



# Management of women with premature ovarian insufficiency

Guideline of the European Society of Human  
Reproduction and Embryology

POI Guideline Development Group

December 2015

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# INTRODUCTION TO THE GUIDELINE

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## Previous guidelines

At the time of the initiation of this guideline, Premature Ovarian Insufficiency [POI] was not addressed by existing guidelines. Comprehensive literature searching did not retrieve any guidelines specifically on the management of women with POI. Premature ovarian insufficiency has been included in several guidelines on infertility, but these mention POI only briefly, with the focus on infertility ([National Institute for Health and Care Excellence, 2013](#)) or menopause ([de Villiers, et al., 2013](#)). Guidance on management of Turner Syndrome was available but this concentrated on the other medical aspects of the syndrome and did not comprehensively address POI ([Bondy and Turner Syndrome Study Group, 2007](#)).

## Guideline development

The Reproductive Endocrinology Special Interest Group of ESHRE initiated a guideline on POI. Membership of the Guideline development group was drawn from the Special Interest Group and the wider membership of ESHRE. Additional group members were recruited from outside ESHRE to contribute specialist expertise in certain topic areas (e.g. cardiology, neurology). A research specialist supported the guideline development. The members of the guideline development group are listed in Appendix 3.

The scope of the guideline was determined by consensus. Guideline development followed a well-documented methodology, universal to ESHRE guidelines. The detailed methodology for this guideline is described in [Appendix 5](#).

## Guideline scope

This guideline offers best practice advice on the care of women with premature ovarian insufficiency, 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 40. The first chapters of this guideline will elaborate on the nomenclature and definition of premature ovarian insufficiency.

Furthermore, this clinical guideline provides recommendations on the initial assessment and management of women with premature ovarian insufficiency. 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, bone 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.

## Target users of the guideline

The guideline covers the care provided by secondary and tertiary healthcare professionals who have direct contact with, and make decisions concerning the care of, women with premature ovarian insufficiency. 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 healthcare professionals of other disciplines (primary healthcare providers, endocrinologists, oncologists,

geneticists, paediatricians, internists). During the review phase and in development of tools for implementation, specific attention will be given to these healthcare professionals.

This guideline is of relevance to European healthcare providers and women with premature ovarian insufficiency. For the benefit of patient education and shared-decision making, a patient version of this guideline will be developed.

## References

Bondy CA, Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007;**92**: 10-25.

de Villiers TJ, Pines A, Panay N, Gambacciani M, Archer DF, Baber RJ, Davis SR, Gompel AA, Henderson VW, Langer R, Lobo RA, Plu-Bureau G, Sturdee DW, International Menopause S. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2013;**16**: 316-337.

National Institute for Health and Care Excellence. Fertility: assessment and treatment for people with fertility problems (update). (Clinical guideline 156.). 2013 from [www.nice.org.uk/CG156](http://www.nice.org.uk/CG156).

# SUMMARY

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## Interpretation on the grades of recommendations (*Vermeulen, et al., 2014*)

Grades of recommendations	Supporting evidence
<b>A</b>	Meta-analysis, systematic review or multiple randomized controlled trials (RCTs) (high quality)
<b>B</b>	Meta-analysis, systematic review or multiple RCTs (moderate quality) Single RCT, large non-randomized trial, case-control or cohort studies (high quality)
<b>C</b>	Single RCT, large non-randomized trial, case-control or cohort studies (moderate quality)
<b>D</b>	Non-analytical studies, case reports or case series (high or moderate quality)
<b>GPP</b>	Expert opinion

The grades of the recommendations is only based on the strength of the supporting evidence. In formulating strong or weak recommendations, the guideline group took the strength of the supporting evidence into account, but weight it against the benefits and harms, and the preferences of clinicians and patients.

### Reference

Vermeulen N, D'Angelo A, de Sutter P, Nelen WLDM. Manual for ESHRE Guideline Development 2014; **Version 2.0**, from [www.eshre.eu](http://www.eshre.eu).

## List of all recommendations

# Introduction to POI (Part A)

### What should this condition be called?

The term “premature ovarian insufficiency” should be used to describe this condition in research and clinical practice.

GPP

### How should POI be defined?

Premature ovarian insufficiency is a clinical syndrome defined by loss of ovarian activity before the age of 40.

POI is characterised by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotropins and low estradiol.

### What is the prevalence of POI in the general population?

The prevalence of POI is approximately 1%. Population characteristics such as ethnicity may affect the prevalence.

In view of the long-term health consequences of POI, efforts should be made to reduce the incidence of POI. Modifiable factors may include:

- gynaecological surgical practice
- lifestyle – smoking
- modified treatment regimens for malignant and chronic diseases.



## Diagnosis of POI (PART B)

### What are the symptoms of Premature Ovarian Insufficiency?

Clinicians should enquire about symptoms of estrogen deficiency in women presenting with oligomenorrhea or amenorrhea.	GPP
POI needs to be excluded in women with amenorrhea/oligomenorrhea or estrogen-deficiency symptoms below the age of 40 years.	GPP

### What investigations should be performed for diagnosis of premature ovarian insufficiency?

The diagnosis Premature Ovarian Insufficiency is based on the presence of menstrual disturbance and biochemical confirmation.	
Although proper diagnostic accuracy in POI is lacking, the GDG recommends the following diagnostic criteria: <ul style="list-style-type: none"> <li>oligo/amenorrhea for at least 4 months, and</li> <li>an elevated FSH level &gt; 25 IU/l on two occasions &gt; 4 weeks apart.</li> </ul>	GPP

### What are the known causes of POI and how should they be investigated?

Chromosomal analysis should be performed in all women with non-iatrogenic Premature Ovarian Insufficiency.	C
Gonadectomy should be recommended for all women with detectable Y chromosomal material.	C
Fragile-X premutation testing is indicated in POI women.	B
The implications of the fragile-X premutation should be discussed before the test is performed.	GPP
Autosomal genetic testing is not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).	GPP
Screening for 21OH-Ab (or alternatively adrenocortical antibodies (ACA)) should be considered in women with POI of unknown cause or if an immune disorder is suspected. Refer POI patients with a positive 21OH-Ab/ACA test to an endocrinologist for testing of adrenal function and to rule out Addison's disease.	C
Screening for thyroid (TPO-Ab) antibodies should be performed in women with POI of unknown cause or if an immune disorder is suspected. In patients with a positive TPO-Ab test, thyroid stimulating hormone (TSH) should be measured every year.	C

There is insufficient evidence to recommend routinely screening POI women for diabetes.	D
There is no indication for infection screening in women with POI.	D
The possibility of POI being a consequence of a medical or surgical intervention should be discussed with women as part of the consenting process for that treatment.	GPP
Although no causal relation has been proved for cigarette smoking and POI, there is a relation to early menopause. Therefore, women who are prone to POI should be advised to stop smoking.	GPP
In a significant number of women with POI, the cause is not identified and these women are described as having unexplained or idiopathic POI.	

How often should tests for autoantibodies be repeated? What do you do in case of a positive test result for autoantibodies?

If 21OH-Ab/ACA and TPO-Ab are negative in women with POI, there is no indication for re-testing later in life, unless signs or symptoms of these endocrine diseases develop.	C
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Test	Implications	
	Positive test	Negative test
<b>Genetic/Chromosomal</b>		
<b>Karyotyping</b> (for diagnosis of Turner syndrome)	Refer to endocrinologist, cardiologist and geneticist	A second analysis of the karyotype in epithelial cells (in case of high clinical suspicion)
<b>Test for Y-chromosomal material</b>	Discuss gonadectomy with the patient	
<b>Fra-X</b>	Refer to geneticist	
<b>Autosomal genetic testing<sup>1</sup></b>		
<b>Antibodies<sup>2</sup></b>		
<b>ACA/21OH antibodies</b>	Refer to endocrinologist	Re-test in case of clinical signs or symptoms
<b>TPO-Ab</b>	Test TSH every year	

<sup>1</sup> not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).

<sup>2</sup> POI of unknown cause or if an immune disorder is suspected.

## What are the implications for relatives of women with POI?

Relatives of women with the fragile-X premutation should be offered genetic counselling and testing.	B
Relatives of women with non-iatrogenic premature ovarian insufficiency who are concerned about their risk for developing POI should be informed that: <ul style="list-style-type: none"><li>• currently there is no proven predictive test to identify women that will develop POI, unless a mutation known to be related to POI was detected</li><li>• there are no established POI preventing measures</li><li>• fertility preservation appears as a promising option, although studies are lacking, and</li><li>• their potential risk of earlier menopause should be taken into account when planning a family.</li></ul>	GPP

## Sequelae of POI (PART C)

### LIFE EXPECTANCY

What are the consequences of POI for life expectancy?

Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease.	C
Women with POI should be advised on how to reduce cardiovascular risk factors by not smoking, taking regular exercise, and maintaining a healthy weight.	GPP

### FERTILITY AND PREGNANCY

What are the consequences of POI for fertility?

Women with POI should be informed that there is a small chance of spontaneous pregnancy.	GPP
Women with POI should be advised to use contraception if they wish to avoid pregnancy.	GPP

What fertility interventions are effective?

Inform women with POI that there are no interventions that have been reliably shown to increase ovarian activity and natural conception rates.	A
Oocyte donation is an established option for fertility in women with POI.	C
Inform women considering oocyte donation from sisters that this carries a higher risk of cycle cancellation.	C
In women with established POI, the opportunity for fertility preservation is missed.	GPP

What are the obstetric risks associated with POI?

Women should be reassured that spontaneous pregnancies after idiopathic POI or most forms of chemotherapy do not show any higher obstetric or neonatal risk than in the general population.	B
Oocyte donation pregnancies are high risk and should be managed in an appropriate obstetric unit. Women and their partners should be encouraged to disclose the origin of their pregnancy with their obstetric team.	C
Antenatal aneuploidy screening should be based on the age of the oocyte donor.	C

Pregnancies in women who have received radiation to the uterus are at high risk of obstetric complications and should be managed in an appropriate obstetric unit.	C
Pregnancies in women with Turner Syndrome are at very high risk of obstetric and non-obstetric complications and should be managed in an appropriate obstetric unit with cardiologist involvement.	D
A cardiologist should be involved in care of pregnant women who have received anthracyclines and/or cardiac irradiation.	D

**How should fitness for pregnancy be assessed in women with 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 karyotype.	C
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.	D
Women with Turner Syndrome should be assessed by a cardiologist with a specialist interest in adult congenital heart disease and should have a general medical and endocrine examination.	GPP
Women with POI should have their blood pressure, renal function, and thyroid function assessed prior to pregnancy.	C
Pregnancy in some women can be of such high risk that clinicians may consider oocyte donation to be life threatening and therefore inappropriate.	GPP

## BONE HEALTH

### What are the consequences of POI for bone health?

POI is associated with reduced bone mineral density (BMD).	B
Reduced BMD is very likely to indicate that POI is associated with an increased risk of fracture later in life, although this has not been adequately demonstrated.	GPP

### What are the treatment options for bone protection and improvement?

Women should maintain a healthy lifestyle, involving weight-bearing exercise, avoidance of smoking, and maintenance of normal body weight to optimize bone health.	GPP
A balanced diet will contain the recommended intake of calcium and vitamin D. Dietary supplementation may be required in women with inadequate vitamin D status and/or calcium intake, and may be of value in women with low BMD.	C
Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.	C
The combined oral contraceptive pill may be appropriate for some women but effects on BMD are less favourable.	C
Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies to women desiring pregnancy.	C

### How should bone health be monitored in women with POI?

It is important to consider bone health at diagnosis in POI, and during ongoing care.	GPP
Measurement of BMD at initial diagnosis of POI should be considered for all women, but especially when there are additional risk factors.	C
If BMD is normal and adequate systemic estrogen replacement is commenced, the value of repeated DEXA scan is low.	GPP
If a diagnosis of osteoporosis is made and estrogen replacement or other therapy initiated, 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.	GPP

## CARDIOVASCULAR HEALTH

What are the consequences of POI for the cardiovascular system?

Women with POI are at increased risk of cardiovascular disease and should be advised of risk factors that they can modify through behavioural change (e.g. stopping smoking, taking regular weight-bearing exercise, healthy weight).	B
All women diagnosed with Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease.	C

Is estrogen replacement cardio-protective?

Despite lack of longitudinal outcome data, hormone replacement therapy with early initiation is strongly recommended in women with POI to control future risk of cardiovascular disease; it should be continued at least until the average age of natural menopause.	C
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Should cardiovascular risk factors be monitored?

Cardiovascular risk should be assessed in women diagnosed with POI. At least blood pressure, weight and smoking status should be monitored annually with other risk factors being assessed if indicated.	GPP
In women with Turner Syndrome, cardiovascular risk factors should be assessed at diagnosis and annually monitored (at least blood pressure, smoking, weight, lipid profile, fasting plasma glucose, HbA1c).	C

## WELLBEING AND QUALITY OF LIFE

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

A diagnosis of POI has a significant negative impact on psychological wellbeing and quality of life.	D
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What are the Management options for reduced quality of life associated with POI?

Psychological and lifestyle interventions should be accessible to women with POI.	B
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## SEXUAL AND GENITO-URINARY FUNCTION

What are the consequences of POI for sexuality?

Routinely inquire about sexual wellbeing and sexual function in women with POI.	GPP
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What are the management options for the effects of POI on sexuality?

Adequate estrogen replacement is regarded as a starting point for normalising sexual function. Local estrogen may be required to treat dyspareunia.	C
Women with POI should receive adequate counselling about the possibility of using testosterone supplementation so that they can make an informed choice, in the knowledge that long-term efficacy and safety are unknown.	B

What treatments are available for genito-urinary symptoms in POI?

Local estrogens are effective in treatment of genito-urinary symptoms.	A
Clinicians should be aware that despite seemingly adequate systemic hormone replacement therapy (HRT), women with POI may experience genito-urinary symptoms. Local estrogens may be given in addition to systemic HRT.	D
Lubricants are useful for treatment of vaginal discomfort and dyspareunia for women not using HRT.	C

## NEUROLOGICAL HEALTH

What are the consequences of POI on neurological function?

The possible detrimental effect on cognition should be discussed when planning hysterectomy and/or oophorectomy under the age of 50 years, especially for prophylactic reasons.	D
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What are the management options for the effect of POI on neurological function?

Estrogen replacement to reduce the possible risk of cognitive impairment should be considered in women with POI at least until the average age of natural menopause.	C
Women with POI should be advised to take lifestyle measures (e.g. exercise, cessation of smoking, maintaining a healthy weight) to reduce possible risks for cognitive impairment.	GPP



## HORMONE REPLACEMENT THERAPY (HRT)

Hormone replacement therapy is indicated for the treatment of symptoms of low estrogen in women with POI.	C
Women should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection.	C

### What are the risks of hormone replacement therapy?

Women with POI should be informed that HRT has not been found to increase the risk of breast cancer before the age of natural menopause.	D
Progestogen should be given in combination with estrogen therapy to protect the endometrium in women with an intact uterus.	B

### What are the options for hormone replacement therapy?

17 $\beta$ -estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement.	C
Women should be informed that whilst there may be advantages to micronized natural progesterone, the strongest evidence of endometrial protection is for oral cyclical combined treatment.	GPP
Patient preference for route and method of administration of each component of HRT must be considered when prescribing, as should contraceptive needs.	GPP

### Monitoring HRT

Once established on therapy, women with POI using HRT should have a clinical review annually, paying particular attention to compliance.	GPP
No routine monitoring tests are required but may be prompted by specific symptoms or concerns.	GPP

### Treatment with androgens

Women should be informed that androgen treatment is only supported by limited data, and that long-term health effects are not clear yet.	C
If androgen therapy is commenced, treatment effect should be evaluated after 3-6 months and should possibly be limited to 24 months.	GPP

## HRT in women with POI and special issues

### Turner Syndrome

Girls and women with POI due to Turner Syndrome should be offered HRT throughout the normal reproductive lifespan.	C
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### BRCA gene mutation or after breast cancer

HRT is generally contra-indicated in breast cancer survivors.	B
HRT is a treatment option for women carrying BRCA1/2 mutations but without personal history of breast cancer after prophylactic bilateral salpingo-oophorectomy (BSO).	C

### Endometriosis

For women with endometriosis who required oophorectomy, combined estrogen/progestogen therapy can be effective for the treatment of vasomotor symptoms and may reduce the risk of disease reactivation.	C
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### Migraine

Migraine should not be seen as a contraindication to HRT use by women with POI.	GPP
Consideration should be given to changing dose, route of administration or regimen if migraine worsens during HRT.	GPP
Transdermal delivery may be the lowest-risk route of administration of estrogen for migraine-sufferers with aura.	D

### Hypertension

Hypertension should not be considered a contraindication to HRT use by women with POI.	GPP
In hypertensive women with POI, transdermal estradiol is the preferred method of delivery.	C

### History of prior venous thromboembolism (VTE)

Women with POI and a history of prior venous thromboembolism (VTE) or thrombophilic disorder should be referred to a haematologist prior to commencing HRT.	GPP
Transdermal estradiol is the preferred route of delivery for women with POI at increased risk of VTE.	B

Obesity

Transdermal estradiol is the preferred method of delivery for women with POI requiring HRT who are obese or overweight.	C
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Fibroids

Fibroids are not a contraindication to HRT use by women with POI.	B
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**COMPLEMENTARY TREATMENTS**

**What complementary treatments are available in POI?**

Women with POI should be advised of risk factors that they can modify through behavioural change (e.g. stopping smoking, taking regular weight-bearing exercise, healthy weight).	GPP
Women should be informed that for most alternative and complementary treatments evidence on efficacy is limited and data on safety are lacking.	B

## PUBERTY INDUCTION

### How should puberty be induced?

Puberty should be induced or progressed with 17 $\beta$ -estradiol, starting with low dose at the age of 12 with a gradual increase over 2 to 3 years.	C
In cases of late diagnosis and for those girls in whom growth is not a concern, a modified regimen of estradiol can be considered.	D
Evidence for the optimum mode of administration (oral or transdermal) is inconclusive. Transdermal estradiol results in more physiological estrogen levels and is therefore preferred.	B
The oral contraceptive pill is contra-indicated for puberty induction.	D
Begin cyclical progestogens after at least 2 years of estrogen or when breakthrough bleeding occurs.	C

# PART A: Introduction to POI

# 1. PREMATURE OVARIAN INSUFFICIENCY (POI)

## Introduction

Primary ovarian insufficiency was first described in 1942 and has, since then, been described with different names and definitions.

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.

## 1.1 Nomenclature

### **KEY QUESTION: WHAT SHOULD THIS CONDITION BE CALLED?**

#### Clinical evidence

The condition addressed in this guideline was first described as Primary Ovarian Insufficiency by Fuller Albright in 1942 (Albright, *et al.*, 1942). Subsequently several different terms have been used, with variation between specialities (e.g. gynaecology, endocrinology) and between countries (e.g. USA, UK). A search of PUBMED, updated from Cooper and colleagues, shows the different terms used to define this condition and their prevalence in PUBMED since 1949 and in the last 5 years (Cooper, *et al.*, 2011).

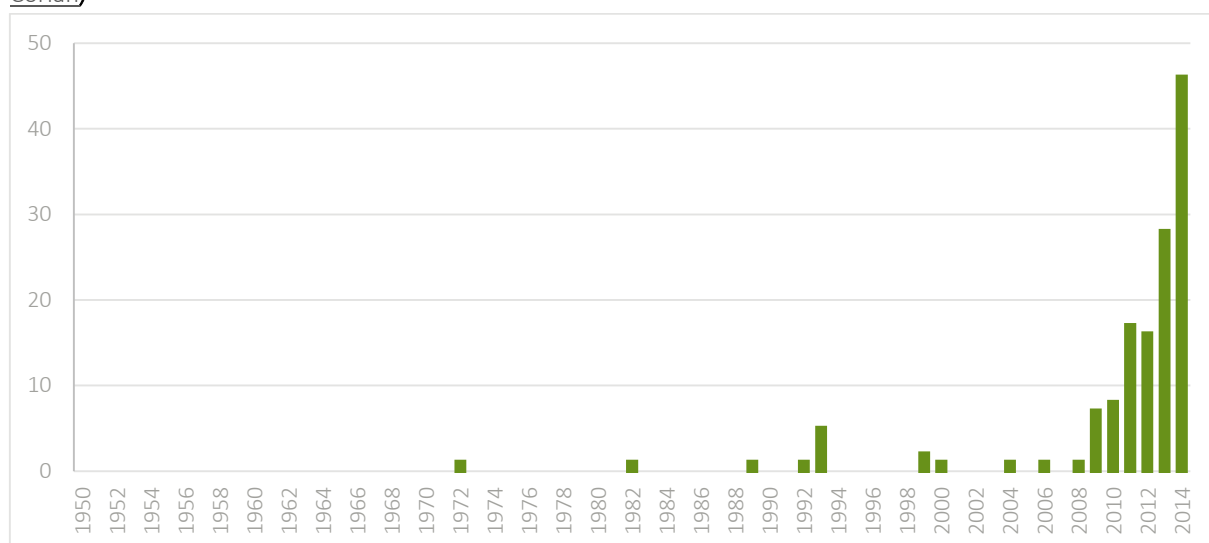
**Table 1.1** Number of papers retrieved in PUBMED in total and in the last 5 years, for the different terms used for POI.

	Number of papers retrieved in PUBMED	Number of papers retrieved in PUBMED, published in the last 5 years
Primary Ovarian Insufficiency	1581	663
Premature Ovarian Failure	1601	573
Gonadal dysgenesis	3057	408
Premature menopause	1011	228
Early menopause	620	170
Hypergonadotropic hypogonadism	346	86
<b>Premature Ovarian Insufficiency</b>	<b>79</b>	<b>70</b>
Ovarian dysgenesis	204	26
Primary ovarian failure	145	20
Hypergonadotropic amenorrhea	52	9
Climacterium praecox	5	0
Menopause praecox	1	0

An objective of the guideline development group was to reach consensus on the use of standard terminology. This would clarify information given to women, improve communication between health professionals, greatly facilitate data collection and audit, and aid future research.

The issue of terminology was discussed within the guideline development group and the advantages and disadvantages of the different terms used in the literature were weighed. From the number of papers retrieved “primary ovarian insufficiency” and “premature ovarian failure” seem to be the preferred terms in current research publications although ‘premature ovarian insufficiency’ has been increasingly used over the last decade (figure 1.1, from PubMed: accessed 1/4/2014). Several papers have discussed nomenclature, but the terminology used depended on the preference of the author.

**Figure 1.1** Number of PUBMED citations using the term “Premature Ovarian Insufficiency” per year. (Alexandru Dan Corlan)



Consensus was easily reached within the experts in the field and the patient representatives to recommend the term “insufficiency” instead of “failure”. It was felt that “insufficiency” more accurately describes the fluctuating nature of the condition, and does not carry the negative connotation of “failure”.

The discussion on “primary” versus “premature” was more problematic. “Primary” was used by Albright in 1942, and many others since, because it emphasizes that the primary defect of the syndrome lies within the ovaries, in contrast to secondary ovarian insufficiency, which originates from a central defect in gonadotropin secretion by the pituitary. This approach is well argued by Cooper and colleagues and this terminology was adopted by an American consensus meeting (Nelson, 2009; Cooper, *et al.*, 2011). The GDG agreed with this scientific backbone for the term “primary ovarian insufficiency”, but wished to define an age limit in order to exclude women in natural menopause from the patient population. Therefore, the guideline development group considered naming the condition “premature primary ovarian insufficiency” or PPOI.

Subsequently a workshop was convened by ESHRE (Special Interest Group for Reproductive Endocrinology, Utrecht, December 2013) and views were expressed by the broader membership. It was felt that in Europe the terms “primary” and “secondary” were widely used to classify amenorrhea in relation to menarche, and thus “primary ovarian insufficiency” would lead to confusion, as it was not synonymous with primary amenorrhoea. This was a minority view of the guideline development group but a clear majority of workshop participants wished to use the terminology “premature ovarian insufficiency”.

### Conclusion and considerations

In developing a guideline for ESHRE, the terminology used must be unambiguous and consistent, in order to ensure clarity, and therefore the consensus opinion of ESHRE members should be adopted.

### Recommendation

The term “premature ovarian insufficiency” should be used to describe this condition in research and clinical practice.	GPP
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## 1.2 Definition of Premature Ovarian Insufficiency

## KEY QUESTION: HOW SHOULD POI BE DEFINED?

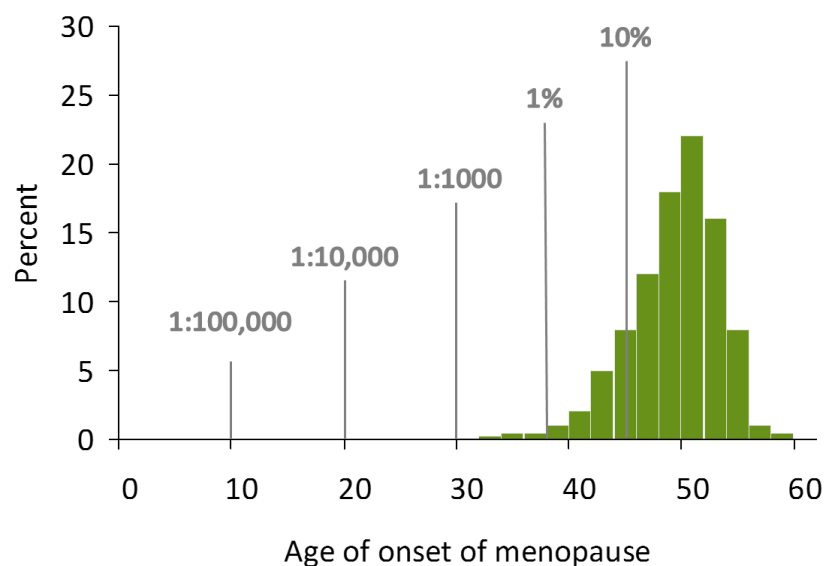
### Clinical evidence

A definition of POI is important to differentiate women with normal menopause from women with POI, as these women have different 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 (see chapter 9).

