifestyle interventions in women with POI, existing evidence suggests that exercise interventions have the potential to enhance QoL and alleviate physical and psychological menopause symptoms.

Exercise training showed blood pressure reductions and positive impacts on cardiovascular fitness and body composition in menopausal women. However, 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.

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.

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

There are many and all quite rare causes of POI that could need pubertal induction, including but not limited to galactosemia, , hypergonadotropic hypogonadism of different genesis, disorders of sex development (complete gonadal dysgenesis ovotesticular dysgenesis, female 45,X/46,XY and others), rare mutations like FSH receptor, LH receptor, FOXL2 and BMP15 mutations, and cancer survivors. (Nordenström *et al.*, 2022, Ke *et al.*, 2023). Most of the available literature on puberty induction in POI concerns studies of girls with Turner Syndrome (TS) (Nordenström *et al.*, 2022).

Five to 10% of girls with TS retain sufficient ovarian function for puberty to start spontaneously and among these patients AMH can be used as a future marker of appropriate ovarian function (Hagen *et al.*, 2010). Most girls show a progressive ovarian failure and need estrogen and progestogen treatment for complete pubertal development and withdrawal bleeding. The attainment of an optimal adult height with growth hormone (GH) therapy is also of importance, in some conditions like Turner syndrome and other conditions with poor linear growth. Lower estrogen doses may stimulate growth, but higher estrogen doses cause acceleration of bone maturation and result in decreased adult height.

It is important to educate the patient that estrogen replacement is usually required until the time of usual menopause to maintain feminization and prevent osteoporosis (Gravholt *et al.*, 2017). Still, recent studies have shown that a considerable percentage of TS patients discontinue therapy in adult life and are lost to follow-up (Ertl *et al.*, 2018, Bernard *et al.*, 2019, Cameron-Pimblett *et al.*, 2019, Viuff *et al.*, 2020). Therefore, the continuum of care through childhood and adolescence into adulthood is mandatory.

PICO Question: How should puberty be induced?

When to start estrogens?

During recent years consensus has evolved concerning the optimal age at which to begin puberty induction. Although estrogens can accelerate bone maturation, and thus estrogen replacement was previously delayed, often until 15 or 16 years of age, to allow additional time for linear growth with growth hormone therapy in TS (Chernausek *et al.*, 2000), there is now consensus that there are ample reasons for starting therapy around 11-12 years of age in all patients with POI (Gravholt *et al.*, 2017, Nordenström *et al.*, 2022). The aims of induction of puberty at the same age as in peers is to achieve further growth, increase BMD, adult uterine and breast configuration, monthly withdrawal bleeds and optimal neurocognitive development. More recently, studies have shown that beginning GH at a younger age in TS, thus providing a longer period of estrogen-free GH treatment, may allow initiation of estrogen therapy, at a low dose, at a more normal age (11-12 years) without loss of adult height (Gravholt *et al.*, 2017, Nordenström *et al.*, 2022). This approach can be considered for other causes of delayed or absent puberty when the condition is known from an early age. One study has also suggested that very early and very low dose estrogen may even be beneficial for growth, but this approach has so far not been included in usual clinical care (Ross *et al.*, 2011).

What preparations, mode of delivery and doses of estrogen should be used?

Multiple forms of estrogen are available; oral estrogens have been the most widely used. However, conjugated equine estrogen preparations (CEE, Premarin®) contain multiple estrogens some of which are not found in humans and are not justified for use in children (Gravholt *et al.*, 2017, Nordenström *et al.*, 2022). Similarly, the oral contraceptive pill is best avoided, because the synthetic estrogen doses are too high and the typical synthetic progestin may interfere with optimal breast and uterine development (Gravholt *et al.*, 2017) and more patients seem to develop hypertension (Cameron-Pimblett *et al.*, 2019).

Furthermore, the oral contraceptive pill is conventionally taken with a pill-free week, resulting in 3 months of estrogen deficiency for each year of use.