In general, POI is described as amenorrhea due to loss of ovarian function 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 causes of POI include chromosomal and genetic defects, autoimmune processes, chemotherapy, radiation, infections and surgery, but many are unidentified (idiopathic).

The age of 40 is set by convention but is supported by clinical observations. From a statistical point of view, the age limit of 40 is approximately two standard deviations (SD) below the average age at natural menopause ( $50 \pm 4$  years). An example of the observed distribution of menopausal ages in a European population is shown in figure 1.2. The prevalence of natural menopause before the age of 40 is 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 natural 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 1.2. Distribution of age at menopause.



### POI or diminished ovarian reserve?

Loss of ovarian function in POI can be entangled with low ovarian reserve, although these are two separate entities representing different patients, with different management needs.

The term ‘ovarian reserve’ encompasses both the quantity and quality of primordial follicles. Low ovarian reserve is a condition in which the ovary loses its normal reproductive potential.

Women with low ovarian reserve often respond poorly to controlled ovarian stimulation resulting in retrieval of fewer oocytes, producing poorer quality embryos and reduced implantation rates and pregnancy rates (Narkwichan, *et al.*, 2013). Incidence of poor ovarian response, a measure of low ovarian reserve, over all assisted conception cycles ranges from 9 to 24% (Keay, *et al.*, 1997). Low ovarian reserve is characterized as regular menses

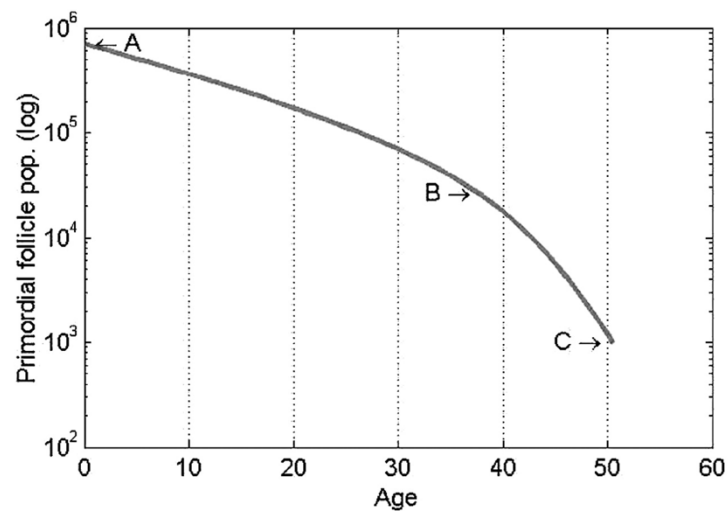


and alterations of ovarian reserve tests, and can be caused by conditions affecting the ovaries, but in most cases is a consequence of age.

The number of oocytes is highest in prenatal life and declines throughout reproductive life, falling to a critically low number around the age of 50 in most women (see also figure 1.3).

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

**Figure 1.3 Primordial follicle population from birth to menopause. The primordial follicle population at birth is ~ 701 000 (A), and at menopause is ~1000 at 50.4 years (C), with an accelerated decline occurring at ~25 000 remaining primordial follicles (B)** (Faddy and Gosden, 1995; Wallace and Kelsey, 2004).



## Conclusion

Premature ovarian insufficiency is a clinical syndrome defined by loss of ovarian activity before the age of 40.

POI is characterised by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotropins and low estradiol.

In this guideline, cessation of ovarian function in women aged between 40 and 45 will be termed early menopause.

## 1.3 Prevalence of Premature Ovarian Insufficiency

### KEY QUESTION: WHAT IS THE PREVALENCE OF PREMATURE OVARIAN INSUFFICIENCY IN THE GENERAL POPULATION?

#### Clinical evidence

##### Epidemiological evidence

We found no recent studies estimating the prevalence of POI. The longitudinal cohort study of Coulam and colleagues, which aimed at establishing the age-specific incidence of POI, found that 1% of women entered natural menopause before the age of 40 (Coulam, *et al.*, 1986). This figure was derived from long-term follow-up of a birth cohort of 1858 women in Rochester, Minnesota. A similar estimate was derived by Krailo and Pike from a national prevalence survey of menopause in the USA (the fitted prevalence of menopause at age 39-40 was 0.012) (Krailo and Pike, 1983). Luborsky and colleagues reported a 1.1% prevalence of POI in a cross-sectional survey of women aged 40-55 years (126/11652 women) (Luborsky, *et al.*, 2003).

The prevalence of early menopause (in the 40 to 44 age group) is ten times higher (Coulam, *et al.*, 1986).

##### Factors affecting age at natural menopause

- **Ethnicity:** Luborsky found that the prevalence of POI in the USA was higher in African-American and Hispanic women than in Caucasians, and the prevalence was lower in women with Chinese and Japanese ancestry (Luborsky, *et al.*, 2003). A recent study showed a prevalence of 2.8% of POI in Chinese women (Wu, *et al.*, 2014).
- **Lifestyle:** smoking is well recognised as a risk factor for earlier onset of menopause (Baron, 1984; van Noord, *et al.*, 1997; Sun, *et al.*, 2012; Gold, *et al.*, 2013). Regular strenuous exercise may postpone menopause (Morris, *et al.*, 2012), although contradictory evidence exists (Bromberger, *et al.*, 1997; Dorjgochoo, *et al.*, 2008). Menopause occurs later in obese women than non-obese (Aydin, 2010; Morris, *et al.*, 2012), although the study of Aydin indicates that rather than BMI, significant premenopausal weight gain or weight loss are associated with later age at natural menopause (Aydin, 2010).
- **Socio-economic factors:** Later menopause has been shown to be associated with higher socio-economic status (van Noord, *et al.*, 1997). Other studies showed that IQ was a strong predictor of age at menopause, i.e. women with lower cognitive scores in childhood reached menopause earlier than women with higher scores (Whalley, *et al.*, 2004; Kuh, *et al.*, 2005).
- **Menarche:** There does not appear to be a correlation between age at menarche and age at menopause (van Noord, *et al.*, 1997; Otero, *et al.*, 2010).

##### Iatrogenic menopause

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, but hysterectomy rates and concurrent bilateral oophorectomy rates are now falling (Vessey, *et al.*, 1992; Kramer and Reiter, 1997; Hill, *et al.*, 2010). Pokoradi found that 8.3% of women born from 1920-1929 experienced a surgical menopause, 18.0% born 1930-1939 and 52.9% of women born 1940-1949 experienced a surgical menopause (Pokoradi, *et al.*, 2011). Of current concern is the rising incidence of iatrogenic POI in cancer survivors, with the increasing success of cancer therapy. Iatrogenic POI may also arise from treatment of serious non-malignant disease such as cyclophosphamide for systemic lupus erythematosus (Huong, *et al.*, 2002; Katsifis and Tzioufas, 2004), or surgery for (ovarian) endometriosis (Coccia, *et al.*, 2011).

All causes of POI, including associated diseases, are summarised in section 3.2

## Conclusion

The prevalence of POI is approximately 1%. Population characteristics such as ethnicity may affect the prevalence.

In view of the long-term health consequences of POI, efforts should be made to reduce the incidence of POI. Modifiable factors may include:

- gynaecological surgical practice
- lifestyle – smoking
- modified treatment regimens for malignant and chronic diseases.

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# PART B: Diagnosis of POI

## 2. SYMPTOMS OF POI

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### Introduction

This chapter explores the symptoms of premature ovarian insufficiency (POI). Diagnosis and investigations to establish the causation of POI are described in chapter 3.

### 2.1 Symptoms of POI

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

#### Clinical evidence

Women with POI may present with symptoms typical of the menopause, sometimes preceded by menstrual cycle changes. Hot flushes and night sweats are characteristic of estrogen deficiency ([Conway, 2000](#)). Vaginal symptoms, dyspareunia and dryness, may be very distressing for the patient ([Davis and Jane, 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](#)).

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.

Symptoms may be transient or intermittent, and may be variable in severity, reflecting the fluctuations in ovarian activity that occur during spontaneous onset of POI ([Welt, 2008](#); [Knauff, et al., 2009](#)). In contrast, women experiencing surgical menopause usually have severe and persistent symptoms.

Young women with primary amenorrhea rarely experience symptoms at presentation, implying that these symptoms are due to estrogen withdrawal rather than estrogen deficiency. In a study aiming to describe differences between clinical features of primary and secondary hypergonadotropic amenorrhea, symptoms of intermittent estrogen deficiency (which were not specified) were reported in 85.6% of the 97 women with secondary amenorrhea, in comparison to 22.2% of the 18 women with primary amenorrhea ( $p < 0.001$ ) ([Rebar and Connolly, 1990](#)).

In untreated women, symptoms often resolve gradually but the time course is variable and unpredictable.

#### Conclusion and considerations

Women with POI may present with typical symptoms of estrogen deficiency, such as vasomotor symptoms. However, the clinical presentation is variable and several misunderstandings exist regarding symptoms in POI.

- Symptoms may intermittently disappear due to fluctuating ovarian function. This, however, does not exclude a diagnosis of POI.
- Some women with POI may not experience any symptoms.
- Women may experience sudden severe symptoms upon cessation of the contraceptive pill.
- Symptoms are less likely in young women with primary amenorrhea.

## Recommendations

Clinicians should enquire about symptoms of estrogen deficiency in women presenting with oligomenorrhea or amenorrhea.	GPP
POI needs to be excluded in women with amenorrhea/ oligomenorrhea or estrogen-deficiency symptoms below the age of 40 years.	GPP

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## 3. DIAGNOSIS AND INITIAL ASSESSMENT

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### Introduction

The diagnosis of POI is usually confirmed in women < 40 years by a combination of a 4-6 month period of amenorrhea or oligomenorrhea (although much shorter duration of amenorrhea is often used for inclusion into studies) and two measurements of elevated follicle stimulating hormone (FSH). The value of FSH, and other tests in 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, the 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.

### 3.1 Diagnosis of Premature Ovarian Insufficiency

#### **KEY QUESTION: WHAT INVESTIGATIONS SHOULD BE PERFORMED FOR DIAGNOSIS OF PREMATURE OVARIAN INSUFFICIENCY?**

#### **Clinical evidence**

POI is characterised by menstrual disturbance, raised gonadotropins, and low estradiol. Follicle stimulating hormone (FSH) levels are used as the gold standard in establishing a diagnosis of POI but there is insufficient high quality evidence on adequate cut-off levels. The literature search resulted in a number of papers, all using FSH>40 (or 20, or 50) as criteria and the reference to older papers, but the diagnostic accuracy of FSH has not been properly described. The original paper by Goldenberg did not show any follicles in ovarian biopsies from women with primary amenorrhea with FSH levels above 33 mIU/ml; in women with secondary amenorrhea no follicles were found when the FSH was >40 mIU/ml ([Goldenberg, et al., 1973](#)).

Some women with POI express FSH levels lower than these proposed cut-off values, particularly women with autoantibodies. La Marca found that women with POI due to steroidogenic cell autoimmunity had significantly lower FSH levels (n=26, range 26-64 mIU/ml, median 37 mIU/ml) compared with idiopathic POI (range 61-166 mIU/ml, median 99 mIU/ml) (P=0.001) ([La Marca, et al., 2009](#)). Since patients with autoimmune POI should be included in the diagnosis, the GDG decided to use a cut off level of FSH > 25 IU/l. This is above the physiological range for FSH even at the pre-ovulatory peak.

There has been interest in more direct markers of ovarian reserve, such as anti-Müllerian hormone (AMH). Serum AMH levels follow the reduction in follicular number over time in healthy women and fall to very low levels prior to menopause. La Marca measured AMH in different groups of patients with secondary amenorrhea and in healthy controls, which indicated that low AMH is more prevalent in POI patients ([La Marca, et al., 2006](#)). However, low AMH may also be found in women with regular cycles and low ovarian reserve. The assay used by most studies to date is insufficiently sensitive in this context, as AMH levels become undetectable approximately 5 years before the menopause. This may change with technical developments. It should be emphasised that women attending fertility clinics with low AMH but regular menstrual cycles should not be diagnosed with POI. As such, this is not the patient population to which the current guideline is targeted.

There is no evidence to include ultrasound. As ovarian function may fluctuate in women with POI, follicular activity may be seen, not distinguishing POI from other diagnoses. There is no evidence to include laparoscopy, with or without ovarian biopsies.



## Conclusion and considerations

The diagnosis of POI is usually confirmed in women < 40 years by a combination of a 4-6 month period of amenorrhea or oligomenorrhea and two serial measurements of elevated FSH taken > 4 weeks apart. In the literature, the accuracy of FSH has not been assessed robustly.

Anti-Müllerian hormone (AMH) is not sufficiently discriminative for a diagnosis of POI.

There are no ideal biochemical markers for the diagnosis in POI, and the existing markers may fluctuate over time. In the absence of high quality evidence, the guideline development group comes to the following recommendations:

## Recommendations

The diagnosis Premature Ovarian Insufficiency is based on the presence of menstrual disturbance and biochemical confirmation.

Although proper diagnostic accuracy in POI is lacking, the GDG recommends the following diagnostic criteria:

- oligo/amenorrhea for at least 4 months, and
- an elevated FSH level > 25 IU/l on two occasions > 4 weeks apart.

GPP

## 3.2 Assessment of causation of Premature Ovarian Insufficiency

### Introduction

The aetiology of premature ovarian insufficiency is wide ranging. POI can be caused by chromosomal and genetic defects, including chromosomal defects, fragile-X syndrome, and autosomal gene defects. POI can also be associated with autoimmune disorders or infections or have an iatrogenic cause, including surgery, radiotherapy, or chemotherapy. Finally, environmental factors are also implicated as determinants of the age of menopause and could be a causative factor in POI. However, in a significant amount of women diagnosed with POI, the causative factor for the syndrome remains elusive, and the term idiopathic POI is appropriate.

In this section, the different causes of POI are explored and investigations aimed at determining cause are explored.

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

### *3.2.a POI caused by chromosomal and genetic defects*

#### Chromosomal defects

#### Clinical evidence

Studies indicate that 10-12% of women diagnosed with POI have chromosomal abnormalities, of which the majority (94%) are X chromosomal abnormalities (X structural abnormalities or X aneuploidy). The incidence of an abnormal karyotype is higher in women with primary amenorrhea (21%) than in those presenting with secondary amenorrhea (11%) (Jiao, *et al.*, 2012; Kalantari, *et al.*, 2013).

A specific age cut-off limit for testing for chromosomal abnormalities is not recommended since among women with secondary amenorrhoea and abnormal karyotype, four (8%) were older than 35, and 16 (33%) were older than 30. (Personal communication, Xue Jiao); among 19 women with POI and abnormal karyotypes, 8 were older than 35 years at diagnosis (personal communication, Femi Janse).

In the presence of a Y chromosome, there is an elevated risk of developing gonadal neoplasia (45%) ([Michala, et al., 2008](#)). In a study of patients with complete gonadal dysgenesis (CGD), all with primary amenorrhoea, 4 of 9 46-XY women had gonadal tumours, 2 of them with and 2 without a SRY gene mutation ([Rocha, et al., 2011](#)).

In a study, 12.2% of women with Turner syndrome (12/114 patients, 95% CI 6.9 – 19.7%) had Y chromosome material by one or more primers applied ([Gravholt, et al., 2000](#)). Therefore it is important that women with TS have had an accurate karyotype. This could incorporate FISH or real-time PCR on buccal epithelial cells or peripheral blood ([Hanson, et al., 2002](#); [Freriks, et al., 2013](#)). Furthermore, Turner syndrome patients should be referred to a geneticist to discuss (in case of a mosaic TS) the risk of aneuploidy in the offspring.

### Conclusion and considerations

Based on the significant prevalence of chromosomal abnormalities in women with POI and the implications thereof, chromosomal analysis is recommended. For chromosomal analysis for Turner Syndrome, karyotyping is the gold standard; although microarray-based comparative genomic hybridisation (array CGH) and other new technologies exist.

Every women with a Y chromosome, whether or not she has a SRY gene mutation, should be counselled about the risk of development of a gonadal tumour and gonadectomy should be advised.

### Recommendations

Chromosomal analysis should be performed in all women with non-iatrogenic Premature Ovarian Insufficiency.	C
Gonadectomy should be recommended for all women with detectable Y chromosomal material.	C

### Fragile-X POI

#### Clinical evidence

The association between a fragile-X mutation (Fra-X) and early menopause was first recognised in 1991 ([Cronister, et al., 1991](#)), but Schwartz and colleagues were the first to describe an association between Fra-X carriers and cessation of menses prior to the age of 40 ([Schwartz, et al., 1994](#)).

Fragile-X syndrome is an X-linked inherited condition caused by a mutation of the fragile-X mental-retardation 1 (FMR1) gene. The full mutation (> 200 CGG repeats) can result in mental retardation but primarily in men who carry the mutation. Women who carry the premutation (55-200 repeats) do not have an increased risk of intellectual disability, but have an increased risk of 13 to 26% to develop POI ([Wittenberger, et al., 2007](#)). The risk of developing POI is not increased in women with the full mutation or intermediate sized CGG repeats (45 – 54 repeats) ([Bennett, et al., 2010](#)).

Studies on the Fra-X premutation in women with POI have found a prevalence of 0.8 to 7.5% in women with sporadic POI (i.e. women without other family members with POI) and up to 13% in women with a positive family

history of POI ([Conway, et al., 1998](#); [Wittenberger, et al., 2007](#); [Murray, et al., 2014](#)). This association between Fra-X premutation and POI was not found in a meta-analysis of 4 papers about POI in an Asian population ([Tosh, et al., 2014](#)).

Fragile-X testing is indicated in all women with POI, not only to establish the causation of POI, but also because the presence of the mutation could have major implications for herself and her family. Family members may be carriers too and therefore have a risk of developing POI and a risk of having (grand)children with fragile-X syndrome. In addition, the patient herself may already have daughters, who may be carriers. This requires careful counselling before the test is performed, including permission from the patient to perform the test. An additional reason to counsel about Fra-X testing is the risk of fragile-X-associated tremor/ataxia syndrome (FXTAS), a late onset neurological problem predominantly in male carriers of the Fra-X-mutation. The clinical features of FXTAS include progressive cerebellar gait ataxia and intention tremor. The penetrance of tremor and ataxia among adult premutation carriers increased with age, exceeding 50% for men aged 70-90 years. Females are also affected but severity and penetrance are less ([Jacquemont, et al., 2007](#); [Hagerman and Hagerman, 2013](#)).

### Conclusion and consideration

Based on its prevalence and severe implications, fragile-X testing is indicated in all women diagnosed with POI (elevated FSH, women <40 years) after careful counselling ([Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada, et al., 2008](#)). Guidelines on genetic counselling for FMR1 are provided by the National Society of Genetic Counsellors, although they do not elaborate on counselling women with POI ([Finucane, et al., 2012](#)). According to their recommendations, pre-test genetic counselling should include education about FMR1-related disorders, discussion of the possibility and implications of detecting a mutation for patients and their families, review of anticipated follow-up options in case a mutation is found, and discussion of anticipated emotional reactions to test results. They also recommend assisting patients with an FMR1 mutation in developing strategies to inform relatives.

### Recommendations

Fragile-X premutation testing is indicated in POI women.	B
The implications of the fragile-X premutation should be discussed before the test is performed.	GPP

### Autosomal gene mutations

#### Clinical evidence

A number of diseases that are diagnosed before puberty, such as galactosaemia (i.e. a genetic condition that affects the body's ability to process galactose), are associated with a higher risk of developing POI. Recently, ovarian imaging studies have pointed to an early onset of ovarian failure, rather than FSH inactivity due to secondary hypoglycosylation, as a potential mechanism for the development of premature ovarian insufficiency in women with galactosaemia ([Gubbels, et al., 2013](#)).

A number of autosomal genes have been suggested as a causative factor of POI. For some of these genes, mutations are identified, while others are listed as candidate genes with a need for further investigation. Ethnically distinct populations may show differences in gene-regulating pathways and genes causing POI ([Qin, et al., 2014](#)).

Most of the genetic studies in POI are candidate gene-driven, meaning that researchers have screened genes known to play a role in folliculogenesis or ovarian function. Therefore, the genes with identified mutations that could result in POI are genes involved in folliculogenesis (f.i. NR5A1, NOBOX, FIGLA, and FOXL2), folliculogenesis growth factors (f.i. BMP15, GDF9, inhibin A), ovarian steroidogenesis (f.i. FSH, FSHR, LH, LHR), or genes identified in syndromes often associated with POI (BLM, WRN, RTS) ([Simpson, 2008](#); [Vujovic, 2009](#); [Chapman, et al., 2015](#))

Recently, Perry reported testing 17 variants identified in a genome-wide association study (GWAS) of normal menopause in cases of early menopause and POI. Four SNPs reached genome-wide levels of significance for early menopause (CRHR1, SLC25A13, MCM6 and MB21D1/C6ORF150) ([Perry, et al., 2013](#)). In addition to candidate gene and SNP-based GWAS studies, copy number variations (CNVs) have been assessed in POI. CNVs are DNA regions >1 kb that vary in number between individuals and contribute toward phenotypic variation and disease susceptibility by altering transcriptional and translational levels, disrupting regulatory elements, or influencing gene dosage levels of adjacent or nearby genes. A first study identified five statistically significant potential candidate CNVs in POI, while more recent studies reported an additional 44 and 25 CNVs. Further research should determine the clinical usefulness of these, and other genetic markers in the diagnosis of POI.

There is no evidence to support testing for FSHR (Follicle-stimulating-hormone receptor), BMP 15 (Bone morphogenetic protein 15), or GDF 9 (Growth-differentiation factor 9) ([Bachelot, et al., 2009](#), [Christin-Maitre, et al., 1998](#)). In addition, there is no indication to screen for the other listed genes, except in POI patients presenting with typical phenotype characteristics of a specific gene mutation. For instance in a women with POI and the typical phenotype characteristics of type 1 Blepharophimosis Epicanthus Ptosis Syndrome (BPES) (dysplasia of the eyelids), the diagnosis should be confirmed by testing for FOXL2 ( alias BPES, Blepharophimosis gene 3q21- 24) ([Harrar, et al., 1995](#)).

## Conclusion and considerations

Many genes have been implicated as causative factors in premature ovarian insufficiency. However, based on the existing evidence, routine screening for autosomal gene mutations in POI patients cannot be recommended. New techniques and further research on the genetic background of POI may change this recommendation in the near future.

## Recommendation

Autosomal genetic testing is not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).

GPP

### 3.2.b POI caused by autoimmune ovarian damage

#### Clinical evidence

Autoimmune disorders are more frequent in POI than in the general population, and POI is more frequent in women with certain autoimmune disorders. Whether this is POI caused by an autoimmune disorder (e.g. coeliac disease), or a random association is not clear for some autoimmune disorders ([La Marca, et al., 2010](#)).

The most clinically important association is with autoimmune Addison's disease, in the context of autoimmune polyendocrine syndrome (APS). Addison's disease and APS type 2 are known to predispose to POI and these women should therefore be counselled and screened for POI. POI of adrenal autoimmune origin is the most frequent type observed in 60 to 80% of patients with autoimmune POI ([Silva, et al., 2014](#)).

POI may also be associated with localized or systemic non-adrenal disorders, such as thyroid diseases, hypoparathyroidism, hypophysitis, type 1 diabetes mellitus, and non-endocrine autoimmune diseases, including Systemic lupus erythematosus (SLE), Sjogren's syndrome, rheumatoid arthritis, immune thrombocytopenic purpura, autoimmune haemolytic anaemia, pernicious anaemia, vitiligo, alopecia areata, coeliac disease, inflammatory bowel diseases, primary biliary cirrhosis, glomerulonephritis, multiple sclerosis, and myasthenia gravis.

A recent study has shown that coeliac disease and inflammatory bowel disease are significantly more prevalent (6/224 (2.7%), and 9/224 (4%), respectively) among Turner Syndrome patients compared with idiopathic POI (1/457 and 0/457, respectively) and the normal US population (0.063% and 0.46%, respectively). The relative risk in Turner patients for coeliac disease is 42.5 (12.4-144.8) and for inflammatory bowel disease is 17.2 (8.5-33.2) ([Bakalov, et al., 2012](#)).

### **Adrenal autoimmunity**

The existence of ovarian autoantibodies was first shown in the 1960's in studies that used indirect immunofluorescence on cryostatic sections of adrenal, ovary, testis, and placenta ([Blizzard, et al., 1967](#)). Although coexistence of autoimmune or immune-mediated disorders is frequent in POI, histological studies on ovarian biopsies have documented that unequivocal signs of oophoritis can be detected only in those women with circulating adrenal or ovarian autoantibodies directed to steroidogenic enzymes (steroid-cell autoantibodies – SCA) ([Hoek, et al., 1997](#)). In the absence of these autoantibodies, no infiltration of ovaries by immune cells has been documented. Accordingly, ovarian biopsy is not indicated for the diagnosis of autoimmune POI as it can be substituted by the determination of SCA in a sample of peripheral blood.

At present, only the detection of SCA can ensure the accurate diagnosis of POI caused by autoimmune ovarian damage. In addition to these autoantibodies, the literature reports the occurrence in POI of autoantibodies directed to different targets including LH receptor ([Moncayo, et al., 1989](#)), FSH receptor ([Ryan and Jones, 2004](#)) and zona pellucida ([Kelkar, et al., 2005](#)). However, these studies are case reports lacking details on the validation and diagnostic accuracy of the antibody assay type used.

SCA are directed against autoantigens expressed by the adrenal cortex, ovary, placenta, and testis. Immunofluorescence studies have shown that SCA can react with all four tissues. Major autoantigens recognized by SCA are 17 $\alpha$ -hydroxylase (17 $\alpha$ -OH) and cytochrome P450 side-chain cleavage enzyme (P450SCC) ([Chen, et al., 1996](#); [Falorni, et al., 2002](#)). Although all the tissue components are present in the ovarian cryostatic sections used for the autoantibody assay, the immunofluorescence pattern of SCA is restricted to the theca cells of the growing follicle with no staining of primary follicles or granulosa cells in secondary and tertiary follicles.

### **Clinical evidence**

Four to five percent of women with POI will be positive for SCA ([La Marca, et al., 2010](#)). In women with autoimmune Addison's disease, SCA occur in approximately 8 to 20% women with isolated adrenal insufficiency or with autoimmune polyendocrine syndrome type 2 (APS-2), and in 40 to 60% women with autoimmune polyendocrine syndrome type 1 (APS-1 or APECED). Circulating SCA can be detected even years before clinical diagnosis of POI and, in women with Addison's disease, may be used to predict a high risk for future development of POI.

In SCA-positive POI selective destruction of theca cells takes place, resulting in low E2 (no substrate), high FSH, high inhibin B and normal AMH (i.e. AMH may or may not be normal for several years, but AMH is no longer detectable after 5 years in 93% of women) ([La Marca, et al., 2010](#)). A progressive decline of AMH levels has been documented in women with POI after initial clinical diagnosis, interpreted as an indirect sign of the progressive extension of the autoimmune infiltration and destruction of ovarian tissue ([Falorni, et al., 2012](#)). In women with POI, measuring of AMH may provide information on the degree of preservation of a residual follicle pool.

Analysis of SCA on cryostatic sections of ovarian tissue from women with POI is limited by the subjectivity of the interpretation of the results and by the variable quality of the substrate used for the assay. Adrenocortical antibodies (ACA) and more specifically 21-hydroxylase autoantibodies (21OH-Ab) appear to be the marker with the highest diagnostic sensitivity for autoimmune POI. In the presence of peripheral 21OH-Ab, SCA on cryostatic sections of ovaries and/or 17 $\alpha$ -hydroxylase antibodies (17 $\alpha$ -OH-Ab) and/or P450SCC antibodies can be detected on cryostatic sections of ovaries in over 90% of cases. In the absence of 21OH-Ab, less than 0.5% of POI patients will be positive for SCA, 17 $\alpha$ -OH-Ab, or P450SCC-Ab, a frequency not statistically different from that expected in the general population.

In cases of idiopathic POI negative for ACA, none were found to be positive for 21OH-Ab or P450SCC-Ab with only 1/17 found positive (in the low range) for 17 $\alpha$ -OH-Ab ([Chen, et al., 1996](#)).

SCA should be analysed in women with autoimmune Addison’s disease, because of the invariable presence of 21OH-Ab for the ongoing adrenal autoimmune process. Basal determination of adrenocorticotrophic hormone (ACTH) should not be used as a routine screening tool, as 2/123 were false positive. Additionally, monitoring cortisol should not be used as screening tool as 3 out of 4 women with adrenal insufficiency were normal ([Bakalov, et al., 2002](#)).

It is recommended that adrenocortical antibodies (ACA) and/ or 21OH-Ab should be measured in every POI patient because of the possibility of subclinical or latent Addison’s disease in POI patients ([Welt, 2008](#)).

In women negative for 21OH-Ab/ACA, there is no indication to analyse these autoantibodies in the future, in the absence of clinical signs or symptoms suggestive for adrenal insufficiency.

### Conclusion and considerations

Although at the moment there is no specific treatment option for autoimmune POI, identification of women with autoimmune POI is clinically relevant for the identification of those cases with subclinical or latent autoimmune Addison’s disease. In addition, it might become important in the near future should in vitro folliculogenesis or in vitro maturation be possible, because of the preserved pool of follicles present in the initial phase of the ovarian autoimmune process.

### Recommendation

<p>Screening for 21OH-Ab (or alternatively adrenocortical antibodies (ACA)) should be considered in women with POI of unknown cause or if an immune disorder is suspected.</p> <p>Refer POI patients with a positive 21OH-Ab/ACA test to an endocrinologist for testing of adrenal function and to rule out Addison’s disease.</p>	<p>C</p>
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### Thyroid autoimmunity

#### Clinical evidence

POI is associated most commonly with thyroid autoimmunity (14–27%) when adrenal autoimmunity is absent ([Hoek, et al., 1997](#); [Kim, et al., 1997](#)). Welt and colleagues have highlighted the common association between thyroid disease and POI, and therefore proposed that thyroid peroxidase autoantibodies (TPO-Ab) should also be assayed in all patients with POI. They advised that thyroid stimulating hormone (TSH) levels should be examined on a yearly basis if thyroid peroxidase antibodies are positive, but screening could occur at 5-year intervals if negative ([Welt, 2008](#)). Another study also showed that the frequency of TPO-Ab (24%) as well as thyroid

dysfunction (20.6%) is higher compared with healthy controls (Goswami, et al., 2006). However, it should be remembered that the expected frequency of TPO-Ab in the general population of women is around 12-15%.

At present, the most sensitive assay to detect an autoimmune thyroid process is the analysis of TPO-Ab (Hollowell, et al., 2002).

Because of its detrimental effects upon fetal neurocognitive development, it is important to treat hypothyroidism in case of pregnancy, or when pregnancy is desired (spontaneous or after oocyte donation) (Haddow, et al., 1999). The impact of subclinical hypothyroidism is less clear, but may still be important.

### Conclusion and considerations

Although untreated hypothyroidism is not life threatening, it can have severe impact on the quality of life. Furthermore, because of the detrimental effects upon fetal neurocognitive development, it is important to treat (subclinical) hypothyroidism in case of pregnancy, or in case a pregnancy is desired (spontaneous or after oocyte donation).

Therefore, screening for thyroid antibodies (TPO-Ab) should be performed in women with POI. In patients with a positive TPO-Ab test, thyroid-stimulating hormone (TSH) should be measured every year. Referral to an endocrinologist should be considered.

In the case of a negative test for TPO-Ab, in the absence of clinical signs or symptoms of hypo- or hyperthyroidism, follow-up of thyroid function should be applied as for the general population of women. There is no consensus in planning periodic analysis for TPO-Ab or TSH in women with POI, if the initial test was negative.

### Recommendation

Screening for thyroid (TPO-Ab) antibodies should be performed in women with POI of unknown cause or if an immune disorder is suspected. In patients with a positive TPO-Ab test, thyroid stimulating hormone (TSH) should be measured every year.	C
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### Diabetes Mellitus type 1

#### Clinical evidence

One study indicates that the prevalence of undetected diabetes in POI is 2.5%. However the study was small (119 POI women) and no demographic details were provided. One of the cases detected had a positive family history for diabetes (Kim, et al., 1997).

#### Conclusion and considerations

Given the consequences of untreated diabetes, the ability to detect these otherwise asymptomatic patients the authors recommended a fasting serum glucose for all POI women and for those with other risk factors also an oral glucose tolerance test (oGTT) (Kim, et al., 1997). However, the GDG considered that only type 1 (autoimmune) diabetes is important and because these patients are usually diagnosed in childhood/adolescence, many years before the onset of POI, there is no indication to routinely screen for diabetes in women with POI.

## Recommendation

There is insufficient evidence to recommend routinely screening POI women for diabetes.

D

### Auto immunity (re)testing in POI

#### **KEY QUESTION: HOW OFTEN SHOULD TESTS FOR AUTOANTIBODIES BE REPEATED? WHAT DO YOU DO IN CASE OF A POSITIVE TEST RESULT FOR AUTOANTIBODIES?**

#### **Clinical evidence**

Approximately 25% of individuals with isolated spontaneous POI are positive for autoimmune markers, although the poor sensitivity and/or specificity of the common autoantibodies make them imprecise tools. Because POI is one component of the autoimmune polyglandular syndromes, the possibility arises that other autoimmune conditions may follow the diagnosis of ovarian insufficiency.

APS-1 is a rare autosomal recessive disease caused by mutation in the AIRE gene presenting mainly in children with candidiasis, hypoparathyroidism and Addison's disease. Ovarian insufficiency occurs in 15% of cases ([Dittmar and Kahaly, 2003](#)).

APS-2 is probably polygenic with an autosomal dominant pattern of inheritance with HLA association. The condition comprises Addison's disease, autoimmune thyroid diseases and/or type I diabetes with an array of less common organ specific autoimmune conditions (e.g. coeliac disease). Ovarian insufficiency occurs in approximately 10% of cases ([Maclaren, et al., 2001](#)).

Only one study has reported longitudinal follow-up in four women with POI and positive adrenal cortex antibodies. From a cohort of 45 women with POI, the four testing positive were followed for between 13 and 64 months ([Betterle, et al., 1997](#)). Three of the women identified progressed to impaired adrenal function and one maintained normal adrenal function.

POI may precede the diagnosis of Addison's disease in polyglandular syndromes, but the efficacy of screening women with idiopathic sporadic POI is uncertain ([Kim, et al., 1997](#)). In general, Addison's disease preceded POI in patients with APS-1 and APS-4, and it followed POI only in APS-2 (mean age of onset POI: 32.8 (18-40) vs APS-2 35.5 (17-62)). It is unclear whether all the POI women in APS-2 were positive for the initial autoimmune screen ([Reato, et al., 2011](#)).

Women with idiopathic sporadic premature ovarian insufficiency show negative results for organ specific autoimmune testing in approximately 75% of cases ([Belvisi, et al., 1993](#); [Conway, et al., 1996](#)). There are no longitudinal studies available providing information on the natural history of autoimmunity in women with POI that are negative at initial screening.

#### **Conclusion and considerations**

In those POI women with **either positive adrenocortical antibodies (ACA) or positive TPO-Ab** referral to an endocrinologist should be offered. The endocrinologist should consider measuring adrenal autoimmunity, adrenocorticotrophic hormone (ACTH), and plasma renin activity, and performing an ACTH stimulation test at five yearly intervals. Measurements of TSH, vitamin B<sub>12</sub>, ferritin and folate could be included to account for the rare possibility of developing pernicious anaemia or coeliac disease.



In those POI women without positive ACA or positive TPO-Ab, but with other markers of autoimmunity, referral to an endocrinologist should be considered.

In POI women with **negative autoantibody tests**, in the absence of clinical signs or symptoms of endocrine diseases follow-up should be applied as for the general population of women. There is no consensus in planning periodic analysis for autoantibody tests in women with POI, if the initial tests are negative.

### Recommendation

If 21OH-Ab/ACA and TPO-Ab are negative in women with POI, there is no indication for re-testing later in life, unless signs or symptoms of these endocrine diseases develop.	C
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### 3.2.c POI due to infectious causes

#### Clinical evidence

Case reports have indicated that viral infections can be followed by ovarian failure, but only mumps oophoritis has been considered a cause of POI, explaining 3-7% of POI cases ([Kokcu, 2010](#)).

There are some studies suggesting that the age at menopause may be lower in HIV-positive women compared with non-HIV women (age at menopause, 46-47 years versus 51 years, respectively). This observation, however, does not show that HIV causes POI; the lower age at menopause in HIV-positive women is probably caused by other factors like smoking, low body weight and social economic factors ([Kojic, et al., 2007](#)).

#### Conclusion and considerations

POI has been reported following various infections, including mumps, HIV, herpes zoster, cytomegalovirus, tuberculosis, malaria, varicella, and shigella. However, none of these, mainly case reports, have been able to establish any cause and effect relationship between the infection and the diagnosis of POI ([Goswami and Conway, 2005](#); [Kokcu, 2010](#)).

### Recommendation

There is no indication for infection screening in women with POI.	D
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### 3.2.d Iatrogenic causes of POI

#### Clinical evidence

Radiotherapy and chemotherapy used to treat malignant or benign diseases can lead to POI ([Koyama, et al., 1977](#); [Howell and Shalet, 1998](#)). The risk of developing POI after radiotherapy is dependent on the radiation therapy field (abdominal pelvic radiation; total body irradiation) and on dose and age ([Lie Fong, et al., 2009](#); [Gracia, et al., 2012](#)) ([Wallace, et al., 2005](#)). Similarly, the gonadotoxic effect of chemotherapy is largely drug-and dose-dependent and is related to age ([Wallace, 2011](#)).

Alkylating agents have been shown to be gonadotoxic in childhood as well in adulthood ([Rosendahl, et al., 2008](#); [Lie Fong, et al., 2009](#); [Decanter, et al., 2010](#); [Gracia, et al., 2012](#)). A 10 year follow-up study of childhood cancer survivors demonstrated that survivors treated with ovarian irradiation and alkylating agents had a lower ovarian

reserve and substantial difficulties in conceiving compared with survivors solely treated with non-alkylating agents (Nielsen, *et al.*, 2013). However, the prognosis for return of ovarian function after cancer therapies may have been underestimated. Schmidt and colleagues recently reported a high rate of spontaneous conceptions in women who had undergone unilateral ovariectomy for cryopreservation prior to chemotherapy and/or radiation therapy (Schmidt, *et al.*, 2013). For obvious reasons, bilateral ovariectomy before the age of 40 results in POI.

No studies were found demonstrating a causal relationship between hysterectomy or tubal sterilization and POI. However, there are studies indicating a relation between an early menopause in women who had undergone a hysterectomy (Siddle, *et al.*, 1987) and in women who had undergone tubal sterilization (Visvanathan and Wyshak, 2000) compared with women without surgery.

Both ovarian surgery for endometrioma and endometriosis as a disease appear to influence age at menopause, and the risk of POI. In one cohort study, it was concluded that bilateral (but not unilateral) surgery for bilateral ovarian endometriosis may lead to POI (Coccia, *et al.*, 2011). Other studies have concluded that ovarian endometrioma surgery is associated with a decline in serum AMH and diminishing the ovarian reserve (Raffi, *et al.*, 2012; Somigliana, *et al.*, 2012).

### Recommendation

The possibility of POI being a consequence of a medical or surgical intervention should be discussed with women as part of the consenting process for that treatment.	GPP
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### 3.2.e Environmental causes of POI

#### Clinical evidence

Smoking, alcohol, nutrition, and exposure to endocrine disruptors are implicated as influencing the age of menopause, but are not readily diagnosable causes of POI.

Although not proven to cause POI, cigarette smoking is toxic to the ovaries, and has been related to an earlier age at menopause:

The prospective cohort study of 5113 postmenopausal health survey respondents study of Pokoradi showed that fifteen or more pack-years of smoking was significantly more common among women in the early natural menopause group than the remaining group. Overall, smokers in this study had a mean age at menopause of 45.6 years (SD 6.04 years) while non-smokers' mean age at menopause was 46.9 years (SD 5.7 years). In this study age at natural menopause was not associated with weekly alcohol consumption, physical activity, BMI at age 30 years, or parity (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).

There is no indication that epilepsy is a cause of POI or vice versa (Isojarvi, 2003).

### Recommendation

Although no causal relation has been proved for cigarette smoking and POI, there is a relation to early menopause. Therefore, women who are prone to POI should be advised to stop smoking.	GPP
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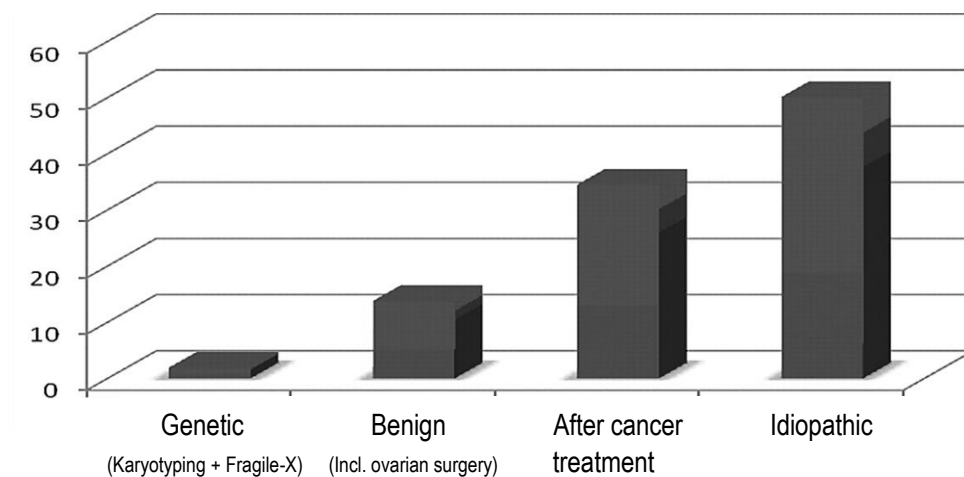
### 3.2.f Idiopathic POI

#### Clinical evidence

Although several causes for POI have been described, in a significant number of women diagnosed with POI, the causative factor for the syndrome remains elusive, even after thorough investigation. These women are diagnosed with unexplained or idiopathic POI. An exact number of women diagnosed with idiopathic POI has not been established, as it is largely dependent on the setting, patient population, and the available investigations for identifying causation.

No primary studies were identified exploring the percentage of women with idiopathic POI. A recent review included a graph on the aetiology of POI cases managed at the West London Menopause and PMS Centre (London, UK), indicating the percentage for genetic (and chromosomal) cases, benign cases (autoimmune/infectious), malignant (as a result of cancer treatment) and idiopathic cases ([Maclaran and Panay, 2011](#)) (see figure 3.1). Other reviews on POI state that in 90% of cases the aetiology is unknown ([Nelson, et al., 2005](#); [Nippita and Baber, 2007](#); [Kokcu, 2010](#)), or “the majority of cases are idiopathic” ([Vujovic, 2009](#); [La Marca, et al., 2010](#)). However, these are only estimations, as none of these reviews refers to a primary study establishing a percentage for idiopathic POI.

**Figure 3.1: Aetiology of premature ovarian failure cases managed at the West London Menopause and PMS Centre, London, UK ([Maclaran and Panay, 2011](#)).**



#### Conclusion

In a significant number of women with POI, the cause is not identified and these women are described as having unexplained or idiopathic POI.

## Summary of diagnostic workup

Test	Implications	
	Positive test	Negative test
<b>Genetic/Chromosomal</b>		
<b>Karyotyping (for diagnosis of Turner syndrome)</b>	Refer to endocrinologist, cardiologist and geneticist	A second analysis of the karyotype in epithelial cells (in case of high clinical suspicion)
<b>Test for Y-chromosomal material</b>	Discuss gonadectomy with the patient	
<b>Fra-X</b>	Refer to geneticist	
<b>Autosomal genetic testing<sup>1</sup></b>		
<b>Antibodies<sup>2</sup></b>		
<b>ACA/21OH antibodies</b>	Refer to endocrinologist	Re-test in case of clinical signs or symptoms
<b>TPO-Ab</b>	Test TSH every year	

<sup>1</sup> not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).

<sup>2</sup> POI of unknown cause or if an immune disorder is suspected.

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## 4. IMPLICATIONS FOR RELATIVES OF WOMEN WITH POI

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### Introduction

The prevalence of familial POI has been reported to be between 4 and 31% of cases in various series ([Conway, et al., 1996](#); [Vegetti, et al., 1998](#); [van Kasteren, et al., 1999](#); [Janse, et al., 2010](#)). In these families with two or more affected females, a genetic aetiology is suggested, but the genetic association with POI cannot always be identified ([Davis, et al., 2000](#)).

Whether or not a genetic association has been identified, women with POI may ask their doctors 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.

The evidence is explored regarding implications for relatives of women with POI in general, and specifically for the extended family of women with POI associated with a fragile-X premutation.

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

#### Clinical evidence

Family association between menopausal age of mothers and their daughters has not yet been confirmed in well-designed studies. There are data pointing to this association arising from epidemiological studies. The study by Torgerson et al reports that the odds ratio of a woman having an early (<45 years) or premature (<40 years) menopause if her mother had experienced an early menopause was 6.02 (95% CI 3.39-10.66) ([Torgerson, et al., 1997](#); [van Asselt, et al., 2004](#)). There are numerous potential biases in such observational studies, particularly 'recall' bias.

Recently, the study of Bentzen evaluated whether the ovarian reserve in a woman is associated with her mother's age at menopause. They reported a significant effect of the age at maternal menopause on both the serum AMH levels ( $p < 0.001$ ) and antral follicle count ( $p = 0.005$ ) in 527 participants (aged 20-40 years). Both median serum AMH and median antral follicle count in daughters showed a more pronounced decline per year for participants with early ( $\leq 45$  years) maternal age at menopause, compared with participants with late maternal age at menopause ( $\geq 55$  years) ([Rosen, et al., 2010](#); [Bentzen, et al., 2013](#)).

The only study to mention the probability of a relative of a POI patient being affected was the retrospective study of Van Kasteren that evaluated 63 idiopathic POI women. Of these 63 women, 14 were registered as having familial POI (i.e. more than one other family member with POI). Further evaluation revealed that only eight women (12.7%) had familial POI. The pattern of inheritance was compatible with either X-linked or autosomal-dominant sex-limited, paternal and maternal, transmission. With autosomal dominant inheritance the risk of POI will be 50% (either maternal or paternal transmission), whereas with X-linked inheritance and paternal transmission this risk may be as high as 100%. However, if the case appears to be sporadic, the risk of other female relatives developing POI will probably be similar to the risk of the general population ([van Kasteren, et al., 1999](#)). This conclusion applies only in classical monogenic inheritance. The opinion of the GDG is that it may well be more complex.

Janse and colleagues compared 58 women with familial POI (at least one other family member with POI) with 142 women with sporadic POI. The incidence of familial POI was 29%. The only difference they observed was a significantly lower maternal age at menopause in women with familial POI as compared to sporadic POI cases

( $41.0 \pm 7.5$  versus  $49.7 \pm 2.6$  yr.,  $p < 0.001$ ) and a significantly higher sex hormone binding globulin (SHBG) level. All other characteristics, such as parity, bone mineral density, and serum follicle-stimulating hormone and lipid levels were similar, as was the incidence of autoimmunity and cytogenetic abnormalities ([Janse, et al., 2010](#)).

Sisters of women with POI may have reduced reproductive potential. Oocyte donation cycles of women donating to their sisters with diagnosed POI had higher cancellation rates and lower ovarian responses compared to that of anonymous donors in one case study. However, implantation and pregnancy rates were similar ([Sung, et al., 1997](#)). The aetiology of POI was not defined in this study though.

### **Fragile-X premutation carriers**

Reproductive and diagnostic options available to fragile-X premutation carriers (oocyte or sperm donation, pre-implantation and prenatal diagnosis, adoption, family history of mental retardation etc.) raise many ethical questions for the patients and their extended families.

The aetiology of POI in fragile-X premutation carriers is unknown and full mutation carriers seem not to develop POI. Furthermore, the onset of POI is difficult to predict and not all fragile-X premutation carriers will develop POI. The review of McConkie-Rosell states that approximately 13 – 24% of women who are premutation carriers (identified through families with fragile-X syndrome) have POI ([McConkie-Rosell, et al., 2005](#)).

The prevalence of women who are carriers of fragile-X syndrome is estimated to be about 1 in 157 in a population without history of mental retardation, developmental abnormalities or autism and 1 in 128 when a positive history exists ([Berkenstadt, et al., 2007](#)).

The evidence supporting fragile-X testing in women diagnosed with POI has been described in chapter 2.2 and based on this, the GDG recommends fragile-X premutation testing is indicated in POI women, but the implications of the premutation should be discussed before the test is performed.

Family history of fragile-X syndrome, fragile-X-associated tremor/ataxia syndrome (FXTAS) or premature ovarian insufficiency (in more than one family member) are indicators for fragile-X testing if the pedigree structure of a woman indicates that she is at risk of inheriting the mutated gene. ([Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada, et al., 2008](#)). This group of patients should be informed about their possibly diminished fertility potential, even in the absence of the clinical onset of POI, and they should be counselled on the possibilities of preimplantation genetic diagnosis (PGD) to avoid the transmission of the full mutation to the next generation.

### **Conclusion and considerations**

In conclusion, although there seems to be a familial factor in POI and there is evidence of heritability of age at menopause, the genetic association in POI has not been elucidated. Research in this area is specifically complicated.

Women with at least one affected family member may be at risk of POI, but currently it is not possible to predict or prevent the onset. Markers of ovarian reserve might be useful, although the predictive value of these markers needs to be established. 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. In addition, there is no evidence of the benefits or otherwise of oocyte freezing for women at risk of developing POI, who may already have impaired ovarian reserve.

The implications for male and female relatives of POI patients with the fragile-X premutation are more extensive than reproductive issues and genetic counselling should be offered.



## Recommendations

<p>Relatives of women with the fragile-X premutation should be offered genetic counselling and testing.</p>	<p>C</p>
<p>Relatives of women with non-iatrogenic premature ovarian insufficiency who are concerned about their risk for developing POI should be informed that:</p> <ul style="list-style-type: none"> <li>• currently there is no proven predictive test to identify women that will develop POI, unless a mutation known to be related to POI was detected</li> <li>• there are no established POI preventing measures</li> <li>• fertility preservation appears as a promising option, although studies are lacking, and</li> <li>• their potential risk of earlier menopause should be taken into account when planning a family.</li> </ul>	<p>GPP</p>

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# PART C: Sequelae of POI

## 5. LIFE EXPECTANCY IN WOMEN WITH POI

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### Introduction

Premature ovarian insufficiency affects not only fertility, but also impacts on 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, or can be caused by treatment for cancer, or prophylactic oophorectomy in women with high risk of developing cancer, which again may largely affect mortality. This chapter reviews the limited evidence and considers whether a diagnosis of POI has significant consequences for life expectancy.

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

### Clinical evidence

Most of the evidence on long-term outcomes of POI comes from observational studies of women who have undergone “surgical menopause”, i.e. bilateral oophorectomy, usually at the time of hysterectomy for benign gynaecological disease, or prophylactic surgery for familial cancer risk. These outcomes may differ from those in women who have experienced spontaneous (non-iatrogenic) POI, which typically has a gradual onset and prolonged fluctuating course, compared to the immediate onset and profound estrogen-deficiency of surgical menopause.

The best-documented series is the Mayo Clinic Cohort Study of Oophorectomy and Aging, from Minnesota USA. This reported very long-term follow-up (38 years) of a cohort of women who had undergone oophorectomy (bilateral n=1097, or unilateral n=1293). Each subject was matched by age to a referent woman from the same population (n=2390). Outcomes were obtained by direct or proxy interviews, medical records in a records-linkage system, and death certificates. Mortality was increased in women after bilateral oophorectomy before the age of 45 years (HR 1.67; 95% CI 1.16-2.40, p=0.006) (Rocca, *et al.*, 2006). The main causes of premature death were cardiovascular disease, osteoporosis and fractures; this series also reported cognitive impairment, dementia, parkinsonism, reduced sexual function and psychological wellbeing (Shuster, *et al.*, 2010).