Oral ethinylestradiol is no longer recommended for puberty induction. Natural estrogens are metabolised in the liver and must be given either orally (Leung *et al.*, 2004) or, to avoid the first pass effect, transdermally. Natural estrogens, i.e. 17β-estradiol, have less pronounced effects on coagulation factors, lipid profiles and blood pressure than synthetic estrogens and are recommended for use in TS (Gravholt *et al.*, 2017) and other forms of hypogonadism (Nordenström *et al.*, 2022), with oral or transdermal estradiol showing similar effects on metabolic parameters (Torres-Santiago *et al.*, 2013). With 17β-estradiol transdermal (TD) patches or percutaneous gel, spontaneous pubertal hormonal changes are mimicked, and normal pubertal development is achieved (Ankarberg-Lindgren *et al.*, 2019).

Puberty is a relatively slow process and the replacement therapy in the induction process should mimic this (Donaldson *et al.*, 2019). Although the appropriate starting dose has yet to be determined, estrogen replacement is usually begun at one-tenth to one-eighth of the adult replacement dose and then increased gradually over a period of 2 to 4 years (Donaldson *et al.*, 2019). To allow for normal breast and uterine development, it seems advisable to delay the addition of progestin at about 18-24 months after starting estrogen or until breakthrough bleeding occurs (Shim *et al.*, 2023).

Based on these principles, suggested age-specific preparations and doses of estrogen substitution therapy in adolescence are listed in Table XII. This table is only a guide and individual tailoring of dose and timing will be required.

TABLE XI ESTROGEN SUBSTITUTION THERAPY IN ADOLESCENCE (ADAPTED FROM (GRAVHOLT *ET AL.*, 2017, KLEIN *ET AL.*, 2018))

Age	Age-specific suggestions	Preparation/dose/comments
11 - 12 years	**If no spontaneous development and FSH elevated, start low dose estrogens**	17β-estradiol (E2) Transdermal: 6.25 µg/day[1] E2 via patch Oral micronized E2: 5 µg/kg/day or 0.25 mg/day
11.5 – 13.5 years	**Gradually increase E2 dose at 6-12 months interval over 2 - 3 years[2] to adult dose**	Transdermal E2: 12.5, 25, 37.5, 50, 75, 100µg/day. (*Adult dose: 100-200 µg/day*) Oral E2: 5, 7.5, 10, 15 µg/kg/day. *(Adult dose: 2-4 mg/day)*
13 – 15 years	**Begin cyclic progestogen after 2 years of estrogen or when breakthrough bleeding occurs or use an IUD**	Oral micronized progesterone 100-200 mg/day or dydrogesterone 5-10 mg/day during 12 – 14 days of the month. Levonorgestrel is used in IUD's.

[1] *the lowest dose commercially available E2 transdermal patches deliver 25 or 50 µg/day; it is not established whether various means of dose fractionation (e.g., administering 1/8, 1/6, 1/4 patch overnight or daily or administering whole patches for 7-10 days per month) are equivalent.*

[2] *with concomitant GH therapy in Turner Syndrome, to achieve an optimal adult height the increase in E2 dose might be relatively slow; while in cases of late diagnosis and for those girls in whom growth is not a consideration, E2 may be started at somewhat higher doses and escalated more rapidly.*

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 *(Gravholt et al., 2017, Nordenström et al., 2022)*. A proposed treatment could be a starting dose of 0.5 mg/day oral micronized E2, or 12.5 µg/day transdermal estrogen. The starting dose of E2 should be increased at 3-6 months

interval over 2 years to adult dose. The starting dose and dose escalations are not evidence-based and should be individualised with monitoring of breast development since too rapid breast development may cause stretch marks and asymmetry. Ultrasound of the uterus can be used to guide the timing of addition of progesterone, although the value of this approach has not been evaluated in prospective setup.