Two other large observational cohort studies compared hysterectomy with bilateral salpingo-oophorectomy (BSO) to hysterectomy alone (Parker, *et al.*, 2009; Jacoby, *et al.*, 2011). These control groups may not differ from the BSO group as much as expected because total abdominal hysterectomy itself is known to cause earlier menopause. The Nurses’ Health Study followed up 29,380 women for up to 24 years and found increased mortality (HR 1.12; 95% CI 1.03–1.21) (Parker, *et al.*, 2009). The Women’s Health Initiative observational study of 25000 women did not detect increased mortality, but had less than 8 years’ follow-up (Jacoby, *et al.*, 2011).

Several epidemiological studies are supportive of an adverse effect of POI. In a Dutch cohort of 12000 women over 17 years, life expectancy was reduced by 2 years in women who had experienced menopause before the age of 40 (Ossewaarde, *et al.*, 2005). There are similar findings in non-European populations: increased all-cause mortality after menopause before 40 was reported in Japanese women (HR 2.10; 95% CI 1.07-4.11) and in South Koreans (HR 1.32; 95% CI, 1.05-1.66, p=0.02) (Amagai, *et al.*, 2006; Hong, *et al.*, 2007). The Shanghai Women’s Health Study showed POI was associated with an increased risk of all-cause (HR 1.29; 95% CI 1.08–1.54) and cancer-specific mortality (HR 1.38; 95% CI 1.05–1.81) (Wu, *et al.*, 2014).

Jacobsen and colleagues studied a cohort of 19309 Norwegian women over 29 years of follow-up; they showed an inverse relationship between age at natural menopause and cardiovascular mortality (Jacobsen, *et al.*, 1997). Van der Schouw and colleagues reviewed the Dutch cohort of 12,000 women over 20 years and calculated that for each year’s delay in menopause the cardiovascular mortality risk decreased by 2% (van der Schouw, *et al.*,

1996). Both these analyses found that the differential risk of early menopause reduced over time, as cardiovascular risk was affected by biological ageing.

Other risk factors may also contribute to premature deaths; in a multivariate analysis women who were obese at the time of interview and who had an oophorectomy before 40 years were more than twice as likely to die (HR 2.23; 95% CI 1.25-3.98) (McCarthy, et al., 2012). No studies were found that studied the effect of smoking in POI.

There are no long-term prospective studies examining the influence of estrogen replacement on mortality after POI. In the Mayo Clinic cohort reported by Rivera, increased mortality was seen mainly in women who had not received estrogen up to the age of 45 years (non-users HR 1.84; 95% CI 1.27-2.68; HRT-users HR 0.65; 95% CI 0.30-1.41; test of interaction, p = 0.01) (Rivera, et al., 2009). In the Women’s Health Initiative study, a randomised controlled trial of HRT versus placebo, secondary analysis showed a possible protective effect of HRT within 10 years of menopause for cardiovascular disease and death, but this was not significant (HR 0.76; 95% CI 0.50-1.16; absolute excess risk -6/10,000 woman-years) (Rossouw, et al., 2007).

### Conclusion and considerations

POI is associated with increased risk of premature death from cardiovascular disease. Both iatrogenic and natural menopause are implicated. The risk may be worsened by contributory factors such as obesity, and may be ameliorated by estrogen replacement therapy, but the quality of evidence is poor.

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

### Recommendation

Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease.	C
Women with POI should be advised on how to reduce cardiovascular risk factors by not smoking, taking regular exercise, and maintaining a healthy weight.	GPP

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## 6. FERTILITY AND PREGNANCY IN WOMEN WITH POI

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### Introduction

As premature ovarian insufficiency 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.

### 6.1 POI and consequences for fertility

#### KEY QUESTION: WHAT ARE THE CONSEQUENCES OF POI FOR FERTILITY?

#### Clinical evidence

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 spontaneous 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 a range of 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](#)).

A more recent 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, including serum estradiol and inhibin B (but not AMH) and the detection of ovarian follicles by ultrasound. A family history of POI and secondary amenorrhea were also predictive of subsequent ovarian activity ([Bidet, et al., 2011](#)).

#### Conclusion and considerations

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

#### Recommendations

Women with POI should be informed that there is a small chance of spontaneous pregnancy.	GPP
Women with POI should be advised to use contraception if they wish to avoid pregnancy.	GPP

## 6.2 Interventions for fertility in POI

### KEY QUESTION: WHAT FERTILITY INTERVENTIONS ARE EFFECTIVE?

#### Clinical evidence

##### *What treatments are available 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 and Schoemaker, 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](#)). In that study, 37 women aged 16-40 years with amenorrhoea and FSH>40IU/L (based on being above the 95%CI of the mid-cycle peak) were randomized to oral estradiol 2mg or no therapy for 6 weeks in a cross-over design. Follicle development to >10mm diameter was detected in most women, and overall 46% of women ovulated at least once with 2 women conceiving during the trial, but there was no apparent effect of estradiol treatment. Ovulation was more common in those with a short duration (<3 months) of amenorrhoea.

Two more recent randomized trials were identified ([Badawy, et al., 2007](#); [Tartagni, et al., 2007](#)). Tartagni and colleagues randomized 50 women with POI to 0.05mg 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 ( $p<0.005$ ). Subanalysis 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. The study by Badawy and colleagues involved treatment of 58 women with idiopathic POI with GnRHa and gonadotrophin therapy with randomization to receive additionally dexamethasone or placebo, on the basis that some such women may have an autoimmune component that might be ameliorated by glucocorticoid ([Badawy, et al., 2007](#)). Ovulation was detected in 6 out of 29 women treated with dexamethasone versus 3 out of 29 women in the placebo group. While this was a statistically significant difference, only cautious conclusions can be drawn due to the small numbers. 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.

The potential beneficial effect of immunosuppression in POI of presumed autoimmune aetiology has been reported in a case report only. A woman with POI and Addison's disease was reported to resume menstruation and conceive after treatment with azathioprine was commenced ([Ferrau, et al., 2011](#)). Pregnancies have also been reported in relation to other causes of POI (e.g. cancer treatments) but no systematic analyses were identified that used POI as the denominator rather than the POI-inducing treatment. An example is the prevalence of pregnancy after total body irradiation, which frequently but not invariably results in POI; it is unclear whether the reported pregnancies were in women who had been diagnosed with POI, or not ([Salooja, et al., 2001](#)).

##### *Are there techniques available for fertility preservation in women with POI?*

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 combining both approaches) have been described in case reports ([Lau, et al., 2009](#); [Balen, et al., 2010](#)) and series ([Borgstrom, et al., 2009](#)) but no resulting pregnancies have been reported.

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 survivors of childhood and adolescent cancer, and sisters of women with POI. 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 very limited, and indeed suggests that normal, regularly cycling women (mostly in their 20's) with low AMH levels do not have reduced fecundability ([Hagen, et al., 2012](#)). However in a slightly older population (aged 30-42), low AMH was however associated with reduced fecundability ([Steiner, et al., 2011](#)). Likewise high natural pregnancy rates have been reported in women following some cancer treatments who underwent fertility preservation pre-treatment ([Schmidt, et al., 2013](#)). This aspect of fertility preservation requires further investigation.

A small number of successful pregnancies have been reported following replacement of ovarian tissue cryopreserved before potentially sterilizing treatments ([Donnez, et al., 2013](#)), but a full appraisal of this approach is outwith the remit of this guideline. This approach of grafting ovarian tissue has also been used in a series of women with POI who had a fertile monozygotic twin sister (thus avoiding tissue rejection) but this will remain a rare occurrence ([Silber and Gosden, 2007](#)).

### **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](#)).

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 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 6.3*).



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 very high rates of complications in pregnancy (*see section 6.3*). 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](#)).

### Conclusion and considerations

There are no known treatments which reliably increase ovarian activity, ovulation rate, and the possibility of conception (strong evidence, review based on seven controlled studies). In a subgroup of women, possibly with less advanced POI, estrogen treatment may increase the ovulation rate. Other techniques, like chemical treatment of ovarian tissue before grafting, have been recently explored and could in the future provide options for fertility treatment in women with POI ([Kawamura, et al., 2013](#)).

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 development 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.

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 6.3](#).

### Recommendations

Inform women with POI that there are no interventions that have been reliably shown to increase ovarian activity and natural conception rates.	A
Oocyte donation is an established option for fertility in women with POI.	C

Inform women considering oocyte donation from sisters that this carries a higher risk of cycle cancellation.	C
In women with established POI, the opportunity for fertility preservation is missed.	GPP

### 6.3 Pregnancy in women with POI

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

**Clinical evidence**

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

***After idiopathic POI***

There are case reports of spontaneous 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 and Schoemaker, 1999](#)). A pilot study of 20 cases 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***

A systematic review on the long-term follow-up of survivors of childhood cancer concluded that chemotherapy has no adverse effects on uterine function or pregnancy outcomes (other than an increase in miscarriage rates in pregnancies conceived soon after chemotherapy) ([Scottish Intercollegiate Guidelines Network \(SIGN\), 2013](#)). The Childhood Cancer Survivor Study, a large multi-centre cohort investigation, showed no increased risk of congenital anomalies in the offspring of survivors, including those exposed to ovarian irradiation or alkylating agents ([Signorello, et al., 2012](#)). However a large retrospective observational study of approximately 6100 offspring of childhood/adolescent cancer survivors showed anthracyclines (doxorubicin or daunorubicin) were associated with low birth weight independent of exposure to radiotherapy ([Green, et al., 2009](#)). A smaller US cancer registry based study of almost 2000 childhood cancer survivors also suggested an increased risk of low birth weight after chemotherapy ([Mueller, et al., 2009](#)).

In contrast, abdomino-pelvic radiotherapy is consistently reported to be associated with poor uterine function with increased risks of late miscarriage, prematurity, low birth weight, stillbirth, neonatal haemorrhage and postpartum haemorrhage ([Bath, et al., 1999](#); [Larsen, et al., 2004](#); [Signorello, et al., 2010](#); [Scottish Intercollegiate Guidelines Network \(SIGN\), 2013](#)). There are also case reports of uterine rupture as well as a possible increase in placental attachment disorders (placenta accreta and percreta) ([Wo and Viswanathan, 2009](#)). Not only is the effect on uterine function dose dependent, but also related to age at the time of exposure, the pre-pubertal uterus being more susceptible ([Bath, et al., 1999](#); [Larsen, et al., 2004](#); [Signorello, et al., 2010](#); [Scottish Intercollegiate Guidelines Network \(SIGN\), 2013](#)).

Green and colleagues report an increase in the risk of late miscarriage (but not first trimester miscarriage) in women who have previously received cranial (RR 1.4; CI 1.02-1.94) or craniospinal radiotherapy (RR 2.22; CI 1.36-3.64) ([Green, et al., 2009](#)).

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 be between a cumulative dose of 250 mg/m<sup>2</sup> ([Scottish Intercollegiate Guidelines Network \(SIGN\), 2013](#)) and 300 mg/m<sup>2</sup> ([Hudson, 2010](#)). There are case reports of peripartum heart failure, which are probably due to exacerbation of pre-existing cardiac dysfunction originating at the time of exposure to anthracyclines or radiotherapy ([Hudson, 2010](#)).

### **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. Small case reports have suggested that these pregnancies may be obstetrically high risk. In the largest cohort study of 232 consecutive oocyte donation pregnancies, there was a high prevalence of miscarriage (40% after identification of a single gestational sac), pregnancy-induced hypertension (22%), prematurity (13%), low birth weight and small for gestational age (18% and 15%, respectively), caesarean section (61%), and postpartum haemorrhage (12%) with the quoted figures relating to singleton deliveries ([Abdalla, et al., 1998](#)). Threatened miscarriage in the first trimester (with subsequent live birth) was also common in the study of Abdalla and colleagues (11%) and in a smaller study by Pados and colleagues (35%) ([Pados, et al., 1994](#); [Abdalla, et al., 1998](#)). While the women included in the Abdalla study had varied reasons for requiring oocyte donation (including 14 with TS), 64% had ovarian failure without other specified morbidity, and this was identified as a significant predictor for miscarriage and small for gestational age. The authors concluded that, while women with an oocyte donation pregnancy should expect a good outcome, they should be cared for in a high-risk antenatal clinic.

A more recent analysis of 205 oocyte donation pregnancies (with the recipient age-matched to women pregnant after ICSI using their own oocytes) confirmed increased risks of early pregnancy bleeding (20.6% vs 10.3%; OR 1.49; 95% CI 1.04-2.15) and pregnancy-induced hypertension (19.1% vs 8.3%; OR 1.50; 95% CI 1.02-2.20), but these differences were not significant in singleton pregnancies ([Stoop, et al., 2012](#)). Caesarean delivery was more common (58.9% vs 46.0%) but there was no adverse effect on gestation or weight at delivery, or any other perinatal outcome. Similar results were reported in another small cohort ([Soderstrom-Anttila, et al., 1998](#)). Analysis of the UK HFEA database indicates that oocyte recipients have an almost two-fold increased risk of preterm birth and low birth weight compared to women using their own oocytes after adjusting for other maternal confounders ([Nelson and Lawlor, 2011](#)).

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)**

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](#)). It is not clear whether it is the underlying karyotype or that the pregnancy was the result of oocyte donation that increases the risks. 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](#)).

**Table 6.1: The prevalence of complications in oocyte donated pregnancies in women with Turner Syndrome (Karnis, 2012).**

	Total	Percentage
<b>Study population</b>		
Number of women with Turner Syndrome who conceived	116	
Number of pregnancies	144	
Number with 45,X karyotype	51	44% of women pregnant through oocyte donation
<b>Complications</b>		
Delivery resulting in live birth	118	82% live birth rate
Aortic dissection	2	1.7% of women pregnant through oocyte donation
Pregnancy-induced hypertensive disorders	36	28% of 130 pregnancies with available data
Pre-eclampsia, eclampsia, HELLP*	22	61% of hypertensive disorders in pregnancy
Gestational diabetes	6	4.6% of 131 pregnancies with available data
Preterm delivery	30	38% of 80 pregnancies with available data
Multiple gestation	7	4.8% of pregnancies
Low birth weight	24	41.4% of 58 pregnancies with available data
Other adverse neonatal outcomes	8	

\*HELLP: haemolysis elevated liver enzymes, low platelets.

Hadnott and colleagues reviewed the published data on TS pregnancies (spontaneous and assisted) from 1960 to 2010 and concluded the risk of a major obstetric complication is 10% (Hadnott, *et al.*, 2011). They estimated the maternal mortality rate to be approximately 3.5%, mainly as a result of aortic arch or aortic valve abnormalities. Pregnancy increased the risk of aortic dissection by an estimated two to five times for women with TS. However, a feature of published case studies was the inconsistent use of pre-conception cardiac screening, which might improve the outcome.

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 45X0 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).

The risk of birth defect or serious neonatal illness was 5 out of 44 (11%) live births in own oocyte pregnancies compared to 8 out of 118 (7%) live births in oocyte donation pregnancies (Karnis, 2012). However, it is not clear whether these figures include both major and minor congenital abnormalities or how many of the affected cases were due to other conditions (e.g. cerebral palsy). In a series of oocyte donation pregnancies in TS women from the Nordic countries, 8 out of 131 (6.1%) children were born with a birth defect and of these 5 were major defects

(3.8%) ([Hagman, et al., 2013](#)). In a series of own oocyte pregnancies in Sweden, 2 or 3 out of 37 live births were affected by a major congenital abnormality (5.4% or 8.1% respectively) (reported by ([Bryman, et al., 2011](#)) and included in the analysis of Karnis and colleagues ([Karnis, 2012](#)).

### Conclusion and considerations

Spontaneous 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. IUGR 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)

NICE recommends 75mg aspirin daily from 12 weeks of pregnancy until delivery for women at risk of pre-eclampsia. 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 to prescribing aspirin should be given in these pregnancies, especially when it is the first pregnancy or in a woman with Turner Syndrome.

Two observational studies concluded that antenatal aneuploidy screening based on the age of the oocyte donor is more accurate than based on the recipients' age.

Pregnancies in women with Turner Syndrome are very high risk and may have a maternal mortality as high as 3.5%. 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.

### Recommendations

Women should be reassured that spontaneous pregnancies after idiopathic POI or most forms of chemotherapy do not show any higher obstetric or neonatal risk than in the general population.	B
Oocyte donation pregnancies are high risk and should be managed in an appropriate obstetric unit. Women and their partners should be encouraged to disclose the origin of their pregnancy with their obstetric team.	C

Antenatal aneuploidy screening should be based on the age of the oocyte donor.	C
Pregnancies in women who have received radiation to the uterus are at high risk of obstetric complications and should be managed in an appropriate obstetric unit.	C
Pregnancies in women with Turner Syndrome are at very high risk of obstetric and non-obstetric complications and should be managed in an appropriate obstetric unit with cardiologist involvement.	D
A cardiologist should be involved in care of pregnant women who have received anthracyclines and/or cardiac irradiation.	D

## 6.4 Fitness for pregnancy in women with POI

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

#### Clinical evidence

Women with POI seeking to embark on pregnancy should be given the same pre-conception advice as any woman with regard to ensuring she is immune to rubella and, ideally, has optimized her 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 6.3*), it would be reasonable to consider a general assessment for all women prior to oocyte donation with measurement of blood pressure and renal function.

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 3.2*. Specifically, thyroid function should be tested, as should adrenal antibodies. A karyotype 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 6.3*). Although some long-term follow up studies of childhood cancer survivors are very reassuring and showed no incidences of peripartum cardiac failure ([van Dalen, et al., 2006](#)), cases have been described ([Gorton, et al., 2000](#); [Bar, et al., 2003](#); [Altena, et al., 2012](#)). 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 Turner Syndrome is very high risk. Three expert groups have reviewed the care of women with TS, two specifically considering pregnancy and pre-conception screening ([Bondy and Turner Syndrome Study Group, 2007](#); [Cabanes, et al., 2010](#)). The recommendations of each are based on systematic reviews of the published literature and expert opinion.

Women with TS considering pregnancy (spontaneous or oocyte donation) should have a thorough medical assessment with special consideration paid to the cardiovascular system. Thyroid and liver function should be updated and screening for diabetes performed ([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. All three reviews recommend that any abnormality should be a contra-indication to pregnancy, including those that have been corrected surgically. This is a very 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.

Aortic dissection occurred in 33% of TS women with an aortic root over 2.5 cm/m<sup>2</sup> 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 ([Cabanes, et al., 2010](#)). The Practice Committee of the ASRM 2012 offers a more conservative recommendation with a cut-off value of 2.0 cm/m<sup>2</sup>. The consensus is that aortic root measurement is best expressed as aortic size index (ASI) due to the short stature of the affected women.

Cabanes and colleagues also recommend a renal ultrasound scan for structural abnormalities and, if hypertensive, for renal artery stenosis along with measurement of urea and electrolytes ([Cabanes, et al., 2010](#)).

## **Conclusion and considerations**

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

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 assessments 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.

## Recommendations

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 karyotype.	C
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.	D
Women with Turner Syndrome should be assessed by a cardiologist with a specialist interest in adult congenital heart disease and should have a general medical and endocrine examination.	GPP
Women with POI should have their blood pressure, renal function, and thyroid function assessed prior to pregnancy.	C
Pregnancy in some women can be of such high risk that clinicians may consider oocyte donation to be life threatening and therefore inappropriate.	GPP

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# 7. BONE HEALTH IN WOMEN WITH POI

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## Introduction

The beneficial effects of estrogen on bone have long been recognized, and likewise the adverse effect of natural menopause on bone loss, mineral density and fracture risk ([Ahlborg, et al., 2001](#); [Sirola, et al., 2003](#); [Banks, et al., 2009](#)).

Estrogen deficiency results in increased bone remodelling. Increased osteoclast activity results in increased bone resorption, and that in turn induces an increase in osteoblast activity and bone formation, however with resorption exceeding formation. The rapid remodelling of estrogen deficiency means there is a net loss of bone, amounting to 2-3% per year early after menopause. Additionally, the slow mineralization of new bone (over at least 6 months) causes new bone to be less mineralized than older bone. The effects on bone resorption are mediated by increased activity of the nuclear factor kappa-B ligand (RANKL) on RANK receptors on osteoclasts and their precursors, and by increases in pro-inflammatory cytokines such as interleukin 1 beta and tumour necrosis factor also leading to an increased bone resorption. The increased bone remodelling is reversible in the short term, but with time the high osteoclast activity results in perforation of the cancellous bone plates so that there is a loss of the bone micro-architecture: this form of bone loss is irreversible, and primarily affects trabecular rather than cortical bone.

However the rate of bone loss after the menopause slows after approximately 10 years, and thereafter is similar to that of eugonadal age-matched men, i.e. is age-related rather than reflecting hormone deficiency after that time point ([Manolagas, et al., 2013](#)).

## 7.1 POI and consequences for bone health

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

#### Clinical evidence

The effect of POI-associated estrogen deficiency on bone is among the most clearly established adverse consequences of the condition, although asymptomatic in most women for many years until a fragility fracture occurs. Low bone mineral density (BMD), usually assessed by dual energy X-ray absorptiometry (DEXA), is a risk factor for fracture ([Marshall, et al., 1996](#)), and widely used as a surrogate in assessing fracture risk and treatment effects, although increasingly fracture itself is the primary outcome of interventional trials. DEXA can identify osteoporosis (defined as bone mineral density more than 2.5 standard deviations below peak BMD for the appropriate reference group (i.e. young women from the same population) with the T-score used to show the difference in number of standard deviations. Osteoporosis is therefore a T-score of  $\leq -2.5$ , with osteopenia defined by a T-score  $\leq -1$  and  $> -2.5$ . Z-scores are also frequently reported and express the number of standard deviations a patient's BMD differs from the average BMD of an age- and sex-matched control group.

Women with POI have reduced BMD, and this has been associated with the presence, degree, and duration of estrogen deficiency. Reduced BMD in POI has been established in many studies investigating women with POI of different aetiologies, compared to reference populations. This includes women with idiopathic POI ([Popat, et al., 2009](#)), Turner Syndrome ([Bakalov, et al., 2003](#); [Freriks, et al., 2011](#)), gonadal dysgenesis ([Park, et al., 1999](#); [Han, et al., 2008](#); [Michala, et al., 2008](#)), following chemotherapy or oophorectomy ([Ratcliffe, et al., 1992](#); [Castaneda, et al., 1997](#); [Hadjidakis, et al., 1999](#)) and in populations of mixed aetiology ([Conway, et al., 1996](#); [Bachelot, et al., 2009](#)). In a study of 323 women with POI (including 73 with Turner Syndrome), aged 17-39 years, BMD was lower in those with primary than secondary amenorrhoea, although lower in both groups than in age-matched controls ([Conway, et al., 1996](#)). In the primary amenorrhoea group, lumbar spine BMD was 26% lower than in controls. BMD was positively related to the presence of follicles on ovarian ultrasound and with uterine volume, used as markers

of estrogen production. Comparable results were reported in a French cohort of 183 women with POI with normal karyotype, median age 28 years ([Bachelot, et al., 2009](#)). Although most (64%) had taken a range of HRT regimens previously, 43.7% had osteopenia and 13.7% had osteoporosis, mostly of the lumbar spine. Factors associated with low BMD were primary amenorrhoea, duration of POI, and low body mass index (BMI).

In a recent report of a large population of 442 mostly Caucasian women with idiopathic POI and mean age 32 years (range 18-42), BMD was also lower than in controls. The difference in BMD was much less than in earlier publications, being 2 to 3% lower than controls at the lumbar spine and hip ([Popat, et al., 2009](#)). BMD was determined at a mean interval since diagnosis of 2.9 years (although there was a mean interval of 4.4 years between the onset of irregular menses and diagnosis). Identified risk factors for low BMD (Z-score <-2) were age <20 years at onset of irregular menses, >1 year delay in diagnosis, low serum vitamin D concentrations and low dietary calcium intake, non-compliance with estrogen replacement and lack of exercise, but not cigarette smoking.

A substantial difference in BMD (8.3%) was also 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](#)). Oophorectomy and chemotherapy for gynaecological cancer has also been associated with low BMD in comparison to oophorectomy for benign indications ([Stavraka, et al., 2013](#)).

The prevalence of osteoporosis in POI appears to be in the range 8-14% ([Bachelot, et al., 2009](#); [Popat, et al., 2009](#)) compared to zero in a small control group ([Popat, et al., 2009](#)). Twelve percent of a group of 150 women with Turner Syndrome, of mean age 31 years, who were undergoing systematized assessment, were found to have osteoporosis, with a further 52% having osteopenia ([Freriks, et al., 2011](#)). Osteopenia/osteoporosis was the most common new diagnosis made, although 70% had been receiving medical care for their Turner Syndrome. Women with Turner Syndrome are frequently of reduced height: BMD should be adjusted to allow for this as otherwise it would be underestimated. A prevalence of osteoporosis of 18% and of osteopenia of 33% was reported in a relatively small group 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](#)).

There are substantial data linking low BMD to fracture risk in postmenopausal women (e.g. ([Johansson, et al., 1993](#); [van der Klift, et al., 2004](#))) but no data have been identified specifically assessing fracture risk in women with POI. Early natural menopause (before 45 years) has been associated with increased risk of vertebral fracture ([Gardsell, et al., 1991](#); [van der Klift, et al., 2004](#)). A questionnaire-based study of 7459 women indicated that menopause before the age of 49 was associated with an increased risk of fracture (OR 1.59) ([Johansson and Mellstrom, 1996](#)), and while in the Million Women Study the relative risk of hip fracture risk was significantly higher in postmenopausal than premenopausal women aged 50-54 years (adjusted RR 2.22; 95% CI 1.22-4.04; p = 0.009), age at menopause had little, if any, effect on hip fracture incidence occurring commonly at older age ([Banks, et al., 2009](#)). A recent prospective analysis in a moderately sized cohort (n= 390) identified that natural menopause before age 47 years, was not associated with increased fracture risk up to age 82 years, but low BMD at age 48 years was, RR 1.36 (CI 1.15-1.62) per standard deviation decrease in baseline BMD ([Svejme, et al., 2013](#)). It therefore appears that while recent menopause may increase the risk of (hip) fracture, this increased risk reduces with time and increasing age, with the latter being the main determinant of fracture incidence.

In an early study comparing women who had undergone a surgical menopause (i.e. BSO, at mean age 45.3 years) compared to hysterectomy alone, the prevalence of fractures at age 70 was significantly higher at 38.9% in the

BSO group compared with 23.5% in the hysterectomy only group, and BMD was lower ([Johansson, et al., 1993](#)). Conversely in the Nurses' Health study of over 29,000 women who had had a hysterectomy, 55.6% with BSO, BSO was not associated with increased risk of hip fracture although mean age at BSO was 46.8 years ([Parker, et al., 2009](#)).

## Conclusion and considerations

The effect of POI-associated estrogen deficiency on bone is among the most clearly established adverse consequences of the condition. Women with POI have been shown to have reduced BMD and possibly an increased risk of fracture later in life.

## Recommendations

POI is associated with reduced bone mineral density (BMD).	B
Reduced BMD is very likely to indicate that POI is associated with an increased risk of fracture later in life, although this has not been adequately demonstrated.	GPP

## 7.2 Interventions for bone health in POI

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

#### Clinical evidence

##### Non-pharmacological approaches

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 ([Rizzoli, 2008](#); [The North American Menopause Society, 2010](#); [Christianson and Shen, 2013](#)). While there are few data directly relating to women with POI, it is considered that the same beneficial effects will apply.

Calcium is essential for bone health, and there is evidence that calcium supplementation in older women reduces the risk of fracture. The recommended nutritional intake (RNI) for calcium is 1000mg/day, and for vitamin D 800IU/day ([Food and Agricultural Organization of the United Nations and World Health Organization, 2001](#)). Many adult women ingest less than this: in patients presenting with a recent fracture in the Netherlands, more than 90% were found to have inadequate vitamin D status and/or calcium intake ([Bours, et al., 2011](#)). Higher calcium intake during growth and early adulthood is associated with higher peak bone mass. There is an important interaction with estrogen status, as estrogen increases gut absorption of calcium ([Shapses, et al., 2012](#)) and decreases renal calcium excretion ([Dick, et al., 2005](#)). However, based on recent concerns of a potential association between calcium supplement use and increased risk of myocardial infarction, calcium supplements should not be prescribed when dietary calcium intake is adequate (1000 – 1200 mg/day) ([Challoumas, et al., 2013](#)).

##### Hormone replacement therapy

Large, randomized trials have shown that HRT in postmenopausal women can improve BMD and reduce vertebral and hip fracture risk ([The Writing Group for the PEPI, 1996](#); [Wells, et al., 2002](#); [Cauley, et al., 2003](#)). European guidance on the diagnosis and management of women with osteoporosis in postmenopausal women is available,

providing a framework for risk assessment and treatment in older women (Kanis, *et al.*, 2013). In contrast, there are very few and mainly small prospective studies of the effects of HRT on BMD in women with POI and none were identified with fracture as a primary outcome.

Estrogen replacement has been shown to have beneficial effects on BMD in women following premenopausal surgical oophorectomy. In a placebo-controlled study of 58 women (mean age 48 years, followed for an average of 9 years) after oophorectomy, mestranol reduced bone loss with less reduction in vertebral body height (Lindsay, *et al.*, 1980). Similarly, in 33 women (mean age 45 years) taking conjugated equine estrogen (0.6mg, with calcium supplementation) for one year after oophorectomy, spine BMD did not fall significantly (-1.5%) whereas it fell by 6.1% in women taking medroxyprogesterone acetate (Prior, *et al.*, 1997). Estrogen treatment also suppressed the rise in bone resorption markers following oophorectomy.

An open-label, randomized controlled crossover pilot trial compared physiological sex steroid replacement (pSSR: transdermal E2, 100-150mcg/day, with vaginal progesterone for 2 weeks per month) with the combined oral contraceptive pill (COCP) in 34 women with POI. The women had a range of aetiologies, including Turner Syndrome and chemotherapy-induced as well as idiopathic POI, and only 18 completed the study (Crofton, *et al.*, 2010). Lumbar spine BMD increased during pSSR treatment, but not significantly during COCP treatment. There were also differences in bone turnover markers, with bone formation markers increasing during pSSR treatment but decreasing during COCP treatment. Bone resorption markers decreased in both groups.

Oral estrogen (0.625mg/day conjugated estrogen with cyclical dydrogesterone) has also been investigated in a prospective study of young women with TS (Kodama, *et al.*, 2012). HRT increased lumbar spine BMD in all groups of women. The age at which adult replacement was initiated was inversely related to the increment in BMD achieved.

Estradiol replacement may have a more beneficial effect on BMD compared to ethinylestradiol, as in the COCP, although the data are limited, see [section 12.3a](#).

### **Pharmacological approaches**

The bisphosphonates alendronate, etidronate and risedronate, the selective estrogen receptor modulator raloxifene and the parathyroid hormone derivative teriparatide all reduce the risk of vertebral fracture in postmenopausal women with osteoporosis (Stevenson, *et al.*, 2005). 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 anti-osteoporosis therapy, since most randomised controlled trial evidence for the efficacy of interventions is based on co-administration with calcium and vitamin D supplements.

The bisphosphonate group of drugs act by reducing bone resorption by being selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of the bone-resorbing osteoclasts. This increases BMD, and there is good evidence that they reduce vertebral fracture risk by 50-60% and non-vertebral fractures by 20 -30% in women with osteoporosis (Stevenson, *et al.*, 2005). In addition to daily administration, these drugs are effective when taken once weekly, and are also effective when administered as annual intravenous treatments.

There are no trials of bisphosphonates in women with POI, but there is evidence that they are beneficial in preventing chemotherapy-associated bone loss in women aged >40 years (e.g. (Shapiro, *et al.*, 2011).

Bisphosphonates remain incorporated in bone for a long period of time, which has led to concern over use in young women, and particularly in relation to future pregnancy. There is no direct evidence but it is regarded as prudent to withdraw oral bisphosphonate therapy for at least 1 year in women planning pregnancy. Risedronate has shorter retention in bone than zoledronate.

Before starting bisphosphonate therapy in younger women it should also be kept in mind that the relation between low BMD and fracture risk depends very much on age ([De Laet, et al., 1997](#); [Kanis, 2002](#)).

### **Selective estrogen receptor modulators (SERMs)**

Selective estrogen receptor modulators (SERMs) have mixed functional estrogen receptor agonist or antagonist activity, depending on the target tissue, and this varies between drugs. Raloxifene reduces bone loss and the risk of vertebral (but not non-vertebral) fractures by 30 to 50 % in postmenopausal women with osteoporosis ([Ettinger, et al., 1999](#)). It increases the frequency of hot flushes and is associated with increased risk of venous thrombosis, but with reduced risk of invasive breast cancer. Other SERMs include bazedoxifene, which also reduces fracture risk in postmenopausal osteoporosis without stimulating breast or endometrium ([Silverman, et al., 2008](#)). Tamoxifen, like other SERMs, is beneficial for bone health in women who are estrogen deficient.

### **Other treatments for osteoporosis**

Teriparatide is given by daily injection for up to 2 years, and reduces the risk of vertebral and non-vertebral fracture. Strontium ranelate also reduces both vertebral and non-vertebral fracture risk in postmenopausal women, although the mechanism of action is unclear. Strontium ranelate should only be used in patients with severe osteoporosis and a high risk of fractures in the absence of alternative treatment options. Furthermore, strontium ranelate should never be prescribed to patients with a history of heart or circulatory problems (based on recommendations of the European Medicines Agency).

Recent developments in understanding of the genetic and biological mechanisms involved in bone resorption has revealed new therapeutic targets for antiresorptive treatments. Several of these new drugs act by targeting specific pathways within the osteoclastic cells. These include denosumab, a receptor activator of RANKL-inhibitor, which given every 6 months subcutaneously, improves bone mineral density and prevents new vertebral and non-vertebral fractures with a similar efficacy to alendronate. Other approaches, such as cathepsin-K inhibitors and antibodies against sclerostin, are in phase III clinical trials.

## **Conclusion and considerations**

There are a number of modifiable risk factors associated with fracture risk that are of potential relevance to young women with POI. These include smoking, lack of exercise, calcium and vitamin D status and alcohol consumption and low body weight ([Christianson and Shen, 2013](#)). Some of these have been associated with low BMD if not fracture risk in women with POI ([Popat, et al., 2009](#)). There appears no reason that the association between these factors and fracture risk would not apply to women with POI, thus it appears appropriate to advice of these modifiable risk factors.

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 there are few data on its effect on fracture risk. The combined oral contraceptive pill is widely used and frequently assumed to provide adequate bone protection but the evidence for this is unclear. ([see section 12.3a](#))

Currently there are no data on the use of non-hormonal treatments for osteoporosis in POI.

## **Recommendations**

Women should maintain a healthy lifestyle, involving weight-bearing exercise, avoidance of smoking, and maintenance of normal body weight to optimize bone health.	GPP
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A balanced diet will contain the recommended intake of calcium and vitamin D. Dietary supplementation may be required in women with inadequate vitamin D status and/or calcium intake, and may be of value in women with low BMD.	C
Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.	C
The combined oral contraceptive pill may be appropriate for some women but effects on BMD are less favourable	C
Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies to women desiring pregnancy.	C

### 7.3 Monitoring bone health in POI

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

##### **Clinical evidence**

Dual-Energy X-ray Absorptiometry (DEXA) is the key investigation in the diagnosis and management of women with suspected osteoporosis. Other techniques include quantitative ultrasound (QUS), quantitative computed tomography (QCT) applied both to the appendicular skeleton and to the spine, peripheral DEXA, digital X-ray radiogrammetry and other radiographic techniques. While DEXA 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. The use of ultrasound assessment in fracture risk prediction has been demonstrated ([Moayyeri, et al., 2012](#)), but it is currently used only as a pre-screening tool, requiring subsequent diagnosis confirmation by DEXA: importantly, ultrasound may be normal in patients with osteoporosis on DEXA ([Pisani, et al., 2013](#)).

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 (currently 45 countries) but the lower age for which this tool is applicable is currently 40 years.

Biochemical markers of bone turnover have been suggested to be useful for the prediction of fractures and rapid bone loss, and for monitoring the treatment of osteoporosis. 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. Significant associations between short-term decrease in markers of bone turnover and reduction in risk of fracture with the use of anti-resorptive agents have been reported but lack of standardization complicates use ([Vasikaran,](#)



*et al., 2011; Johansson, et al., 2014*) and they are currently not recommended in clinical practice (*Burch, et al., 2014*).

Initial assessment of bone health may include DEXA scan to provide a baseline measurement. However, if the duration of POI is short and estrogen therapy is initiated, it is unclear whether DEXA should be performed in all women. Long duration of estrogen deficiency or other risk factors (e.g. history of low impact fractures) should lead to DEXA assessment. If a baseline DEXA is performed, and BMD is within the normal range, it is unclear whether BMD measurement should be routinely rechecked. DEXA involves X-rays, which should be avoided unless there is a specific indication, although radiation exposure from DEXA is very low.

HRT induced improvements in BMD are relatively small (approximately 2 % per year) when compared to the error of repeat measurements (1–2 %). Therefore the interval between repeat measurement must be fairly long and a 5-year interval has been suggested in European guidance (*Kanis, et al., 2013*). However, when there is 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.

### Conclusion and Considerations

Based on several studies showing that women with POI have reduced BMD (see section 7.1), BMD measurement may be considered.

Dual-Energy X-ray Absorptiometry (DEXA) is the most reliable assessment for BMD and the amount of ionising radiation used is very small. When repeat measurements are indicated, intervals of several years are required based on the limitations of DEXA for measuring small changes in BMD.

Furthermore, BMD testing may be considered useful if the results will influence a management decision, i.e. change in treatment.

### Recommendations

It is important to consider bone health at diagnosis in POI, and during ongoing care.	GPP
Measurement of BMD at initial diagnosis of POI should be considered for all women, but especially where there are additional risk factors.	C
If BMD is normal and adequate systemic estrogen replacement is commenced, the value of repeated DEXA scan is low.	GPP
If a diagnosis of osteoporosis is made and estrogen replacement or other therapy initiated, 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.	GPP

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## 8. CARDIOVASCULAR HEALTH IN WOMEN WITH POI

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### Introduction

Since the end of the 1950's it has been recognised that women show increased cardiovascular morbidity after premenopausal oophorectomy (Robinson, *et al.*, 1959; Parrish, *et al.*, 1967). It has been postulated that women with POI may be at higher risk for cardiovascular disease (CVD) and death due to loss of ovarian function and subsequent deficiency of endogenous estrogens. Several 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.

### 8.1 POI and consequences for the cardiovascular system

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

#### Clinical evidence

Many cohort studies have shown that women with natural POI before the age of 40 years have earlier onset of coronary heart disease (Atsma, *et al.*, 2006) and increased CVD mortality (van der Schouw, *et al.*, 1996; Cooper and Sandler, 1998; Hu, *et al.*, 1999; Jacobsen, *et al.*, 1999; de Kleijn, *et al.*, 2002; Jacobsen, *et al.*, 2003, 2004; Mondul, *et al.*, 2005; Lokkegaard, *et al.*, 2006; Hong, *et al.*, 2007; Baba, *et al.*, 2010; Gallagher, *et al.*, 2011).

A meta-analysis involving 10 observational studies comprising 190,588 women followed for 4-37 years found POI an independent though modest risk factor of ischemic heart disease and overall CVD, but not of stroke (Roeters van Lennep, *et al.*, 2014). This association between POI and ischemic heart disease was significant in Western populations and not in Asian populations. A different impact of POI is also reported by Shanghai Women's Health Study with CVD mortality being only non-significantly increased (Wu, *et al.*, 2014).

Women undergoing prophylactic 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.*, 2009; Barrett-Connor, 2013). A population-based prospective study from Japan showed that women experiencing menopause before the age of 40 are at an increased risk of cerebral infarction (Baba, *et al.*, 2010).

In the study of van der Schouw and colleagues, the distinction was made between early natural and surgical menopause with an HR of 1.67 (95% CI 1.16-2.40) for CVD mortality in women with early natural menopause compared to women with menopause > 51 years (van der Schouw, *et al.*, 1996).

It is possible that increased cardiovascular risk factors predispose to an earlier age at menopause, perhaps via an effect on ovarian blood flow. Kok and colleagues found a link between heart disease risk and age at natural menopause in the Framingham Heart Study cohort (Kok, *et al.*, 2006). It is difficult to know if these findings extend to women with spontaneous POI as only three women had cessation of periods under the age of 40 years in the cohort considered, whose age at study entry ranged from 38 to 55 years.

#### ***Cardiovascular effects of spontaneous and surgical POI***

Women with pre-menopausal estrogen deficiency develop earlier signs of endothelial dysfunction (Kalantaridou, *et al.*, 2004) and premature atherosclerosis (Clarkson, 2007).

Early menopause has been newly identified as a risk factor for non-procedurally-related venous thromboembolism (Canonica, *et al.*, 2014).

After correction for age, body mass index, and smoking, women with POI presented with significantly higher triglyceride and marginally lower HDL levels than controls of the same age range not using oral contraceptives (Knauff, *et al.*, 2008).

Surgical menopause (hysterectomy and bilateral oophorectomy for benign conditions) in pre-menopausal women (aged 46-53 years) induced an increase in total, LDL cholesterol, and lipoprotein(a) within the next 2-3 months; HDL cholesterol decreased significantly during 3 months (Bruschi, *et al.*, 1996).

In a group of recently menopausal women, specific platelet functions and concentrations of circulating activated cell membrane-derived procoagulant microvesicles changed with individual components of the metabolic syndrome (Jayachandran, *et al.*, 2011). The prevalence of the metabolic syndrome increases with menopause and may also contribute to the acceleration of CVD thereafter.

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 suggests 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 have a higher prevalence of 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, 2008b). A bicuspid aortic valve is also associated with aortic wall abnormalities including ascending aortic dilatation, aneurysm formation, and aortic dissection. There seems to be generalized dilatation of major vessels in women with Turner Syndrome, including the brachial and carotid arteries as well as the aorta. Estrogen deficiency contributes to greater intima-media thickness and altered wall dynamics, but not to increased calibre of vessels (Ostberg, *et al.*, 2005).

Adults with Turner Syndrome have a high prevalence of electrocardiographic conduction and repolarization abnormalities, right axis deviation, T-wave abnormalities, accelerated atrioventricular conduction, and QTc prolongation (Lin, *et al.*, 1998).

A major concern in Turner Syndrome (TS) remains the rare but often fatal aortic dilatation, dissection or rupture in relatively young individuals. 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). Systemic hypertension is common in TS and, therefore, may be the most important treatable risk factor for aortic enlargement and dissection (Bondy and Turner Syndrome Study Group, 2007).

In addition to the burden of congenital heart defects, women with TS are twice as likely to develop coronary heart disease and/or cerebrovascular disease as the general population (Gravholt, *et al.*, 1998). Women with TS have an excess of several cardiovascular risk factors including hypertension, obesity, impaired glucose tolerance, and hyperlipidaemia (Turtle, *et al.*, 2013). In 1400 women with TS, CVD mortality was four times higher compared to healthy women (Swerdlow, *et al.*, 2001).

### **Conclusion and considerations**

Women with POI show increased cardiovascular morbidity and mortality regardless of the cause of the ovarian insufficiency.

Patients with Turner Syndrome have a higher prevalence of aortic coarctation and bicuspid aortic valve, thus being at higher risk for infective endocarditis and development of clinically significant aortic stenosis or regurgitation; they also have a more than doubled chance of developing coronary heart and cerebrovascular disease, and an increased risk of aortic dilatation and rupture.

All patients with newly diagnosed Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease (baseline ECG and echocardiography and/or CT or MRI) and periodically monitored. Periodic screening of the aortic diameter appears to be justified also in individuals without congenital heart disease ([Bondy, 2008a](#)). Monitoring frequency and treatment modalities have to be decided on an individual basis until more information on outcomes becomes available. Annual screening of cardiovascular risk factors is mandatory.

## Recommendations

Women with POI are at increased risk of cardiovascular disease and should be advised of risk factors that they can modify through behavioural change (e.g. stopping smoking, taking regular weight-bearing exercise, healthy weight).	B
All women diagnosed with Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease.	C

## 8.2 Estrogen replacement and cardiovascular risk factors in POI

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

#### Clinical evidence

##### Spontaneous and surgical POI

Oophorectomy and early menopause are associated with a markedly increased incidence of coronary heart disease 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](#)).

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 normal 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 typical 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 ([Mercurio, et al., 2004](#)). Similarly, Kalantaridou and colleagues reported that young women with premature ovarian insufficiency (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 HRT in women with natural or surgical premature menopause have not been studied in long-term trials ([Hendrix, 2005](#); [Kalantaridou, et al., 2006](#)).

In an observational Danish female nurses study ([Lokkegaard, et al., 2006](#)), 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. For the group of women experiencing menopause after oophorectomy, a threefold increase in ischemic heart disease was observed among never users compared to ever

users of hormone therapy (however, based on few cases). The effect of hormone therapy was most pronounced for the subgroup of current users in 1993 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<sup>2+</sup> kinetics in coronary endothelial cells thus having antiarrhythmic effects in cardiac myocytes (Nakajima, *et al.*, 1999). There is also evidence that estrogens 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).

Due to the complexity of estrogen and progestogen receptor systems, there may be different effects of HRT in younger and healthier women (e.g. women with early menopause starting treatment within 3 years of their final menstrual period), in comparison with older women (e.g. women with age at menopause higher than 50, starting treatment 10 years after their final menstrual period) (Atsma, *et al.*, 2006; Ouyang, *et al.*, 2006). A higher level of enzymes involved in estrogen metabolism and higher expression of the estrogen receptors have been observed in the vascular smooth muscle cells obtained from the aortas of women with mild atherosclerosis than in the cells obtained from the aortas of women with severe atherosclerosis (Nakamura, *et al.*, 2005). These observations agree with experimental data from different animal models indicating that estrogen administration protects against atherosclerosis only if vessels are healthy without established atherosclerosis (Clarkson, 1994; Mikkola and Clarkson, 2006) In more advanced stages of atherosclerosis, oral estrogen administration can have negative effects on the cardiovascular system via its prothrombotic effects possibly contributing to plaque instability (Clarkson, 1994; Walsh, *et al.*, 2000). In comparison with a 12-month standard regimen, physiological sex-steroid replacement therapy (transdermal estradiol 100µg + 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 replacement therapy (17β-estradiol at 1mg, 2mg, and 4mg) resulted in a reduction of carotid intima-media thickness along with increased serum HDL and decreased plasma glucose (Ostberg, *et al.*, 2007).

### Turner Syndrome

Short-term studies of HRT in adult women with Turner Syndrome have failed to show a favourable effect on lipid profile (Gravholt, *et al.*, 1998; Elsheikh, *et al.*, 2000). The lack of effect on serum lipids suggests that the effects of HRT on aortic compliance may be mediated by improvement in endothelial function.

### **Conclusion and considerations**

Hormone therapy in POI has beneficial effects on plasma lipids, blood pressure, insulin resistance, and endothelial function. There is an urgent need for large-scale long-term randomized prospective studies to determine the optimal routes and regimens of HRT. In the absence of long-term randomized prospective data, treatment should be individualized according to choice and risk factors.

### **Recommendation**

Despite lack of longitudinal outcome data, hormone replacement therapy with early initiation is strongly recommended in women with POI to control future risk of cardiovascular disease; it should be continued at least until the average age of natural menopause.	C
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## 8.3 Monitoring of cardiovascular risk factors

### Introduction

Although the absolute CVD risk in women at middle age is still relatively low, premature estrogen deficiency adds to the 'life-time' CVD risk in women.

Conventional risk stratification for cardiovascular disease using various charts (e.g. SCORE based on gender, age, smoking status, systolic blood pressure and total cholesterol or the ratio of total cholesterol/HDL) may fail as POI women may be classified falsely as low risk because they are young. The SCORE chart currently suggested by the guidelines from the European Society of Cardiology (ESC) is not available for age groups younger than 40 years ([Perk, et al., 2012](#)). However, women with POI are at high relative risk for cardiovascular disease compared with individuals of the same age, as explored in section 8.1.

### **KEY QUESTION: SHOULD CARDIOVASCULAR RISK FACTORS BE MONITORED?**

### Clinical evidence

#### Spontaneous and surgical POI

Among standard coronary risk factors such as serum cholesterol, blood pressure, and obesity, only serum cholesterol increases at the time of menopause, and this is related to the increase in coronary heart disease observed after menopause. Women with early menopause have a higher prevalence of coronary heart disease than those experiencing late menopause. This is partly related to the exposure to higher serum cholesterol levels for a longer period than in those experiencing late menopause. The increase in serum cholesterol at the time of menopause is greater than that after menopause (from early to late post-menopause). This is consistent with the finding that menopause affects serum cholesterol, but not BMI or systolic blood pressure (BP) ([Akahoshi, et al., 2001](#)). In the study of Knauff, loss of ovarian function at a very early age (< 40 years) was associated with higher triglycerides and marginally lower HDL ([Knauff, et al., 2008](#)).

Glucose metabolism may be abnormal in women with POI and autoimmunity may contribute, to a small extent, both to type 1 diabetes and POI. In a study of patients with POI and normal karyotype, a high prevalence of coexisting endocrine disease was found but only 2.5% had glucose abnormalities, which were attributed to autoimmune mediated beta-cell dysfunction. Unfortunately, antibody testing was not performed ([Kim, et al., 1997](#)).

The presence of cardiovascular risk factors in elderly women shows a need for specific indicators of health. Women over 65 show a steadily increasing trend for the next years. A change in lifestyle during menopausal years and in the presence of cardiovascular risk factors can reduce morbidity and mortality for cardiovascular disease, also in elderly women ([Perk, et al., 2012](#)).

#### Turner Syndrome

In addition to the burden of congenital heart defects, women with Turner Syndrome have an excess of several cardiovascular risk factors including hypertension, obesity, impaired glucose tolerance, and hyperlipidaemia. Annual screening for these risk factors should be performed and, if relevant, smoking cessation should be discussed (see Summary Table 8.1 for cardiovascular risk factors). Standardized multidisciplinary evaluation is effective; girls with Turner Syndrome benefit from a careful transition to ongoing adult medical care ([Freriks, et al., 2011](#)).

Hypertension has been reported in up to 50% of adults and a quarter of adolescents with Turner Syndrome. There are no clear recommendations on blood pressure (BP) thresholds or targets for the treatment of hypertension in women with Turner Syndrome. Some authors suggest that BP should be lower than in healthy women ([Turtle, et al., 2013](#)). Other authors have alternatively suggested introducing antihypertensive therapy based on the presence



of two of the three risk factors for aortic dissection, which include hypertension, a bicuspid aortic valve and dilated aortic root, aiming for a systolic BP < 140 mmHg with a tricuspid aortic valve, or < 120 mmHg with a bicuspid aortic valve (Conway, *et al.*, 2010). There is no evidence to suggest which antihypertensive agent is most effective in reducing BP, or which might be favoured for delaying aortic dilatation. Women with Turner Syndrome may have an activated renin-angiotensin system so an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) may be logical (Turtle, *et al.*, 2013). Beta-blockers are an appropriate alternative because resting tachycardia is a common clinical finding, but they may further increase the risk of glucose intolerance (Dahlof, *et al.*, 2005).

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 Turner Syndrome compared with those who have a normal karyotype and POI (elevation of LDL and triglycerides).

### Conclusion and considerations

There are no validated tools for screening risk for CVD 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 'life time' risk for CVD. Furthermore, serum cholesterol and obesity, but not blood pressure, increase during natural menopause.

However, screening for cardiovascular risk factors at diagnosis may be indicated as lifestyle measures during pre-menopause improve health in later years. The GDG considered that blood pressure, weight (with height) and smoking habit should be monitored annually as a minimum, with lipids, fasting glucose and HbA1c being assessed if indicated.

Women with 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 relevant, smoking cessation should be discussed. 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.