Effects of estrogen therapy

Breast and pubic hair

Both oral and transdermal estrogens induce normal breast maturation in hypogonadal girls. Bannink and colleagues showed that with low, increasing doses of oral 17β-estradiol in 56 GH-treated TS girls without spontaneous start of pubertal development starting at mean age 12.7 (± 0.7) years, breast and pubic hair development were similar to that in normal Dutch girls up to Tanner stage B5 and P5 (adult stage), albeit with a 2-year delay (Bannink *et al.*, 2009). Nabhan and colleagues found no significant differences in breast development after 1 year of oral estrogen or transdermal estrogen in 12 GH-treated TS girls (Nabhan *et al.*, 2009).

Uterine size

In the study of Nabhan and colleagues, 12 prepubertal GH-treated girls with TS were randomized to oral conjugated estrogen or transdermal estrogen for 1 year. Uterine growth was significantly greater in the transdermal 17β-estradiol group (Nabhan *et al.*, 2009). In a study of 40 girls with TS receiving 17β-estradiol with a dose escalation regime uterine growth was recorded after 6-12 month, although the size of the uterus was smaller than in age-matched girls (Obara-Moszynska *et al.*, 2021). In another study 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 (Bannink *et al.*, 2009), also reported in other studies also reported in other studies (Paterson *et al.*, 2002, Snajderova *et al.*, 2003). In contrast, 18 GH-treated girls with TS (5 with spontaneous puberty and 13 receiving estrogen therapy from age 14.6 (± 2.2) years), all girls had normal uterine length and volume at final assessment at age 17.1 (± 2.8) years (McDonnell *et al.*, 2003). A study comparing transdermal 17β-estradiol at a dose of 100 microgram versus oral 17β-estradiol at a dose of 2 mg found normal uterine size in both groups comparable to normative data (Lindsay Mart *et al.*, 2023). A study comparing 2 mg versus 4 mg 17β-estradiol orally, showed that more TS females in the high dose group achieved a normal adult uterine size (Cleemann *et al.*, 2011). A retrospective study using oral estradiol valerate using a standard protocol showed that after pubertal induction of TS girls (n=75) showed that in the subset that could be analysed many did not achieve a normal uterine size (Guo *et al.*, 2019).

One retrospective study of a mixed group of females (n=95) with TS, POI, and gonadotropin deficiency, all needing pubertal induction showed lower average uterine volume. Treatment for pubertal induction was mixed, with some being treated with oral contraceptive pill, some with transdermal E2 and some with low dose ethinyl estradiol, and no direct comparison was performed. A large proportion of patient had uterine size below the normal range after pubertal induction (Burt *et al.*, 2019). Another recent retrospective study of a mixed group of females (n=95), including POI and hypogonadotropic hypogonadism of all causes, all receiving a standardized protocol with transdermal estrogen being increased at fixed times with similar dose increases, reported a reduced uterine volume in most of evaluated patients (27 out of 45). Determinants of low uterine volume was previous irradiation (47% had POI due to cancer treatment) and E2 dose at introduction of progestins (Rodari *et al.*, 2023).

Metabolic actions and bone

Metabolic actions of oral versus transdermal estrogen in adolescents have been examined in 4 short-term randomized trials. In one study aiming at comparing the metabolic effects of oral versus transdermal estrogen, it was concluded that the route of delivery does not adversely affect the metabolic

effects of GH in young girls with TS (Mauras *et al.*, 2007). In another study, no significant differences in change of IGF-I, lipid profile, BMI SD score, fat mass, or fat free mass was found between oral and transdermal estradiol (Nabhan *et al.*, 2009), although spine BMD was affected more positively by transdermal treatment. In a third study comparing oral and transdermal 17β-estradiol, with E2 concentrations titrated to normal range in both groups, there were no difference after 12 months treatment in body composition, BMD, lipid oxidation, resting energy expenditure and metabolic parameters (Torres-Santiago *et al.*, 2013).