### Recommendations

Cardiovascular risk should be assessed in women diagnosed with POI. At least blood pressure, weight and smoking status should be monitored annually with other risk factors being assessed if indicated.	GPP
In women with Turner Syndrome, cardiovascular risk factors should be assessed at diagnosis and annually monitored (at least blood pressure, smoking, weight, lipid profile, fasting plasma glucose, HbA1c)	C

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# 9. QUALITY OF LIFE IN WOMEN WITH POI

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## Introduction

There is no universally accepted definition of 'quality of life'. It could even be said that quality of life (QOL) is what QOL scales pertain to measure, and multiple methods exist. The World Health Organisation (WHO) defines QOL as the individual's "perceptions of their position of life in the context of the culture and value system in which they live and in relation to their goals, standards and concerns" ([Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument \(WHOQOL\), 1993](#)). The WHO has created a scale with six domains: physical health, psychological state, levels of independence, social relationships, environmental features, and spiritual concerns. Similar domains are constructed for most QOL scales. The domain scores are usually added up to yield an overall QOL score. The usefulness of a composite QOL score is debatable in health research, since few health conditions or interventions would claim such widespread impact as to include environmental and spiritual effects. This issue has been raised for POI research ([Kotz, et al., 2006](#)).

## 9.1 POI and consequences for quality of life

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

#### Clinical evidence

The term QOL is often used interchangeably with psychological wellbeing and has become something of a cliché ([Utian, 2005](#)). Within the POI literature on QOL, few studies had set out to specifically and systematically examine QOL patterns and their physical and psychosocial predictors.

The criticism goes beyond the validity of the QOL measure used. POI is not a homogenous and fixed state. 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 quality of life domains, so that the confounding effects of education, occupation, and income may need to be controlled for. For example, a retrospective study with women who had undergone prophylactic salpingo-oophorectomy 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.

The research on POI and quality of life has not yet reached the stage of being able to map specific aspects of POI across different dimensions of QOL. Therefore, this chapter will concentrate on psychological wellbeing where it is a specific focus of POI research.

#### Long-term conditions

In general, long-term medical conditions are associated with a higher prevalence of psychological and mental health difficulties ([Depression in Adults with a Chronic Physical Health Problem: Treatment and Management, 2010](#)). Poorer mental health is known to detrimentally affect capacity to self-manage health maintenance regimes and lifestyle changes leading to poorer health outcome and higher usage of healthcare services ([Improving Access](#)

to [Psychological Therapies, 2008](#)). However, psychological research has focused mainly upon more common chronic diseases. It is currently unclear to what extent POI-affected women compare to other medical populations in terms of distress and wellbeing. With these limitations in mind, studies of varying quality and scale appear to point to a higher prevalence of psychological distress.

### POI

POI is said to be associated with an increased lifetime risk for major depression ([Schmidt, et al., 2011](#)). An early cross-sectional observational study using standardised questionnaires with clinic attendees at a premature ovarian insufficiency clinic found that the women reported high levels of depression and perceived stress and lower levels of self-esteem and life satisfaction, compared to normative data ([Liao, et al., 2000](#)). A more recent cross-sectional opportunistic descriptive study involving clinic patients and support group members also suggested poorer psychosocial adjustment in women with POI ([Mann, et al., 2012a](#)).

A number of comparative studies can also be identified in the literature. In one of them a higher risk of depression and anxiety was reported by women who had had a hysterectomy with oophorectomy compared to without oophorectomy ([Farquhar, et al., 2006](#)), although the groups were not entirely comparable in terms of pre-surgery depression ([Shifren and Avis, 2007](#)). More recently, 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 found 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 highlighted that a reduction in psychological wellbeing is not always accountable in terms of cancer diagnosis and risk. Likewise, a study that compared women who have experienced natural and surgical menopause for benign conditions found that HRQOL was worse for women who have had a surgical menopause ([Bhattacharya and Jha, 2010](#)).

A strong predictor of post-surgical menopause mental health is previous mental health ([Shifren and Avis, 2007](#)). It is important for future studies to control for this factor, if the research is about identifying psychological sequelae. In terms of clinical management, women with a previous mental health history may benefit from additional pre-surgical counselling.

It has been hypothesised that for some women, the association between POI and depression may be suggestive of an overlapping pathophysiology ([Schmidt, et al., 2011](#)). Psychosocial explanations have also been put forward. A study found that scores on Illness Uncertainty, Purpose in Life and Stigma were significantly implicated in scores on Anxiety and Depression, whilst scores on Goal Reengagement and Purpose in Life were associated with scores on Positive Affect ([Davis, et al., 2010](#)). A further study found significant positive relationships between spiritual and functional well-being ([Ventura, et al., 2007](#)).

### Infertility

Few clinicians would dispute the high level of distress in women affected by infertility. Clinical observations are borne out by extensive qualitative research ([Olshansky, 1996](#)). It has been argued that emotional responses to infertility should be understood within a bereavement model ([Syme, 1997](#)). Women and men often choose to keep their fertility problem a secret ([Slade, et al., 2007](#)), and thereby self-limit their access to social support. This may partly account for the low levels of social support reported by people with fertility problems ([Orshan, et al., 2009](#)). Fertility concerns were reported by 71% of the sample in a descriptive study involving clinic patients and support group members, but a strong relationship with self-reports of psychosocial functioning measures was not demonstrated ([Mann, et al., 2012a](#)).

### Vasomotor symptoms

The prevalence of hot flushes and night sweats and their impact on wellbeing is most studied in natural menopause (see for example ([Freeman and Sherif, 2007](#))). Vasomotor symptoms are associated with sleep problems, which may affect mood states, social participation and work performance, as well as overall health-related quality of life ([Utian, 2005](#)). Research in natural menopause further suggests there are important cognitive, emotional, and

behavioural variations in symptom experience and reporting, so that their impact on women can be expected to be highly variable (Hunter and Mann, 2010).

Research suggests that surgical menopause is associated with more severe climacteric symptoms (Benshushan, et al., 2009), although the surgery and natural groups of women differed in age and other potentially confounding parameters. Vasomotor symptoms were reported by a third of women in a recent opportunistic study (Mann, et al., 2012a), but the presence of symptoms explained only a small amount of the variance in psychosocial functioning.

**Conclusion and Considerations**

The limited evidence would suggest that women with POI report lower levels of psychological wellbeing compared to women in the general population. Currently it is far from certain whether this constitutes the psychological sequelae of having a chronic condition or is particular to POI per se.

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 already exist.

**Recommendation**

A diagnosis of POI has a significant negative impact on psychological wellbeing and quality of life.	D
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**9.2 Interventions for improving quality of life in women with POI**

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

**Clinical evidence**

POI is a physical health condition that affects multiple body systems so that some impact on health-related quality of life 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 does not always follow that every woman reporting a reduction in quality of life 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 patients are informed about their diagnosis could significantly affect their level of distress, and that patients expressed a need for clinicians to spend more time with them and provide more information about their condition (Groff, et al., 2005).

**Medical interventions**

One of the rare reviews that focused specifically on the effects of hormone interventions on quality of life in surgically postmenopausal women pointed out a number of methodological deficiencies in the literature (Kotz, et al., 2006). The authors concluded that estrogen with or without testosterone may improve general well-being 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 well-being in some women but only at supra-physiological levels of total testosterone and physiological levels of free testosterone. Since then however, there has been a report based on a randomized, placebo-controlled, parallel-

design investigation of 128 women with 46,XX spontaneous POI over a 12-month period ([Guerrieri, et al., 2014](#)). The research team concluded that augmentation of standard estrogen/progestin therapy with physiologic testosterone in young women with POI did not change reported quality of life 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.

Vasomotor symptoms could be implicated in a reduction of quality of life for some women. For women who need or wish to avoid hormone therapy, there is a need for additional targeted therapies, validated by results from controlled clinical trials that are safe, efficacious, cost-effective, and well tolerated by symptomatic women ([Utian, 2005](#)). 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 quality of life measures ([Rada, et al., 2010](#)).

### 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 psychological clinician, and service constraints. To date however, there is no authoritative evaluative research in 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).

From the 1980s, the evaluation of psychological treatments for hot flushes and night sweats (HFNS) began to appear in the literature, mainly as an alternative to hormone replacement therapy (HRT) for midlife menopause. The highest level evidence to date comes from a randomised controlled trial of a simplified form of cognitive behavioural therapy (CBT) ([Mann, et al., 2012b](#)). The report suggested that both CBT and usual care resulted in a 38% reduction in HFNS frequency. However, compared with the usual care group, the women in the CBT group showed statistically significant and lasting reductions in subjective problem rating of HFNS and improvements in quality of life. Although the trial was carried out with patients with breast cancer unable to use HRT for symptom control, there is no a priori reason why the benefits would not apply to women who suffer from HFNS for other medical reasons.

The psychosocial effects of CBT/relaxation, physical exercise, and a combination of the two interventions were compared in a RCT involving 422 breast cancer patients reporting treatment-induced vasomotor symptoms ([Duijts, et al., 2012](#)). Both interventions, separately and in combination had positive health and wellbeing effects. However, treatment adherence was not optimal. Further development may be required and with different POI clinical populations before these interventions could be incorporated as standard care provision for POI.

Where infertility is centrally implicated in a significant reduction of wellbeing, several hundreds of reports have pointed to psychological interventions ([Boivin, 2003](#)). However, very few specific recommendations have been made as to what the goals and methods should be, let alone how to evidence the effects. A wide range of psychological approaches for infertility have been described that may be relevant in supporting adjustment to the diagnosis of POI. In one review ([Boivin, 2003](#)), twenty-five studies were classified into three categories of intervention: 1) counselling; 2) focussed education (including sex therapy, coping training, support and stress reduction, autogenic training and preparatory information); and 3) 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 quality of life 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.

Managing a stigmatised identity can be expected to be a central psychological task for many women diagnosed with POI. Struggles with stigma may manifest themselves in terms of avoidance to discuss POI, even with close family members and friends. Stigmatisation is generally believed to predispose people to poorer mental health. Studies with women (and men) presenting with fertility problems have confirmed the association between degrees of stigmatisation and psychological distress (Slade, et al., 2007; Davis, et al., 2010). Interestingly, distress 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.

Group interventions can directly help women to reduce social isolation and there is robust evidence for cognitive behavioural group interventions for overcoming problems of self-esteem (Morton, et al., 2012), should this be implicated in an individual’s reduced quality of life, although this is not specific to POI.

An educated patient has a better chance of becoming a healthier one. Open multi-disciplinary education forums to facilitate learning and processing of the multiple aspects of the condition are a cost-effective way of meeting this need, reducing social isolation, and improving patient experience. However, research is needed to evaluate their impact on different dimensions of quality of life.

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.

**Conclusion and Considerations**

How a woman approaches her situation will depend on 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, there is no evidence that additional medical interventions directly lead to significant psychological benefits. Psychological interventions for problems that are associated with POI can lead to positive benefits on quality of life, although the evidence does not come from POI per se.

**Recommendation**

Psychological and lifestyle interventions should be accessible to women with POI.	B
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# 10. SEXUAL AND GENITO-URINARY FUNCTION IN WOMEN WITH POI

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## Introduction

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. The current literature cannot confidently answer questions on female sexuality and POI in ways that are helpful to affected women and close others. Detailed exploration of the potential sexuality effects of POI can only be achieved via multi-method studies with directly relevant samples and preferably without pre-emptive search for medical interventions. This kind of patient-centred primary research is sparse in the clinical literature.

## 10.1 POI and consequences for sexuality

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

#### Clinical evidence

Direct studies of POI and sexuality are limited ([Graziottin and Basson, 2004](#)). Most of the available research has been with women with natural midlife menopause. There are studies on surgical menopause but almost all on a single dimension – sexual desire, with very limited engagement with the multiple dimensions of female sexuality. The effects of life cycle stage, for example for affected adolescent and young adult women, are virtually unknown.

There are similarities between natural and surgical menopause, in terms of the prevalence of vasomotor symptoms and potential attendant sleep disturbance or fatigue, as well as vaginal dryness and dyspareunia. However, studies with these two populations can introduce confounding variables, rendering them at best partially comparable and generalizable to spontaneous POI. In the case of natural menopause, any sexual effect may be age-related (for the women and their sexual partners). In the case of oophorectomy with hysterectomy prior to menopause, the effects may be influenced by the shortening of the vagina, loss of sensitivity and the emotional sequelae of the threat of the illness that had necessitated major surgery ([Rodriguez, et al., 2012](#)). Neither of these scenarios is directly applicable to spontaneous POI.

In terms of research with women presenting with POI, any significant sexual problems could be a primary effect of the physiological changes, or secondary to the attendant emotional burden of the diagnosis, perhaps especially infertility ([King, 2003](#)), which can be expected to have consequences on self-evaluations and relationships for many women and, for some, even (additional) economic hardship as a result of marital ineligibility. Fertility treatment comes with unpredictability and uncontrollability and can be expected to have its own emotional and sexual impact ([Slade, et al., 1997](#)). Therefore, the question of the sexual effects of POI on women is far from straightforward.

Two components of sexual problems have been identified for normal menopause: 1) uncomfortable or painful intercourse from vaginal dryness that becomes more common as menopause progresses; and 2) sexual changes not definitively strongly associated with hormonal changes, such as altered libido and arousal, which are recognised to be associated also with changes in personal, social and economic conditions ([NIH, 2005](#)).

The Cochrane review on concomitant prophylactic oophorectomy at elective hysterectomy failed to identify significant negative psychological or sexual effects on adequately estrogenised premenopausal women ([Orozco, et al., 2008](#)). This aspect of the overall conclusion – deemed tentative by the authors, was partially supported by a case controlled study of sexual function in young women with spontaneous 46,XX POI ([Kalantaridou, et al., 2008](#)). In this rare report that is directly relevant for spontaneous POI and sexuality, the women with POI reported

relatively normal sexual function on the DISF-SR – a widely used evaluation tool. Serum total testosterone levels were significantly correlated with the DISF-SR composite score. However, whilst the proband group scored lower than a control group of menstruating women, there was no statistically significant difference in the number of probands with composite scores below the second centile.

A case-control study evaluating sexual well-being in women with POI concluded that women with POI have diminished general and sexual well-being and are less satisfied with their sexual lives than control women. Of the women with POI, 59% used HRT. There was no difference in sexual well-being or satisfaction between women taking HRT and women not taking HRT. Finally, the authors did not find an association between lower androgen levels and sexual functioning ([van der Stege, et al., 2008](#)).

In contrast, a smaller study of women with spontaneous POI reported a much higher prevalence of sexual dysfunction (62.1%) compared to age-matched controls (OR 2.78, IC 1.29 TO 5.98, P<0.05), using a different validated assessment tool, the Female Sexuality Function Index (FSFI) ([de Almeida, et al., 2011](#)). There are several key differences in study design that could explain these discrepant findings. Women had to be sexually active to be included in the latter study but not the former one. The FSFI was completed at an interview with a psychologist, whereas the DISF-SR is a self-assessment questionnaire. Finally, the prevalence of sexual dysfunction in the control group appears to be high (38%) in the study by de Almeida and colleagues, although this reflects the definition of sexual dysfunction used.

It is important to note that not all women identified by medical researchers as presenting with hypoactive sexual desire disorder (HSDD - a value-laden term heavily contested by academic experts and women’s advocacy groups) have low testosterone levels, and no single testosterone level predicts low female sexual function ([Schwenkhagen and Studd, 2009](#)). Therefore, a number of other factors are likely to be relevant, such as aetiology, life stage, and relationship quality.

An earlier study assessed the psychosexual wellness (as opposed to sexual function, a more performance-based construct) with a group of women aged 19 to 40 with POI ([Liao, et al., 2000](#)). Diminished psychosexual wellness was identified using several of the Multi-dimensional Sexuality Questionnaire subscales. Compared to the MSQ norms, the patient population yielded lower scores on Sexual Esteem, Sexual Assertiveness, and Sexual Satisfaction, and higher on Sexual Anxiety and Sexual Depression.

## Conclusion and considerations

Female sexuality may well be affected by POI, probably at least partly by emotional burden especially of infertility consequent upon it. Given the absence of inter-disciplinary coherence to inform question formulation, findings on the sexual consequences of POI should be interpreted prudently. It is highly unlikely that any finding is generalizable to women across age groups and cultural and economic conditions. Women’s ability to sexually self-determine will profoundly shape their sexual outlook in relation to POI and generally.

Research on sexuality is dominated by a focus on treatment development. This may have contributed to the absence of a rich and nuanced clinical description of the relationship between POI and multiple aspects of female sexuality, and an authoritative knowledge of the mitigating mechanisms and factors based on biological, psychological, and social differences between women. Furthermore, whilst most studies acknowledge multiple factors in sexual experiences, from hormonal to spiritual, there is a lack of commitment to collect quality information from socially diverse samples within a coherent inter-disciplinary framework.

## Recommendation

Routinely inquire about sexual wellbeing and sexual function in women with POI.	GPP
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## 10.2 Interventions for sexuality in POI

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

#### **Clinical evidence**

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'.

#### Estrogen

Estrogen is important for the health and function of the genito-urinary system and dyspareunia will affect sexual function and desire. The treatments for this are reviewed in section 10.3. Estrogen may also be important for other components that contribute to female sexuality, possibly affecting peripheral as well as central neurotransmission (Sarrel, 1987; Rubinow, *et al.*, 1998). However, factors other than estrogen may influence sexuality in POI. A small Brazilian case control study of 36 sexually active women with spontaneous POI aged 18 to 40 years who were taking HRT still had lower scores on the Female Sexual Function Index (FSFI) than did age-matched normal controls (Pacello, *et al.*, 2013). Scores in all domains of the FSFI were lower in the POI group, including reporting more pain and poorer lubrication. This was despite normal vaginal flora and hormonal vaginal cytology, suggesting the cause might not be estrogen-related. The authors reported a lower score for the POI group in a subjective vaginal health index, which included assessing vaginal mucosa elasticity, epithelial integrity, fluid secretion, pH, and "humidity". Although a single clinician assessed all participants, the study was not blinded and the vaginal health index scores did not correlate with the pain and lubrication domains of the FSFI.

#### Testosterone

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.

From about 2000, a series of randomised, placebo-controlled trials of testosterone patches with oophorectomised women have been carried out, 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; Davis, *et al.*, 2008; Panay, *et al.*, 2010). All of the studies have declared conflicts of interest, in terms of involvement from the pharmaceutical industry in study design, statistical analysis and in some cases assistance with the manuscript. Some review papers of testosterone-based interventions also present conflict of interest (Alexander, *et al.*, 2004; Kingsberg, *et al.*, 2008). 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. Whilst adverse events were reported as mild or minimal (always from the researchers' point of view), long-term health and harm remains unknown.

A large number of factors caution against routine recommendation of testosterone therapy. First of all, a large number of exclusion criteria were deployed in the research, 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. Secondly, studies tend not to report the number of eligible women who decline treatment, rendering the level of acceptability to patients unknown (for example, many women may prefer non-medical treatments). Evaluation of patient preferences and experiences by an independent assessor is seldom provided. Thus far the most intensively studied population is Caucasian (and presumably heterosexual) women, making the evidence not yet applicable to other populations. The most frequently treated sexuality dimension is libido, or what the researchers called HSDD, limiting the applicability to other sexual problems. Finally, the small increase in the number of satisfying sexual activities per month renders the clinical significance of treatment rather debatable.

Testosterone patches were used in most of the quoted trials, but they are no longer available, requiring off label use of testosterone gels at 1/5th to 1/10th the male dosage.

### Non-medical approaches

A range of dedicated professional services exist 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 limited knowledge as to what type of intervention works best, for what, in what way, and for whom. Knowledge needs to improve significantly to enable women with POI to make a truly informed choice.

Non-medical approaches for women and couples affected by POI have received scanty scientific attention. 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](#)). Research is underway to evaluate mindfulness-based approaches ([Brotto and Basson, 2014](#)). The trialling of these approaches are however at their infancy.

### Conclusion and considerations

Without a clear conceptual framework for describing and making sense of clinical and non-clinical observations, treatment studies can be said to be premature, and findings are likely to be confusing. Adequate estrogen replacement, with additional local treatment if necessary for dyspareunia, should be ensured in women with POI and sexual dysfunction.

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 short-term use of testosterone patches of 300 µg daily, with the understanding that long-term risks are unknown.

For these 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 may be more acceptable to more women with or without partners.

### Recommendations

Adequate estrogen replacement is regarded as a starting point for normalising sexual function. Local estrogen may be required to treat dyspareunia.	C
Women with POI should receive adequate counselling about the possibility of using testosterone supplementation so that they can make an informed choice, in the knowledge that long-term efficacy and safety are unknown.	B

## 10.3 Genito-urinary symptoms in POI

### KEY QUESTION: WHAT TREATMENTS ARE AVAILABLE FOR GENITO-URINARY SYMPTOMS IN POI?

#### **Clinical evidence**

Prolonged hypoestrogenemia may lead to vulvovaginal atrophy. The prevalence of genito-urinary symptoms in spontaneous POI has not been reported. In women with iatrogenic POI after breast cancer treatment the prevalence of moderate to severe dyspareunia and vaginal dryness was 42% and 49%, respectively ([Leining, et al., 2006](#)). Vaginal lubricants, moisturizers and HRT (both systemic and topical) are used to treat genito-urinary symptoms, such as vaginal dryness, irritation, urinary frequency and incontinence. There are few trials relating specifically to POI and therefore evidence derived from menopause at a regular age has also been used.

#### *Vaginal lubricants and moisturizers:*

Vaginal lubricants and moisturizers may be used when there is a need for local treatment where systemic treatment is contra-indicated, or if women still experience genito-urinary symptoms despite of an appropriate dose of HRT. In a small study of 36 women with POI using HRT (estradiol 1mg or 2mg plus norethisterone acetate (n=21) or conjugated estrogen 0.625mg plus medroxyprogesterone acetate (n=15)), it was identified that these women still had worse sexual performance with more pain and poorer lubrication compared with women with a normal gonadal function. Vaginal trophism, assessed through vaginal cytology, vaginal pH and vaginal health index, was worse according to vaginal health index; however, in both groups the scores were trophic ([Pacello, et al., 2013](#)).

A small double-blind randomised controlled trial (36 participants) compared a gel containing hyaluronic acid to a placebo gel over a 3-month period. Both treatments were found to improve vaginal atrophy scores, erythema, and dryness when compared with baseline and the group using the gel containing hyaluronic acid also had an improvement in burning and itching compared with baseline. However, when the groups were compared directly no significant differences were found ([Grimaldi, et al., 2012](#)). Another double-blind RCT involved 62 postmenopausal women with vaginal atrophy and compared the use of a genistein (a phytoestrogen) vaginal pessary with the use of a hyaluronic acid vaginal pessary daily for 15 days a month for three months. Both treatments improved genital symptom scores, colposcopic and cytological features from baseline, although genistein was more effective on genital symptom score ( $p < 0.001$  vs. hyaluronic acid; other comparisons between the groups not significant) ([Le Donne, et al., 2011](#)).

#### *Local HRT*

The 2006 Cochrane Review on local estrogens for vaginal atrophy included 19 trials with 4162 postmenopausal women ([Suckling, et al., 2006](#)). To date, two very small (39 and 30 participants) open-label trials have assessed a non-hormonal vaginal moisturizer versus vaginal estrogen, both over a 12 week period. In both trials, similar improvements were seen in both groups ([Nachtigall, 1994](#); [Bygdeman and Swahn, 1996](#)). Vaginal estrogen cream significantly improved vaginal health index score as opposed to moisturizing gel in one of the trials: vaginal dryness (weighted mean difference [WMD] 4.46, 95% CI 0.76 to 6.16), vaginal moisture (WMD 1.04; 95% CI 0.77 to 1.31), vaginal fluid volume (WMD 1.04, 95% CI 0.74 to 1.34) and vaginal elasticity (WMD 1.10; 95% CI 0.79) ([Suckling, et al., 2006](#)). When comparing the efficacy of different estrogenic preparations (in the form of creams, pessaries, tablets and the estradiol-releasing vaginal ring) in relieving the symptoms of vaginal atrophy, results indicated significant findings favouring the cream, ring, and tablets when compared to placebo and non-hormonal gel ([Suckling, et al., 2006](#)).

#### *Systemic HRT:*

There are no randomised controlled trials assessing the use of HRT in the treatment of genito-urinary symptoms specifically in POI. The two largest studies in this area addressed the use of selective estrogen receptor modulators

(SERMs). However, there is no indication for SERMs in the clinical context of POI due to their side-effects of vasomotor symptoms (Bachmann, *et al.*, 2010).

There are two observational studies that assess genito-urinary symptoms, amongst other outcomes, in women with POI who chose to take HRT or not. In one study, of 31 women with menopause because of chemotherapy prior to stem cell transplantation, 16 chose to take HRT. At baseline, examination revealed genital atrophy in all 31 women on examination; 54% had symptoms of vulvovaginal atrophy (dyspareunia, itch, burning sensation) and 42% had urinary tract symptoms (dysuria, urinary frequency, mild urinary incontinence). With systemic HRT (various preparations were used), 53% of patients had improvement of vulvovaginal atrophy after 5 weeks (range, 4–12) and 53% had resolved genito-urinary disturbances after 5 weeks (range, 4–8) (Piccioni, *et al.*, 2004). The other study was a questionnaire study of 450 women (mean ages in the three groups 40–45) at high risk of ovarian cancer. Women were either premenopausal at the time of prophylactic bilateral salpingo-oophorectomy (BSO), or were premenopausal at assessment (undergoing gynaecological screening). Of the participants who had BSO (36%), 47% were taking HRT (HRT users). In the BSO group, HRT users and non-users reported similar sexual function as measured by the pleasure, discomfort, and habit scales of the Sexual Activity Questionnaire. Amongst the BSO group, women on HRT had higher levels of sexual discomfort due to vaginal dryness and dyspareunia compared with non-BSO group ( $p < 0.01$ ) (Madalinska, *et al.*, 2006) (table 10.1).