A five-year study with 20 TS females around 15 years at start of treatment, using 2 and 4 mg of 17β-estradiol given orally found similar BMD accrual, but more favourable lean body increments during higher dose treatment, which led to normalization of circulating estradiol levels (Cleemann *et al.*, 2017).

Cardiovascular actions

Cardiovascular risk, both due to congenital and acquired disease, is increased in TS, as well as other forms of POI and HRT is thought to decrease this risk. One epidemiological study show that treated compared with untreated TS have a lower risk of being prescribed antihypertensives, antidiabetics and thyroid medications, and stroke was also less frequent, results pointing towards a protective effect of HRT (Viuff *et al.*, 2020). A five-year prospective study with 20 TS females around 15 years at start of treatment, using 2 and 4 mg of 17β-estradiol given orally found similar development in blood pressure, irrespective of the 17β-estradiol dosing (Brun *et al.*, 2019).

Cognitive function

Cognitive challenges are frequent among females with TS, and can encompass domains such as attention, working memory, executive function/cognitive control, perceptual-motor and visual-spatial skills, visual memory, language, motor function, social cognition, and academic achievement. Patients with TS receiving estradiol for pubertal induction seemed to have exhibit the expected maturational changes in brain development studied by MRI (Li *et al.*, 2019, O'Donoghue *et al.*, 2020). Whether such cognitive challenges apply to other groups of females needing pubertal induction is unknown. Likewise, it is unknown if age-appropriate 17β-estradiol treatment affects maturational brain development in a similar manner.

Monitoring

It is important that pubertal induction mimics physiology as closely as possible to support linear growth and gradually induce puberty at an age and tempo within the normal range for peers. This is important for psychosocial wellbeing, bone health, uterine growth, future pregnancy prospects and possible neurocognitive benefits.

We suggest monitoring biochemically with measurement of estradiol, FSH and LH at regular intervals during pubertal induction, for example every 3-6 month. At some point it will make sense to measure bone density with DXA and ultrasound scan of the uterus can be used to guide the timing of addition of progesterone.

Recommendations

Puberty should be induced or progressed with 17β-estradiol, starting with low dose at the age of 11 with a gradual increase over 2 to 3 years.	⊕⊕◯◯	**STRONG**

In cases of late diagnosis and for those girls in whom growth is not a concern, a modified regimen of estradiol can be considered.	⊕◯◯◯	**STRONG**

Evidence for the optimum mode of administration (oral or transdermal) is inconclusive. Transdermal estradiol may result in more physiological estrogen levels and may therefore be preferred.	⊕◯◯◯	CONDITIONAL

The oral contraceptive pill should not be used for puberty induction.	⊕◯◯◯	**STRONG**

The guideline group recommends starting cyclical progestogens after about 2 years of estrogen therapy or when breakthrough bleeding occurs.	**GPP**

Justification

Estrogen therapy should be started from the age of 11 years onwards when there has been no spontaneous start to puberty or progression of breast 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 (Ankarberg-Lindgren *et al.*, 2019, Donaldson *et al.*, 2019).

It is suggested to use unopposed estradiol for at least 18-24 months before adding a progestogen to allow for regular menstrual periods (Gravholt *et al.*, 2017, Klein *et al.*, 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 (Gravholt *et al.*, 2017, Klein *et al.*, 2018).

With increasing doses of oral and transdermal 17β-estradiol normal breast and pubic hair development can be achieved (Gravholt *et al.*, 2017, Klein *et al.*, 2018). With higher starting doses of E2 and/or more rapid dose escalation, breast development should be monitored for stretch marks and asymmetry.

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 primary ovarian insufficiency. Suffice to say, more research is needed in other causes of POI.

Research recommendation.

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, 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 develop in conditions like Turner syndrome remains an enigma and should also be investigated.

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Annex 1 Guideline group.

This guideline was developed by the ESHRE POI Guideline Development Group (GDG).

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Annex 2 Abbreviations.

21OH-Ab	21-hydroxylase antibodies	HSCT	Hematopoietic stem cell transplantation
AFC	low antral follicle count	HSDD	hypoactive sexual desire disorder
AMH	Anti-Müllerian hormone	HT	Hormone therapy
AOA	anti-ovarian autoantibodies	Hx	Hysterectomy
AOR	adjusted odds ratio	LDL-C	low-density lipoprotein cholesterol
APS-1	autoimmune polyendocrine syndrome	LET	local estrogen therapy
ART	Assisted reproduction technologies	LVEJ	left ventricular ejaculatory function
ASI	aortic size index	MAC	Myeloablative conditioning regimen
ASM	appendicular skeletal muscle mass	MAR	Medically assisted reproduction
BMD	bone mineral density	MCI	mild cognitive impairment
BMI	body mass index	MD	mean difference
BP	Blood pressure	MPA	medroxyprogesterone acetate
BPA	bisphenol A	MRI	magnetic resonance imaging
BSO	bilateral salpingo-oophorectomy	NGS	Next generation sequencing
BTM	bone turnover markers	OR	Odds ratio
CAD	coronary artery disease	PCBs	polychlorinated biphenyls
CBT	cognitive behavioural therapy	PCR	Polymerase Chain Reaction
CEE	Conjugated equine estrogens	PFASs	perfluoroalkyl and polyfluoroalkyl substances
COC	combined oral contraceptive pil	PFS	progression-free survival
CVD	cardiovascular disease	POI	Premature ovarian Insufficiency
DDT	dichlorodiphenyltrichloroethane	POPs	Persistent organic pollutants
DHEA	Dehydroepiandrosterone	PR	progesterone receptor
DOR	diminished ovarian reserve	QoL	quality of life
DXA	Dual-Energy X-ray Absorptiometry	RCT	RCT
E2	estradiol	RIA	Radio-Ligand Binding Assay
EDC	endocrine disrupting chemicals	RR	Relative risk
EE	estrogen ethinylestradiol	RRBSO	Risk reducing BSO
ELISA	Enzyme-linked immunosorbent assay	RT	radiotherapy
EMBx	endomyocardial biopsy	SCA	Steroid-cell autoantibodies
ER	estrogen receptor	SERMs	Selective estrogen receptor modulators
ERT	estrogen replacement therapy	SHBG	sex hormone binding globulin
FMR1	Fragile X mental retardation 1 gene	SLE	systemic lupus erythematosus
FRAX	Fragile X premutation	SMD	Standardised mean difference
FSFI	Female Sexual Function Index	SNRIs	serotonin-norepinephrine reuptake inhibitor
FSH	Follicle stimulating hormone	SOC	serous ovarian cancer
FSIAD	female sexual interest and arousal disorder	SSRIs	selective serotonin reuptake inhibitors
FTAS	Fragile X-associated tremor/ataxia syndrome	SUI	stress urinary incontinence (SUI)
FXPOI	Fragile X-associated POI	TC	total cholesterol
FXS	Fragile X syndrome	TPO Abs	Thyroid peroxidase autoantibodies
FXTAS	Fragile X-associated tremor/ataxia syndrome	TS	Turner Syndrome
GH	growth hormone	TXS	Tripple X syndrome
GSM	genitourinary syndrome of menopause	UAM	Usual age of menopause
HCP	health care providers	VHI	vaginal health index
HDL-C	high-density lipoprotein cholesterol	VVA	vulvovaginal atrophy
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance	WES	whole exome sequencing
HPV	human papillomavirus	WGS	whole genome sequencing
HR	Hazard ratio	WHO	World Health Organization
HRQoL	health-related quality of life	WMD	weighted-mean difference
HRT	hormone replacement therapy		

Annex 3 List of research recommendations.

Risk factor, diagnosis and causation.