These findings of improved genito-urinary symptoms with HRT are supported by studies in older women. The National Institute of Health (NIH), European Menopause and Andropause Society (EMAS) and International Menopause Society (IMS) recommend estrogen treatment for vaginal dryness (NIH, 2005; Skouby, *et al.*, 2005) (Sturdee, *et al.*, 2010). EMAS recommends using both systemic and topical estrogen initially if symptoms are severe, followed by just topical treatment, for which no long-term risks have been identified (Skouby, *et al.*, 2005).

**Table 10.1 Prevalence of vaginal dryness, dyspareunia, and loss of libido in women after prophylactic bilateral salpingo-oophorectomy (BSO) using HRT or not, compared to premenopausal women undergoing gynaecological screening (Madalinska, *et al.*, 2006).**

	BSO		Premenopausal	p-value	
	HRT user	HRT non user		BSO-HRT user versus premenopausal	BSO –HRT user versus BSO –HRT nonuser
Vaginal dryness	13%	24 %	2%	0.002	ns
Dyspareunia	12%	17%	3%	0.008	ns
Loss of libido	16%	22%	4%	0.002	ns

## Conclusion and considerations

Genito-urinary symptoms, such as vaginal dryness, irritation, urinary frequency, and incontinence, are associated with hypoestrogenism. The exact prevalence of these symptoms in women with POI is not known. Vaginal lubricants, moisturizers and HRT (both systemic and topical) can be used to treat genito-urinary symptoms. Vaginal lubricants and moisturizers may be used when there is a need for local treatment where systemic treatment is contra-indicated, or if women still experience genito-urinary symptoms despite an appropriate dose of HRT. Both local and systemic HRT seem to be effective in relieving genito-urinary symptoms, although RCTs involving women with spontaneous POI have not been undertaken.



## Recommendations

Local estrogens are effective in treatment of genito-urinary symptoms.	A
Clinicians should be aware that despite seemingly adequate systemic hormone replacement therapy (HRT), women with POI may experience genito-urinary symptoms. Local estrogens may be given in addition to systemic HRT.	D
Lubricants are useful for treatment of vaginal discomfort and dyspareunia for women not using HRT.	C

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# 11. NEUROLOGICAL FUNCTION IN WOMEN WITH POI

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## Introduction

Neurological function here was defined for the purpose of this review as objectively assessed cognitive function including memory, dementia, and Parkinson's disease. Stroke is discussed in chapter 8 on cardiovascular health in POI. There are only very few studies available which have directly investigated POI and effects on neurological function. Clinical evidence was divided into spontaneous POI, including genetic disorders and unknown causes (idiopathic), and iatrogenic POI, including oophorectomy and following treatments for breast cancer. Additional indirect evidence includes experimental modelling of POI in studies investigating GnRH agonist treatment in premenopausal women.

## 11.1 POI and consequences for neurological function

### KEY QUESTION: WHAT ARE THE CONSEQUENCES OF POI ON NEUROLOGICAL FUNCTION?

#### Clinical evidence

##### Genetic disorders and POI/early menopause

Cognitive function has been assessed in women with particular genetic disorders reported to have increased likelihood of POI. Women with Turner Syndrome, on average, have worse emotional recognition and lower visuospatial, attentional, working memory and executive function compared to controls matched for age, height, total IQ and socioeconomic status (Ross, *et al.*, 2006).

Fragile-X syndrome is an X-linked inherited condition caused by a mutation of the FMR1 gene, resulting in mental retardation, especially in males. Male carriers of the Fra-X-mutation are also at risk of fragile-X-associated tremor/ataxia syndrome (FXTAS), a late onset neurological problem characterised by ataxia, visuospatial problems, and hypofrontality. Women are less affected (Jacquemont, *et al.*, 2007; Hagerman and Hagerman, 2013). Female carriers of the FMR1 premutation, i.e. those at risk for developing POI, do not suffer from mental retardation and showed similar IQ and cognitive profile as compared to controls (Bennetto, *et al.*, 2001; Wittenberger, *et al.*, 2007). Women with the full mutation had significantly lower IQ, spatial ability, visual memory and executive functioning (but not verbal memory) in comparison to the premutation carriers and controls. Differences were smaller in comparison with IQ-matched controls (Bennetto, *et al.*, 2001).

Trisomy X (47, XXX) is often associated with POI and learning difficulties, such as language and motor (hypotonia) developmental delays, and attentional/executive and socio-emotional behavioural problems (Tartaglia, *et al.*, 2010).

Two studies found that in women with Down's syndrome, an earlier natural age at menopause was independently associated with an increased risk of an earlier onset of dementia (Schupf, *et al.*, 2003; Coppus, *et al.*, 2010). Data on POI were not available.

As the cognitive impairments in these disorders occur before the menopause and apparently do not respond well to estrogen treatment, they probably reflect the genetic abnormalities, rather than a lack of organizational effects of sex steroids.

##### Spontaneous idiopathic POI

No studies were identified that directly investigated neurological function in women with spontaneous POI (without interferences of estrogen treatment).

One cross-sectional observational study compared cognitive function of women with POI (spontaneous POI with normal karyotypes, who were all treated with HRT) with women matched for IQ, education and age and women with TS (Ross, *et al.*, 2004). Overall, women with POI performed similar on the cognitive tests compared to controls; only verbal memory functions were slightly but non-significantly lower in POI women. Women with TS, despite apparently adequate estrogen treatment, had relative difficulty with measures of spatial/perceptual skills, visual-motor integration, affect recognition, visual memory, attention, and executive function.

Indirect evidence from observational studies suggests that an earlier natural menopause might be associated with an increased risk for dementia and cognitive impairment (Hong, *et al.*, 2001; McLay, *et al.*, 2003; Hogervorst, *et al.*, 2011). However, not all studies found an early menopause or a different type of menopause (surgical vs. natural) to be a significant risk factor for Alzheimer's disease (AD) (Amaducci, *et al.*, 1986; Broe, *et al.*, 1990; Paganini-Hill and Henderson, 1994; Kawas, *et al.*, 1997; Baldereschi, *et al.*, 1998; Waring, *et al.*, 1999), while some even found the reverse (Geerlings, *et al.*, 2001).

Observational data on non-iatrogenic POI thus could not be found and the association between natural early menopause and later life dementia risk may be confounded by childhood and/or lifetime deprivation and/or genetic programming affecting cognitive reserve as well as ovarian reserve (Richards, *et al.*, 1999; Whalley, *et al.*, 2004; Kok, *et al.*, 2006; Velez, *et al.*, 2010).

### **Iatrogenic POI after oophorectomy**

Several retrospective observational studies suggested that surgical menopause may, when untreated with estrogen replacement, result in an increased risk for Parkinson's disease by a factor 1.68 (hazard ratio [HR] 1.68; 95%CI 1.06-2.67) (Rocca, *et al.*, 2008) and cognitive impairment/dementia risk by almost a factor 2 (HR 1.46; 95%CI 1.13-1.90) (Rocca, *et al.*, 2007; Phung, *et al.*, 2010; Bove, *et al.*, 2014). These studies all found that the earlier the age at surgical menopause, the higher the risk of neurological functional decline. However, another systematic review on the effect of surgical menopause (in pre- and postmenopausal women) on cognitive functioning reported that some studies suggest a detrimental effect on cognition, while others found no effect. The reviewers commented that all trials on this topic have substantial methodological problems (Vearncombe and Pachana, 2009).

Data from the Mayo clinic with a 15 to 52 year follow-up reported that oophorectomy for non-malignant reasons (n=1489) increased the risk of cognitive impairment by 46% (HR 1.46; 95%CI 1.13-1.90) (Rocca, *et al.*, 2007). Oophorectomy before age 38 increased this risk by a factor 2.89 (HR 2.89; 95%CI 1.86-4.48) (Rocca, *et al.*, 2007). Women undergoing unilateral oophorectomy were younger and separate analyses of this group showed an overall increased risk of cognitive impairment by 64% (HR 1.64 ; 95%CI 1.20-2.23). When unilateral oophorectomy occurred before age 41, this risk was almost a factor 2 higher (HR 1.98; 95%CI 1.26-3.11), and before age 34 it was 4.61 times higher (HR 4.61; 95%CI 2.52-8.43). The risk of Parkinsonism was also increased after untreated unilateral oophorectomy with hysterectomy before age of 41 (HR 3.58; 95%CI 1.61–7.98) (Rocca, *et al.*, 2008). However, small numbers in sub-analysis could have led to an overestimation of the risk. In addition, most (70%) of women undergoing unilateral oophorectomy had also undergone hysterectomy leading to POI.

In a Chinese study, unilateral oophorectomy (with or without hysterectomy) performed before age of natural menopause was also associated with worse word recall, one of the first markers of dementia (Zhou, *et al.*, 2011). In a Nationwide Historical Cohort Study in Denmark, hysterectomy with or without oophorectomy was shown to modestly increase the risk for dementia with onset before the age of 50: hysterectomy only (OR 1.38; 95% CI 1.07–1.78), hysterectomy with unilateral oophorectomy (OR 2.10; 95%CI 1.28–3.45), and with bilateral oophorectomy (OR 2.33; 95%CI 1.44–3.77) (Phung, *et al.*, 2010).

These data only pertained to early onset dementia and cognitive impairment. A recent US-based longitudinal study investigated older women without dementia at baseline (n=1884, mean age 78 years at assessment, n=607 had undergone surgical menopause), and with a follow-up up to 18 years. Each year of earlier surgical menopause

was similar to the cognitive effects associated with 6 months of aging. An earlier age at time of surgical menopause also significantly decreased episodic memory ( $p = 0.0003$ ) and semantic memory ( $p = 0.002$ ), often early indicators of Alzheimer’s disease. An earlier age at surgical menopause was also associated with a higher burden of a global measure of AD neuropathology ( $p = 0.038$ ), in particular of neuritic plaques ( $p = 0.013$ ). Analyses were adjusted for age, education and smoking. In this study, there was no association between age at natural menopause and cognition at follow-up. Data on type of surgery were not reported (Bove, *et al.*, 2014).

Several smaller prospective studies also showed that surgical menopause has an acute detrimental effect on cognitive (in particular verbal memory) function, although these studies were not limited to women who had undergone surgical menopause before the age of 40 (Sherwin, 1988; Nappi, *et al.*, 1999). The negative effect on verbal memory was worse when surgery occurred at a younger age (Nappi, *et al.*, 1999). Another prospective 6 month follow-up study of women (average age 41 years,  $n=53$ ), undergoing surgical menopause indicated a decline in global cognitive function, whereas controls had stable function over time (Farrag, *et al.*, 2002).

In summary, data specific for POI are lacking, but indirect evidence points to the conclusion that hysterectomy with or without oophorectomy for benign reasons before the natural age of menopause increases dementia risk and its markers. This risk seems to be increased with younger age at the time of surgery.

### Iatrogenic POI after breast cancer treatment

A systematic review summarized studies investigating cognitive function after chemotherapy-induced menopause associated with breast cancer treatment (Vearncombe and Pachana, 2009). No consistent conclusions could be drawn from the included studies as only few considered menopausal status as a possible contributor to cognitive dysfunction after chemotherapy and setup, data, and results are mixed.

## Conclusions and considerations

Acutely, iatrogenic POI may be associated with a sharp decline in verbal memory functions. Several longer-term prospective and retrospective observational studies suggest that women with POI after hysterectomy and oophorectomy without hormone replacement treatment had accelerated cognitive decline and a higher increased risk for dementia and Parkinson’s disease.

Differences in findings and the lack of strong conclusions may be explained by experimental design of the studies; not stratifying for age at induction, not including women with cognitive impairment or too young an age at assessment, not recording whether hormone treatment was given up to age 50, and whether or not hysterectomy had also been performed.

## Recommendation

The possible detrimental effect on cognition should be discussed when planning hysterectomy and/or oophorectomy under the age of 50 years, especially for prophylactic reasons.	D
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## 11.2 Interventions for improving neurological function in POI

### Introduction

Hormone treatment for neurological function after menopause at any age is a much debated and highly contentious issue. For older women (> age 60 years) the health risks of treatment exceed the benefits. In an ancillary study of the WHI, postmenopausal women using HRT had an increased risk for a diagnosis of probable dementia as compared to placebo-controls (HR 2.05; 95% CI 1.21-3.48) (Shumaker, *et al.*, 2003). However, the question remains whether younger women with POI might benefit from estrogen treatment to help reduce

cognitive impairment and the risk of dementia in later life ([Vearncombe and Pachana, 2009](#); [Hogervorst, 2013](#); [Henderson, 2014](#); [Rocca, et al., 2014](#)).

Advocates of treatment point to the abundance of basic science data suggesting estrogens' propensity to protect the aging brain (i.e. there is biological plausibility) ([Hogervorst, et al., 2009a](#)), and some (but not all) limited observational data showing increased risk of cognitive impairment after early (surgical) menopause, which in these studies and several small randomised controlled trials was reversed by estrogen treatment.

## **KEY QUESTION: WHAT ARE THE MANAGEMENT OPTIONS FOR THE EFFECT OF POI ON NEUROLOGICAL FUNCTION?**

### **Clinical evidence**

#### **Hormone treatment for spontaneous POI**

The effect of different treatments on neurological function in Turner Syndrome girls has been reported in several studies from the same research group. Only one study was found directly comparing women with POI (n=89) to women with Turner Syndrome (TS) (n=94) and premenopausal controls (n=96) matched for verbal IQ and socioeconomic status, and of similar age. POI and TS women both received estrogen treatment. Women with POI overall had similar performance as controls (but had non-significant lower immediate verbal recall performance). However, despite hormone treatment, women with TS performed worse on visuospatial tests, nonverbal memory, emotional recognition, and attentional/executive function ([Ross, et al., 2004](#)).

The effect of different treatments on neurological function in Turner Syndrome girls has been reported in several studies from the same research group. Estrogen replacement (ethinylestradiol, 12.5-50 ng/kg.day) improved motor speed and nonverbal processing time compared to placebo-treated TS girls (aged 10-12 years.); the estrogen-treated TS group resembled normal controls ([Ross, et al., 1998](#)). Comparable results were obtained for verbal and non-verbal memory ([Ross, et al., 2000](#)).

The effect of androgen replacement therapy was investigated in TS girls, aged 10 to 14 years; 64 TS girls were randomized to receive oxandrolone or placebo for 2 years. The oxandrolone-treated group had improved performance on the working memory domain score after 2 years compared to the placebo group ( $p < 0.03$ .), although not at shorter time points ([Ross, et al., 2003](#)).

Finally, neurocognitive function was assessed - as a secondary outcome - in a study on the effect of growth hormone (GH) treatment (1 to 7 years) on final adult height in TS girls. In this study, GH treatment effects did not affect nonverbal neurocognitive function ([Ross, 2005](#)).

Overall, these limited data suggest that estrogen treatment is adequate and necessary to prevent cognitive decline or low cognitive function in spontaneous POI, but may be less effective in women with TS where some cognitive dysfunction may remain despite treatment.

#### **Modelling POI using GnRH analogues**

POI or acute estrogen deficiency can be modelled by administration of GnRH analogues.

One RCT used add-back therapy of low dose conjugated equine estrogen (0.625 mg) after chemical menopause induction using leuprolide acetate in 19 young women (average age 34 years  $\pm$  2 years) with a fibroid uterus. This study showed a decline in verbal memory performance which was reversed by estrogen treatment (as assessed by Paragraph recall, but not seen on Digit span or visual memory tests) ([Sherwin and Tulandi, 1996](#)). Similar findings were reported by other studies ([Craig, et al., 2007](#); [Craig, et al., 2008](#)).

In contrast, Owens and colleagues reported that 4 months of GnRH agonist-induced ovarian suppression had no effect on cognitive performance measures in 16 asymptomatic healthy premenopausal women ([Owens, et al.,](#)

2002). Similarly, Schmidt and colleagues found no evidence for a decline in measures of cognitive performance in young women after GnRH agonist (Lupron)-induced ovarian suppression. They also did not find an estradiol-related improvement in cognitive test performance (no changes in measures of attention, concentration, or memory function (either verbal or visual)) (Schmidt, *et al.*, 2013). More research needs to be done in this area to model POI.

### **Hormone treatment for POI after oophorectomy**

Indirect evidence from RCTs in early surgical menopause (women aged mid to late forties) suggests that the decline in verbal memory and some other functions (abstract thinking, speed of information processing) was reversed when using high dose intramuscular estradiol or testosterone compared to placebo (Sherwin, 1988, 1994; Hogervorst and Bandelow, 2010). These findings were consistent with a small study showing an average of 10 words more recalled after a high dose intramuscular injection of estradiol or testosterone (Sherwin, 1988). In another RCT from this group, verbal memory remained stable with estradiol treatment, whereas it declined in the placebo group (Phillips and Sherwin, 1992).

In the observational studies mentioned above investigating risk for cognitive impairment/dementia, estrogen treatment up to age 50 (Rocca, *et al.*, 2007) or for 10 years within the 5 years around that natural age of menopause (Bove, *et al.*, 2014) eliminated the risk of cognitive impairment and dementia, which was worse with a younger age at menopause. In the study by Bove and colleagues, there was no significant effect of hormone use on cognitive decline in this study with 'ever' versus 'never use' or 'duration of use'. However, duration of hormone use in this study was associated with slower decline in global cognition when administered within the 5-year perimenopausal window.

This beneficial effect of hormone replacement in women who had undergone surgical menopause was not always found in one systematic review including women undergoing surgery pre- and postmenopausal (without separate analysis) (Vearncombe and Pachana, 2009). However, women in the included RCTs who did not respond to hormone treatment were all older than 50 years of age. The lack of effect in this group was also described by Rocca and colleagues (Rocca, *et al.*, 2011; Rocca, *et al.*, 2012). The 'Window of Opportunity theory' substantiated by observational and basic sciences data also suggests that effects of estrogens are most beneficial when given before or around the natural age at menopause, especially for women undergoing an earlier menopause (Hogervorst, *et al.*, 2009a).

Finally, two observational studies reported that women with surgical menopause who were still using hormone therapy a decade after natural menopause (around age 60) actually had worse memory function than those untreated with hormones ((File, *et al.*, 2002) n=36 age 51-72 years; (Kritz-Silverstein and Barrett-Connor, 2002) n=885 age >60 years), although another small (n=35) cross sectional study of women with bilateral salpingo-oophorectomy (BSO) and hysterectomy aged over 65 years showed that those who were taking hormone treatment performed better on verbal and constructional ability than non-users (Verghese, *et al.*, 2000) suggesting against this theory. However, another large study (n=6110; n=441 BSO; age 45 to 64 years) also showed that former, but not current hormone users who had undergone surgical menopause had better verbal fluency (a type of verbal memory test) at a 3 year follow-up than treated and untreated controls who had undergone natural menopause (Szklo, *et al.*, 1996). No baseline data were given in this study.

Hence, the majority of these studies suggest that hormone treatment up to the age of 50 may be beneficial for neurological function in women who have undergone an early (surgical) menopause with hysterectomy and that this does not increase risk for dementia. Hormone treatment at an older age (>60 years of age) may confer added risk for dementia and vascular disease.

### **Hormone treatment for dementia**

Two Cochrane reviews have suggested that neither transdermal estradiol nor conjugated equine estrogens have any positive effects on cognition in women without dementia (Lethaby, *et al.*, 2008; Hogervorst, *et al.*, 2009b). However, some short-term positive effects on cognition (for up to 4 months) with either type of estrogen were



reported in women with dementia ([Hogervorst, et al., 2009b](#)). Whether these data can be extrapolated to POI is currently unknown.

## Conclusions and considerations

There is a relatively weak quality of evidence with contrasting conclusions ranging from no effect of estrogen treatment ([Vearncombe and Pachana, 2009](#)) to possibly some effect ([Hogervorst and Bandelow, 2010](#); [Hogervorst, 2013](#)) to a substantial effect and risk for cognitive impairment/dementia without hormone treatment ([Rocca, et al., 2011](#); [Rocca, et al., 2012](#)). Differences in meta-analysis conclusions may be due to insufficient analyses of differences in methods ([Vearncombe and Pachana, 2009](#)) or selective reporting ([Rocca, et al., 2011](#); [Rocca, et al., 2012](#)) and different methods used for case control/cohort studies, including retrospective assessment which is unreliable regarding reports of age at menopause and a lack of follow-up.

Some prospective data exist and several short-term small RCTs showed significant effects of chemical and surgical menopause on verbal memory function, which could be reversed by estradiol or testosterone.

Insufficient data may exist for firm recommendations, but limited data in POI from two observational studies and indirect data suggesting acute effects of chemical and surgical menopause, which can be reversed by estrogen treatment when given up to age 50. There is no evidence of adverse effects of estrogen replacement therapy on brain function before the age of natural menopause (at age 50) but this may not be true after the age of natural menopause.

Hormone treatment should probably be part of a lifestyle change to reduce risk for vascular disorders associated with later life 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](#)).

## Recommendations

<p>Estrogen replacement to reduce the possible risk of cognitive impairment should be considered in women with POI at least until the average age of natural menopause.</p>	<p>C</p>
<p>Women with POI should be advised to take lifestyle measures (e.g. exercise, cessation of smoking, maintaining a healthy weight) to reduce possible risks for cognitive impairment.</p>	<p>GPP</p>

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## 12. HORMONE REPLACEMENT THERAPY

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This chapter focuses on treatment with sex steroids, Hormone Replacement Therapy (HRT), for women with POI. A summary of the indications for use of HRT in these women is given, each of which were described in full detail in previous chapters (chapters 5-11). An overview of possible adverse effects of HRT use in women with POI is provided. The next section reviews the choice of existing preparations, regimen, route of administration, dosage, and recommendations of treatment duration. The final part of this chapter focuses on special indications and high-risk women within the POI group.

### 12.1. Indications for HRT

#### Vasomotor symptoms

The occurrence of vasomotor symptoms is a major reason for women with POI to use hormone replacement therapy (HRT). Data derived from studies in women with iatrogenic POI support the use of HRT for relief of vasomotor symptoms ([Absolom, et al., 2008](#)). A study of 31 women with chemotherapy-induced POI investigated the effect of HRT in those women who were willing to take it (15/31) ([Piccioni, et al., 2004](#)). Compared with those that did not take HRT, this group had a significant reduction in hot flushes, insomnia, and psychological and emotional changes (all improved in 66%). Another retrospective cohort study in 164 women after prophylactic bilateral salpingo-oophorectomy showed that the prevalence of hot flushes and night sweats was significantly lower in 87 women using HRT (any type), as compared to women not using HRT (hot flushes (20% vs. 41%) and night sweats (25% vs. 39%) ([Madalinska, et al., 2006](#)). Notably, previous studies of HRT use among women experiencing natural menopause have demonstrated larger reductions in vasomotor symptoms ([MacLennan Alastair, et al., 2004](#)).

Whilst there is little evidence on the efficacy of HRT for vasomotor symptoms in women with spontaneous POI, clinical experience is that vasomotor symptoms in women with POI respond rapidly to systemic HRT. Therefore, HRT is widely used for this indication.

#### Life expectancy

POI is associated with increased risk of premature death from cardiovascular disease. Both iatrogenic and spontaneous POI are implicated. The risk may be ameliorated by estrogen replacement therapy, but the quality of evidence is poor and limited to two studies. One study reported increased mortality mainly in those women with POI who had not received estrogen up to the age of 45 years ([Rivera, et al., 2009](#)). The second study, the Women's Health Initiative study, showed a possible protective, but non-significant, effect of HRT within 10 years of menopause for cardiovascular disease and death ([Rossouw, et al., 2007](#)).

#### Bone health

The beneficial effects of estrogen on bone health have long been recognized, and likewise the adverse effect of natural menopause on bone loss, mineral density and fracture risk ([Ahlborg, et al., 2001](#); [Sirola, et al., 2003](#); [Banks, et al., 2009](#)). Estrogen has a major effect on both cortical and trabecular bone turnover through stimulatory effects on osteoblast and inhibitory effects on osteoclast differentiation, activity and cell survival ([Manolagas, et al., 2013](#)). Women with POI have reduced bone mineral density, and this has been associated with the presence, degree and duration of estrogen-deficiency ([Bachelot, et al., 2009](#); [Leite-Silva, et al., 2009](#)). The prevalence of osteoporosis in women with POI appears to be in the range 8-14% ([Bachelot, et al., 2009](#); [Popat, et al., 2009](#)). In a group of 150 women with Turner syndrome (mean age 31 years) undergoing standardized multidisciplinary assessment, 12% were found to have osteoporosis, with a further 52% having osteopenia ([Freriks, et al., 2011](#)).

Large, randomized trials have shown that estrogen therapy in postmenopausal women can improve bone mineral density and reduce vertebral and hip fracture risk ([Wells, et al., 2002](#); [Cauley, et al., 2003](#)). Evidence is limited on

the effect of HRT on fracture risk in women with POI, but estrogen replacement has been shown to have beneficial effects on bone mineral density in women with POI ([Prior, et al., 1997](#); [Crofton, et al., 2010](#)), and Turner Syndrome ([Kodama, et al., 2012](#)).

### **Prevention of cardiovascular disease**

Women with POI are at increased risk for impaired endothelial function ([Kalantaridou, et al., 2004](#)), early onset of coronary heart disease ([Atsma, et al., 2006](#)) and increased cardiovascular mortality ([Cooper and Sandler, 1998](#); [Jacobsen, et al., 1999](#); [de Kleijn, et al., 2002](#); [Jacobsen, et al., 2003](#); [Mondul, et al., 2005](#)). Women undergoing prophylactic 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., 2009](#); [Barrett-Connor, 2013](#)). Premature atherosclerosis ([Clarkson, 2007](#)), increased risk for non-procedurally-related venous thromboembolism ([Canonico, et al., 2014](#)), and unfavourable lipid profiles ([Knauff, et al., 2008](#)) has been identified in women with both spontaneous and surgical POI.

There are no RCTs on the effect of HRT on cardiovascular function in women with POI. However, observational and non-randomised intervention studies have shown a decrease in myocardial infarction risk ([Bain, et al., 1981](#)), improved endothelial function ([Kalantaridou, et al., 2004](#)), and no increased risk of ischemic heart disease ([Lokkegaard, et al., 2006](#)) or cardiovascular disease-associated mortality ([Rivera, et al., 2009](#)) in those using estrogen replacement.