1. *Further research is required to (i) identify and clarify risk factors for POI, in addition to those related to early menopause, especially the role of socio-economic factors, lifestyle and environmental chemicals; and (ii) identify and quantify strategies that may mitigate modifiable risk factors.*
2. *Further research is required to establish the optimal FSH criteria for the diagnosis of POI or a sensitive and specific alternative biomarker that is readily available.*
3. *Ongoing research both in animal models and humans is required to identify additional genes involved in POI and to allow uncovering of molecular defects in non-coding regions of known genes, copy number variations and structural variations.*
4. *Exploration of how genetic variants combine with environmental factors to determine the clinical phenotype is also needed. This will markedly enhance the positivity of genetic testing, availability of genetic testing and development of novel management strategies.*
5. *Improvements in genetic sequencing techniques and interpretive approaches may provide a more precise determination of the mechanisms underlying ovarian dysfunction, facilitate screening, diagnosis, and cost-effectiveness.*
6. *Research into methods for reliable prediction of POI and monitoring of ovarian function in relatives of women with non-iatrogenic POI is needed. Further research into the outcomes of fertility preservation in the specific group of women with a family history of POI is indicated.*

Management

7. *Further research is required to (i) clarify fracture risk associated with POI and the effect of HT on this outcome; (ii) determine the best strategies for monitoring of bone health including screening interval, role of bone turnover markers and newer imaging modalities; (iii) investigate the effect of exercise on muscle parameters and bone density in women with POI; (iv) clarify the role bone specific agents in managing POI associated osteoporosis; (v) clarify the changes in muscle mass and function associated with POI; (vi) identify strategies for assessment and monitoring of muscle health in this population including defining sarcopenia; and (vii) examine the role of HT and other strategies to maintain muscle health.*
8. *There is a need for long-term randomized prospective studies to determine the optimal routes, doses, and regimens of HT. In the absence of long-term randomized prospective data, treatment should be individualized and carefully monitored.*
9. *QoL research is needed involving prospective studies with the use of comprehensive scale validated in women with spontaneous and iatrogenic POI.*
10. *The role of medical and psychological interventions in improving QoL should be implemented with the aid of adequate instruments developed in collaboration with women with POI of different aetiologies.*
11. *Studies conducted in a multidimensional perspective are needed to assess sexual changes in women with POI and the entity of distress.*
12. *A process of care specifically developed for women with POI presenting sexual symptoms is warranted.*
13. *A better understanding on the effects of different type and dose of systemic estrogens alone or in combination with specific progestogens on sexuality of POI is warranted.*
14. *Studies should evaluate the safety of testosterone when applied for a longer period (more than 6 months) to improve sexual function in POI.*

15. *More research is needed to understand the difference between iatrogenic and non-iatrogenic POI in terms of testosterone levels and testosterone treatments.*
16. *More research conducted specifically in women with POI is needed on hormonal approaches for genitourinary symptoms.*
17. *Studies should explore the efficacy and safety of laser therapy and other non-hormonal approaches to relief genitourinary symptoms in women with POI, especially in those with contraindications to vaginal estrogen.*
18. *Research is needed to further clarify the pathogenetic mechanisms mediating the effects of POI, both non-iatrogenic and iatrogenic, on adverse neurological outcomes including cognitive decline and dementia. In addition, further research is needed to confirm the beneficial effects of ERT in women who underwent POI, both with and without menopausal symptoms.*
19. *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.*
20. *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, 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 develop in conditions like Turner syndrome remains an enigma and should also be investigated.*

Annex 4 Methodology.

Guideline development

European Society of Human Reproduction and Embryology (ESHRE) guidelines are developed based on the Manual for ESHRE guideline development (Vermeulen *et al.*, 2020), which can be consulted at the ESHRE website (www.eshre.eu/guidelines). The principal aim of this manual is to provide stepwise advice on ESHRE guideline development for members of ESHRE guideline development groups. The manual describes a 12-step procedure for writing clinical management guidelines by the guideline development group, supported by the ESHRE methodological expert (see Figure 12 Guideline development: 12-step procedure).

FIGURE 15 GUIDELINE DEVELOPMENT: 12-STEP PROCEDURE

The current guideline was developed with support of ESHRE, CREWhiRL, ASRM and IMS. The associations covered expenses associated with the guideline meetings (travel, hotel, and catering expenses) associated with the literature searches (library costs, costs associated with the retrieval of papers) and with the implementation of the guideline (printing, publication costs). Except for reimbursement of their travel expenses, guideline group members did not receive any payment for their participation in the guideline development process.

Once the ESHRE Executive Committee approved the guideline application and the guideline's scope, deliberations took place regarding the composition of the guideline group. Professionals with comprehensive expertise and diverse perspectives from ESHRE, CREWhiRL, ASRM and IMS were included in the guideline group, as well as patient representative. The ultimate goal was to achieve a well-rounded composition that encompassed a balanced representation of expertise, gender, and geographical location.

Key Questions

A meeting of the guideline development group was organised to discuss the key questions and redefine them through the PICO process (patients – interventions – comparison – outcome). The key questions drafted for the 2015/2016 guideline were re-used but modified according to progressive understanding and recent developments with regards to interventions for POI.

The current guideline is structured around 38 key questions.

Evidence search and synthesis.

Based on the defined key words for each of the key questions, literature searches were performed by the methodological expert (N. Vermeulen). Key words were sorted to importance and used for searches

in PUBMED/MEDLINE and the Cochrane library. We searched the databases from inception up to January 30th, 2024.

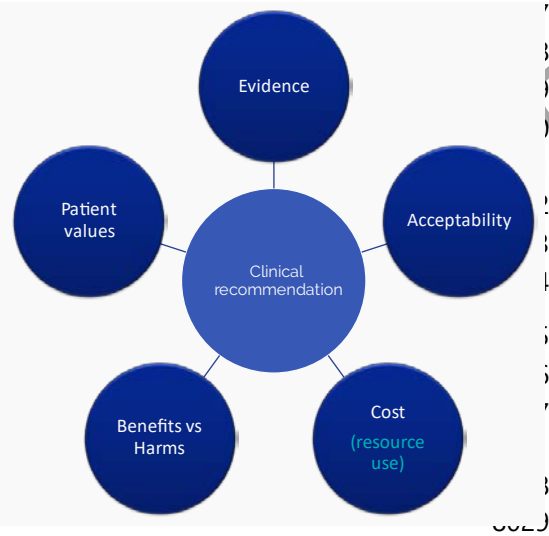
Literature searches were performed as an iterative process. In a first step, systematic reviews and meta-analyses were collected. If no results were found, the search was extended to randomised controlled trials, and further to cohort studies and case reports, following the hierarchy of the levels of evidence. References were selected or excluded by the methodological expert and expert guideline group member based on title and abstract and knowledge of the existing literature. If necessary, additional searches were performed to get the final list of papers. The quality of the selected papers was assessed by means of the quality assessment checklist, defined in the ESHRE guideline manual. Next, the evidence was collected and summarised in an evidence table. The quality assessment and completion of evidence tables were performed by the expert guideline group members.

Summary of findings tables are usually prepared according to the GRADE approach for all interventions with at least two studies (RCTs) per outcome. For the interventions in the current guideline, such evidence is not available, and hence no summary of findings tables were produced.

Recommendations

Guideline group meetings were organised to discuss the draft recommendations and the supporting evidence and to reach consensus on the final formulation of the recommendations.

For each recommendation, it is mentioned whether it is strong or weak and what the quality of the supporting evidence was.



In the justification section, more data are provided on the interpretation of the supporting evidence and how other factors (i.e., balance between desirable and undesirable effects, certainty of the evidence of effects, certainty in how people value the outcome, and acceptability) were considered. Costs and resource impact were only discussed where relevant.

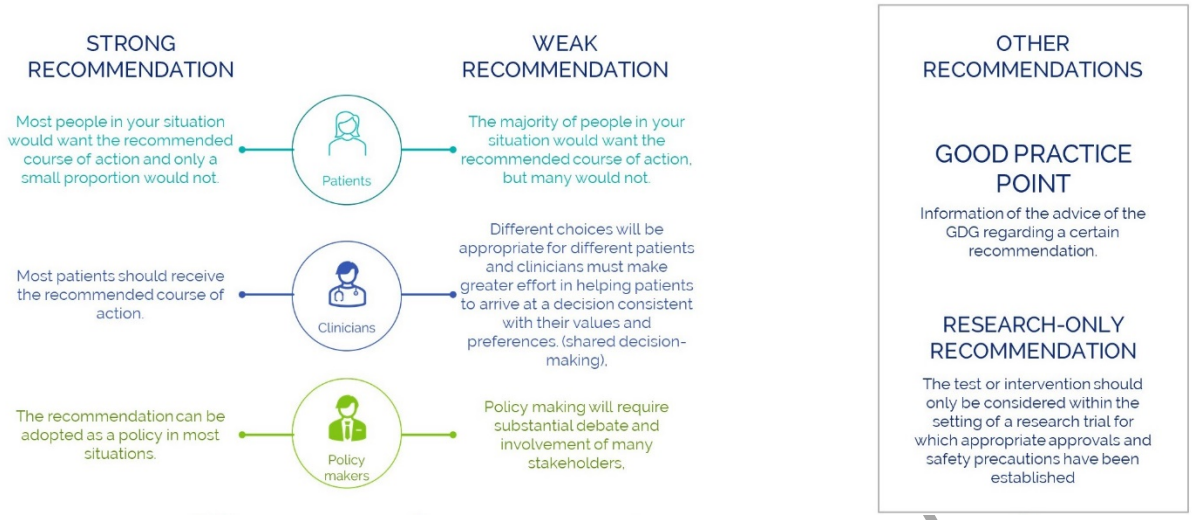
In a final step, all evidence and recommendations were combined in the ESHRE guideline: "Premature Ovarian Insufficiency".

Implications of recommendations

We labelled the recommendations as either ''strong'' or ''weak" according to the GRADE approach, with appropriate wording for each option. Suggested interpretation of strong and weak recommendations by patients, clinicians and health care policy makers is described in Figure 3.

Good practice points (GPPs) are used to emphasize the importance of patient participation in decision making about specific procedure, provide advice on the management of specific surgical procedures for which there is an evidence-based recommendation, or advise caution where there is perceived risk of harm but no available direct evidence of such harms.

8040 **FIGURE 16 IMPLICATIONS OF THE STRENGTH OF THE RECOMMENDATIONS**



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8042 ## Review of the Guideline draft

8043 After finalisation of the guideline draft, the review process was initiated. The draft guideline was
8044 published on the ESHRE website, accompanied by the reviewers' comments form and a short
8045 explanation of the review process. The guideline was open for review between 17 April and 27 May
8046 2024.

8047 ## Guideline Implementation strategy

8048 The standard dissemination procedure for all ESHRE guidelines comprises publishing and
8049 announcement.

8050 Each guideline is published on the ESHRE Website. A summary of the recommendations will be
8051 published in Human Reproduction Open, and simultaneously in Fertility & Sterility and Climateric.
8052 Translation and resource development will be led by CRE WHiRL and modelled on the example of the
8053 international PCOS guideline (https://www.monash.edu/medicine/mchri/pcos/guideline).

8054 ## Schedule for updating the guideline.

8055 The current guideline will be considered for revision in 2028 (four years after publication). An
8056 intermediate search for new evidence will be performed two years after publication, which will inform
8057 the guideline group of the necessity of an update.

8058 Every care is taken to ensure that this publication is correct in every detail at the time of publication.
8059 However, in the event of errors or omissions, corrections will be published in the web version of this
8060 document, which is the definitive version at all times. This version can be found at
8061 www.eshre.eu/guidelines.

8062 For more details on the methodology of ESHRE guidelines, visit www.eshre.eu/guidelines