### **Quality of life**

The limited available evidence would suggest that women with POI report lower levels of psychological wellbeing compared to women in the general population. The evidence for improvement of quality of life following HRT usage is limited, and shows that estrogen with or without testosterone may improve general well-being in some surgically menopausal women, for whom the level of serum estrogen achieved a premenopausal range. ([Kotz, et al., 2006](#)). The authors reported an additional positive effect of adding testosterone to the treatment regimen, which was not detected in a recent RCT ([Guerrieri, et al., 2014](#)). The latter study concluded that augmentation of standard estrogen/progestin therapy with physiologic testosterone in young women with POI did not change reported quality of life or self-esteem and had minimal impact on mood.

As vasomotor symptoms could be implicated in a reduction of quality of life for some women with POI, relief of these symptoms with HRT, as described above, may have an indirect positive effect on quality of life.

### **Sexual function and genito-urinary symptoms**

Evidence on the optimal treatment for women with POI and sexual dysfunction is scarce and commercially biased towards androgens. Adequate estrogen replacement should be ensured as estrogen is important for the health of the genito-urinary system, sexual function, and desire.

Genito-urinary symptoms, such as vaginal dryness, irritation, urinary frequency, and incontinence, are associated with hypoestrogenism and therefore prevalent in women with POI. Vaginal lubricants, moisturizers and HRT (both systemic and topical) can be used to treat genito-urinary symptoms. Vaginal lubricants may be used when there is a need for local treatment where systemic treatment is contra-indicated, or if women still experience genito-urinary symptoms despite of appropriate dose of HRT ([Le Donne, et al., 2011](#); [Grimaldi, et al., 2012](#); [Pacello, et al., 2013](#)). Both local and systemic HRT seem to be effective in relieving genito-urinary symptoms ([Nachtigall, 1994](#); [Bygdeman and Swahn, 1996](#); [Piccioni, et al., 2004](#); [Madalinska, et al., 2006](#)).

### **Neurological function**

The evidence on the effect of hormone treatment on the cognitive function in women with POI is relatively weak with contrasting conclusions ranging from no effect of estrogen treatment to possibly some effect, to a substantial effect and risk for cognitive impairment/dementia without hormone treatment ([Vearncombe and Pachana, 2009](#); [Hogervorst and Bandelow, 2010](#); [Rocca, et al., 2011](#); [Rocca, et al., 2012](#); [Hogervorst, 2013](#)). The effect of different

treatments on neurological function in Turner Syndrome girls has been reported in several studies from the same research group. Estrogen replacement improved motor speed, verbal and non-verbal memory, and non-verbal processing time compared to placebo-treated TS girls (aged 10-12 years) ([Ross, et al., 1998](#), [2000](#)).

Limited data in POI and indirect data suggest significant effects of chemical and surgical menopause on verbal memory function, which could be reversed by estradiol ([Rocca, et al., 2011](#); [Rocca, et al., 2012](#); [Hogervorst, 2013](#)). For women who underwent bilateral salpingo-oophorectomy before the onset of menopause, studies suggest that hormone treatment up to the age of 50 may be beneficial for neurological function ([Sherwin, 1988](#); [Phillips and Sherwin, 1992](#); [Sherwin, 1994](#); [Hogervorst and Bandelow, 2010](#)). This contrasts with the findings that HRT at an older age (>60 years of age) may confer added risk for dementia and cardiovascular disease.

## Recommendations

Hormone replacement therapy (HRT) is indicated for the treatment of symptoms of low estrogen in women with POI.	C
Women should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection.	C

## Summary table of indication for the prescription of HRT in women with POI

Sequelae of POI	Indication for HRT	Supporting recommendation / conclusion
Vasomotor symptoms	YES	<i>Hormone replacement therapy is indicated for the treatment of vasomotor symptoms in women with POI.</i>
Genito-urinary symptoms	YES	<i>Both systemic &amp; local estrogens are effective in treatment of genito-urinary symptoms.</i>
Life expectancy	?	<i>Life expectancy appears to be reduced due to cardiovascular mortality: HRT may be of indirect benefit.</i>
Bone health	YES	<i>Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.</i>
Cardiovascular health	YES	<i>Despite lack of longitudinal outcome data, hormone replacement therapy with early initiation is strongly recommended in POI to control future risk of cardiovascular disease; it should be continued at least until the average age of natural menopause.</i>
Quality of life	?	<i>Quality of life appears to be reduced: HRT may be of indirect benefit.</i>
Sexual function	YES	<i>Adequate estrogen replacement is regarded as a starting point for normalising sexual function. Local estrogen may be required to treat dyspareunia.</i>
Neurological function	?	<i>Estrogen replacement to reduce the possible risk of cognitive impairment should be considered in women with POI at least until the average age of natural menopause.</i>

## 12.2 Risks of HRT

## **KEY QUESTION: WHAT ARE THE RISKS OF HORMONE REPLACEMENT THERAPY?**

### **Clinical evidence**

In this section, the evidence for risks of HRT in women with POI is summarized and supplemented with applicable data from normal menopause when evidence was scarce.

#### **12.2.a Breast cancer**

The incidence of breast cancer in women with POI has been sparsely investigated. It has been hypothesised that risk may be reduced in women with untreated POI who have less estrogen exposure. 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 at menopause, and this risk seems lowest in women experiencing menopause before the age of 40 years (2012). 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). Wu and colleagues found a decreased incidence of breast cancer in women with POI compared with normal menopausal women (OR=0.59; 95% CI 0.38-0.91) after adjustment for confounding factors (Wu, *et al.*, 2014).

From a theoretical stance, women with POI taking replacement therapy with body-identical estradiol in physiological doses should not have a higher risk of breast cancer than women with normal ovarian estrogen production (Wu, *et al.*, 2014). Only two papers (from one research group, reporting the same cohort of patients) looked into the effects of HRT (conjugated equine estrogen and medroxyprogesterone acetate) on breast tissue in women with spontaneous POI. In postmenopausal women, increased breast density, as assessed by mammography, is associated with increased breast cancer risk. The first study compared mammography results of 31 POI patients to 31 postmenopausal women both using identical HRT regimens with a mean duration of 50 months. They concluded that there was no statistically significant difference in breast density between the two groups (Soares, *et al.*, 2010). The other study compared these mammography findings with 31 regularly menstruating age-matched controls and again found no statistically significant differences. Here the authors concluded that periods of hypoestrogenism followed by hormone therapy resulted in no changes in breast density in women with POI (Benetti-Pinto, *et al.*, 2008).

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 estrogen replacement

A report on 62 women with Turner syndrome described the effect of prolonged (longer than 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 is 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).

One 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, 1462 cases of breast cancer were identified. When evaluating breast cancer incidence by age among women exposed and unexposed to HRT, 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 0.07-2.01) and 45-49 (RR 0.62, 95% CI 0.62-1.22). In women over 50 exposed to HRT, breast cancer incidence was significantly elevated compared to unexposed women, RR ranging from 1.19 (95% CI 0.96-1.46) for ages 50-54 to 3.71 (95% CI 2.16-5.94) for ages 65-67 (Ewertz, *et al.*, 2005).

A higher risk of breast cancer has been demonstrated with the continuous combined estrogen-progestogen regimen compared with the cyclical one, in several large cohort studies of postmenopausal women

(Lambrinoudaki, 2014). However, since the risk of breast cancer for women with POI may well 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 also been considerable debate on the effect of different progestins on the risk of breast cancer (Stahlberg, *et al.*, 2004; Seeger and Mueck, 2008); however the evidence relates to normally menopausal women and there are no data in POI. In a recent review paper, it was suggested that the type of progestin may modulate breast cancer risk, with limited evidence supporting a favour for micronized progesterone over synthetic progestins (Davey, 2013).

### Recommendation

Women with POI should be informed that HRT has not been found to increase the risk of breast cancer before the age of natural menopause.	D
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### 12.2.b Endometrial cancer and endometrial hyperplasia

Estrogen-only HRT is associated with increased risk for endometrial hyperplasia and endometrial cancer in normally menopausal women. According to the Cochrane Library review on oral HRT and endometrial hyperplasia, all doses of unopposed estrogen therapy lead to a significant increase of approximately 50% for endometrial hyperplasia within three years. They conclude that the risks of regimens combining estrogens with continuous progestogens are not significantly different from placebo at two years (Furness, *et al.*, 2012).

To date, 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 normal menopause, only combined estrogen-progestogen therapy should be used in women with POI and an intact uterus.

The oral contraceptive pill reduces the risk of endometrial hyperplasia in women with normal ovaries and so it is reasonable to expect that it will have the same effect in women with POI (Eshre Capri Workshop Group, 2005).

Different regimens for HRT are reviewed in [section 12.3.b](#).

### Recommendation

Progestogen should be given in combination with estrogen therapy to protect the endometrium in women with an intact uterus.	B
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### 12.2.c Stroke

No evidence was identified on the risk of stroke for women with POI treated with HRT. Studies on the use of HRT in older postmenopausal women 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](#)). 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](#)).

### 12.2.d Thromboembolic disease

Only one study on the risks of thromboembolism and HRT use for women with POI was identified, and that was of a minority sub-group within the WHI study. This looked into venous thromboembolism (VTE) occurring in women on HRT 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. However, analyses restricted to non-procedure-related VTE showed a U-shaped relationship between age at 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 at menopause between 40 and 49 years (adjusted HR 1.8, 95% CI 1.2-2.8) while using HRT ([Canonica, et al., 2014](#)).

Available evidence on VTE risk in HRT users with menopause at a regular age has shown increased risk, which becomes most apparent in the first year of HRT use: absolute risk after one year's use: 7 per 1000 (95% CI 4 to 11, with RR 4.28; combined continuous HRT) ([Marjoribanks, et al., 2012](#)).

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., 2009](#)). The evidence on VTE risk in OCP users is relevant to women with POI using OCP because they are in the same age group. 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 OCP users such as smoking and obesity therefore also apply for women with POI using OCP.

## 12.3. HRT – treatment options

### **KEY QUESTION: WHAT ARE THE OPTIONS FOR HORMONE REPLACEMENT THERAPY?**

In contrast to postmenopausal women in their fifties and older, the need for hormone replacement therapy (HRT) in younger women with POI extends beyond the need for symptom relief (the primary indication for HRT in the postmenopausal age group). As reviewed in the previous chapters, evidence suggests that HRT 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.

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

Research on the optimal HRT 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 normal menopausal women above the ages of 45-50 years. As a consequence of the sparse evidence, recommendations for HRT in POI must necessarily be based on theoretical knowledge about physiology and endocrinology, and extrapolated from the evidence of HRT in normal menopause. Thus recommendations in this chapter are primarily based on “best clinical practice” supplemented by evidence where it exists. Patient preference is important for compliance and must therefore be taken into consideration when prescribing.



### 12.3.a Type of preparations: Estrogens and progestogens

#### Estrogens

There are three types of estrogen that are available for hormone replacement: estradiol (the main ovarian estrogen 17 $\beta$ -estradiol is the active component), ethinylestradiol (a synthetic estrogen) and conjugated equine estrogens (CEE - derived from pregnant mare urine).

The main goal of HRT for women with POI is to mimic normal physiological endocrinology with regard to estrogen replacement. Oral contraceptives contain the potent synthetic estrogen ethinylestradiol, which in effect provides more steroid hormone than is needed for physiologic replacement, with unfavourable effects on lipid profile, on haemostatic factors and with an increased risk of thromboembolic events related to the progestogen and first pass effect of the liver. A few studies indicate that combined oral contraceptives may have a negative impact on bone mineral density (BMD) in younger women, but the evidence is presently too limited for definite conclusions ([Warholm, et al., 2012](#)). Achieving an inadequate peak bone mass increases the risk of osteoporosis and bone fracture in later life. Other studies have shown that physiological sex steroid replacement with 17 $\beta$ -estradiol has a beneficial effect on bone mass acquisition mediated by increased bone formation and decreased bone resorption. In an open-label randomized controlled crossover trial including 34 women with POI, [Crofton and colleagues](#) found that lumbar spine BMD increased significantly after 12 months treatment with a physiological sex steroid replacement regimen including transdermal 17 $\beta$ -estradiol and sequential progesterone compared with oral ethinylestradiol and norethisterone. Also bone formation markers, BALP and P1NP increased significantly with the former combination, but decreased with the synthetic estrogen regimen ([Crofton, et al., 2010](#)). In another publication based on the same study population [Langrish and colleagues](#) found that the physiological replacement regimen caused lower mean blood pressure, reduced plasma angiotensin II and reduced s-creatinine without altering plasma aldosterone concentrations, compared with POI women treated with oral contraceptives ([Langrish, et al., 2009](#)). These findings may have major implications for the future cardiovascular health of young women with POI, who require long-term sex steroid replacement therapy.

No studies were identified that compared the effects of conjugated equine estrogen with ethinylestradiol or estradiol in women with POI. One case study demonstrated a beneficial effect of CEE on bone mineral density in Turner Syndrome women ([Kodama, et al., 2012](#))

There are now new contraceptive pills containing estradiol, however, as yet, there are no comparative studies on the risks OF VTE with these preparations and so the indications for their use in women with POI should remain contraception.

#### Progestogens

Progesterone protects the endometrium from the mitogenic effect of estrogen, as discussed in Section 12.2.b. There is a lack of evidence on the effect and role of various progestogen preparations in HRT for women with POI. 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 normally postmenopausal women appears to favour “body-identical” (micronized natural) progesterone. It appears to have a better cardiovascular safety profile when compared to synthetic progestogens ([Mueck, 2012](#)). Also, as described above, micronized natural progesterone may be preferred over synthetic progestogens with regard to breast cancer risk ([Davey, 2013](#)). A randomised controlled trial demonstrated that micronized natural progesterone given in an oral dose of 200mg/day for 12 days per 28 day cycle was as good 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 estradiol (CEE) ([The Writing Group for the PEPI, 1996](#)).

## Conclusion and considerations

There have been very few studies comparing different types 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 (COCP) and the risks may be lower. In addition, the risks of using the COCP in the general female population, though small, are well documented and are not dependent on the presence of functioning ovaries (see [\(Dragoman, 2014\)](#) for a review). However, if compliance is improved only with the use of the COCP, then this is a reasonable alternative, or if contraception is required. There are no data comparing the benefits or risks of 17 $\beta$ -estradiol with CEE for women with POI, but in the opinion of the GDG, the former is preferable as it is more likely to be physiological.

No studies were identified comparing the different types of progestogen replacement for women with POI. An RCT in postmenopausal women taking HRT demonstrated that oral cyclical micronized natural progesterone was as good as either cyclical or continuous medroxyprogesterone acetate for endometrial protection. Natural progesterone may have a more favourable cardiovascular profile and possibly a reduced risk of breast cancer.

### 12.3.b Regimens

Continuous estrogen replacement is required to avoid symptoms of estrogen deficiency. Some women using the combined oral contraceptive pill for estrogen replacement will be symptomatic during the pill-free (or inactive pill) week. Unopposed estrogen therapy is associated with an increased risk of endometrial hyperplasia after 1 to 3 years of treatment at all doses in postmenopausal women. Therefore, estrogen replacement in postmenopausal women with an intact uterus should always be supplemented with a progestogen to prevent endometrial hyperplasia and increased risk of malignant neoplasia ([\(Furness, et al., 2012\)](#)). This risk is likely to be the same in women with POI and an intact uterus, so unopposed estrogen replacement should not be given to this group.

Studies of menopausal women over 50 years of age have shown that supplementation with cyclical progestogen (progestogen for 10 days or more a month or 14 days up to every 12 weeks) lowers (but not eliminates) this risk, while continuous combined estrogen-progestogen therapy may even prevent endometrial hyperplasia and cancer ([\(Furness, et al., 2012\)](#)). 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 ([\(Morch, et al., 2012\)](#)).

A cyclical regime stimulating active functioning of the endometrium with regular proliferation and withdrawal bleedings is preferred in women aiming for pregnancy by oocyte donation ([\(O'Donnell, et al., 2012\)](#)). This is a particularly important consideration when commencing HRT in adolescents with primary amenorrhea in order to establish normal endometrial development (see Chapter 13). The atrophic effect on the endometrium of the contraceptive pill may also be a reason to avoid its use for HRT in this group, at least until after a period of treatment with a cyclical combined regime.

Younger women are more likely to experience break-through bleeding with continuous combined HRT than older postmenopausal women. Women with POI who desire bleed-free HRT (and contraception) may benefit from using the levonorgestrel intrauterine system with appropriate estrogen replacement.

## Conclusion and considerations

Extrapolation of the evidence concerning continuous combined and cyclical combined HRT regimes in postmenopausal women leads to the recommendation that the latter is preferable for most women with POI. The exact length of the cycle can be individualized to the patient, but probably should not be longer than 12-weeks to protect the endometrium from hyperplasia and malignant change.

Some estrogen replacement regimens are protective against endometrial cancer in healthy women. The OCP and continuous combined HRT both decrease risk in healthy women and so are probably safe in POI women. Those

desiring a pregnancy may be better treated with a sequential regimen rather than a continuous combined one, even though the risk of endometrial hyperplasia/carcinoma may be slightly higher.

Women with POI but an absent uterus will not need progestogen supplementation and can therefore be replaced with unopposed estrogen-only therapy. Estrogen alone has the least influence on the breast tissue in postmenopausal women ([Stefanick, et al., 2006](#)).

### ***12.3.c Route of administration***

#### ***Estrogens***

Systemic estrogen can be administered orally or through transdermal patches and gels. Both routes are widely used. Subcutaneous implants and, more recently, nasal sprays and injectable estrogen preparations are also available, although not in all European countries. Local estrogen treatment can be administered in the form of an estrogen-releasing vaginal ring and estrogen-based vaginal creams and pessaries. Locally administered estrogen is mainly prescribed for genito-urinary symptoms ([Suckling, et al., 2006](#)), and is not believed to carry a risk of endometrial hyperplasia if used in the licensed dosage ([see section 10.3 for details](#))

The major advantage of transdermal estrogen is avoidance of the first-pass metabolism in the liver ([Chetkowski, et al., 1986](#)). Compared to oral administration, the transdermal route can achieve higher plasma levels of circulating estradiol with a lower treatment dose and therefore fewer circulating estrogen metabolites, closer matching the normal premenopausal state ([Goodman, 2012](#)).

There is a vast amount of data regarding the route-dependent effect of the metabolic actions of estrogen. However, most studies were done in older post-menopausal women. Oral estrogen leads to suppression of insulin-like growth factor I (IGF-I) concentrations, while transdermal estrogen does not have a negative effect on IGF-I; postmenopausal women on oral HRT developed increased fat mass and decreased lean mass, whereas patients treated with transdermal HRT had no change in body composition; transdermal HRT also appears to have a beneficial effect on serum lipid profiles, inflammatory markers, and blood pressure; oral estrogen therapy may more significantly increase renin substrate, thus increasing the risk of hypertension ([Divasta and Gordon, 2010](#)).

Postmenopausal women over 50 years of age have a lower risk of myocardial infarction with transdermal estrogen compared with oral ([Lokkegaard, et al., 2008](#)), a lower risk of deep vein thrombosis ([Nelson, 2009](#); [Canonic, et al., 2010](#); [Renoux, et al., 2010b](#)) and no excess risk of stroke ([Renoux, et al., 2010a](#)). Also, breast density is less pronounced in postmenopausal women treated with transdermal preparations compared to oral ([Goodman, 2012](#)). It is unclear whether these apparent advantages of the transdermal route also apply to women with POI in general, who are replacing a deficiency as opposed to prolonging estrogen exposure beyond the reproductive age.

A cross-over trial of 5 women with POI investigated the effect of oral versus transdermal estradiol for 1 month on hepatic proteins. The oral form increased hepatic proteins, whereas the transdermal did not ([Steingold, et al., 1991](#)).

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 growth hormone in young girls with Turner Syndrome ([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](#)). Two studies concluded that transdermal estradiol may be preferred over oral administration for puberty induction, as the transdermal route may have less deleterious effect on hepatic metabolism and may be associated with lower total estrogen exposure and be more physiological than oral estrogen ([Jospe, et al., 1995](#); [Torres-Santiago, et al., 2013](#)).

However, there have been no large randomized trials and most have involved postmenopausal women. Therefore, their applicability to women with 46-XX POI and adolescents and young adults with TS remains to be proven ([Davenport, 2010](#)). Transdermal administration may be preferable for certain high-risk women with POI, for example, those who smoke, experience migraine or have risk factors for venous thromboembolism ([Davies and Cartwright, 2012](#)) (see also [section 12.5](#) below).

Transdermal patches may result in local skin irritation and some 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 other might see it. Estradiol gel is available, but younger women may still prefer oral HRT ([Davies and Cartwright, 2012](#)).

Estradiol implants are not widely available in Europe. 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. Renewal every 6 months results in supra-physiological estradiol levels ([Wahab, et al., 1997](#)) and strongly positive effects on bone mass ([Wahab, et al., 1997](#); [Khastgir, et al., 2003](#)). 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 ([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.

### Progestogens

Progestogens can be administered via the oral, transdermal (as a patch), or intra-uterine routes. No studies were identified comparing route of administration for synthetic progestins 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 older, naturally menopausal women. Subdermal implants and intramuscular depot preparations are also available, although these are licensed as contraceptive devices and no data exists for their use in HRT for endometrial protection.

If the woman prefers a bleed-free regimen, local treatment with a progestogen-releasing intra-uterine system (IUS) will provide sufficient protection from endometrial hyperplasia ([Ewies and Alfhaily, 2012](#)), with fewer side effects compared to systemic progestogen treatment ([Pirimoglu, et al., 2011](#)). This regimen also provides contraception.

Micronized progestogens are available to use orally, vaginally and as transdermal (cream) preparations. Vaginal progesterone may have the benefit of achieving higher levels within the target organ (uterus) but with lower doses. Small studies have shown that vaginal administration of natural micronized progesterone is more effective than oral progestogen supplementation in creating an “in-phase” secretory endometrium after estrogen endometrial priming in women with POI ([Fatemi, et al., 2007](#)).

An open-label randomised controlled trial examined the effect of sequential vaginal progesterone gel 4% (45 mg) or 8% (90 mg) on endometrial histology as part of an HRT regimen for women with secondary amenorrhoea. The women in the study were aged 18-45 years but of the 127 participants only 21 had POI (others needed HRT for other reasons e.g. hypopituitarism). Endometrial biopsies were used to assess progestational changes, which were found in 92% of the 4% group and 100% of the 8% group. None of the patients had endometrial hyperplasia but the study period was only 3 months ([Warren, et al., 1999](#)). The same group published an observational study of women with secondary amenorrhoea (40 with hypothalamic amenorrhoea; 9 with POI) found no changes in emotional symptoms over 3 cycles of combined HRT using vaginal micronized progesterone gel (4% or 8%) ([Shantha, et al., 2001](#)). The gel was used on alternate days starting on Day 15 for 6 applications.

Cyclical vaginal natural 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 50mcg estradiol patches (Di Carlo, *et al.*, 2010). However, the trial did not assess the endometrium histologically and follow up was only for 1 year.

In a study of 54 postmenopausal women above the age of 50, Vashisht and colleagues found that 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).

## Conclusion and considerations

Transdermal estrogen may be the preferred route of administration with a lower side-effect profile: however, the data is not definitive and patient preference must be taken into account when prescribing.

The safety of transdermal natural progesterone has not been established for endometrial protection, although there is evidence that the endometrium does respond to vaginal progesterone gel.

No evidence directly applicable to women with POI was identified for route of administration for synthetic progestogen, but there is no reason to believe it should be any different from that regarding postmenopausal women. There is evidence that the endometrium does respond to vaginal natural progesterone. However, women with POI are potentially using HRT for longer than those with a normal menopause. As above, patient preference and contraceptive needs should be considered when prescribing.

### 12.3.d Dose

#### Estrogen

The purpose of estrogen replacement in women with POI is both to treat symptoms of low estrogen as well as to prevent the long-term health consequences of the loss of ovarian estrogen production. In order to maximize benefit but to minimize any risks of treatment, especially since women with POI may potentially be using replacement therapy for many years (see Section 12.3.e), the lowest effective dose of hormone should be used. However, no dose-response trials were identified for women with POI.

There are studies on the effect of estradiol dose on bone mineral density, breast density and lipids in older postmenopausal women, but these data may not apply to women with POI, who, being younger, may require higher doses. For example, bone mineral density increases in postmenopausal women taking 0.3mg/day conjugated equine estrogen (Lindsay, *et al.*, 2002) but in young women with Turner syndrome, low-dose estrogen (below 0.625mg/day) was less effective in increasing BMD than an adult-dose of 0.625mg/day (Kodama, *et al.*, 2012).

Cyclical transdermal estradiol at a dose of 100µg/day week 1 then 150µg/day weeks 2 to 4 for 12 months improved bone mineral density, reduced markers of bone breakdown and increased markers of bone formation in a small group of young women with POI due to a variety of causes (average age 27 years) (Crofton, *et al.*, 2010).

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 would appear reasonable to aim for physiological estradiol levels as found in the serum of women with normal menstrual cycles, average 50-100 pg/ml (180-370 pmol/l) (Mishell, *et al.*, 1971; MacNaughton, *et al.*, 1992). These levels can be achieved with 100µg estradiol 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 was 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).

### Progestogen

Women with POI and an intact uterus taking estrogen replacement require progestogen therapy to protect against endometrial carcinoma. 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 daily or 2.5mg medroxyprogesterone acetate (MPA) at the moderate to high doses of estrogen that should be provided for women with POI. Sequential regimens require 10mg MPA for a minimum of 10 to 12 days per month, or 200mg micronized oral progesterone (Furness, *et al.*, 2012). This large systematic review and meta-analysis only considered oral HRT in postmenopausal women and no equivalent data was identified for transdermal estrogen in women with POI.

### **12.3.e Duration**

No evidence was identified regarding the duration of HRT for women with POI. In order to prevent the long-term health consequences of the loss of ovarian function, the consensus of the GDG was that HRT should be continued at least until the age of natural menopause, i.e. around 50 years old. This is in line with the recommendation of other organizations (Pitkin, *et al.*, 2007; Vujovic, *et al.*, 2010). Subsequently, recommendations for hormone therapy in natural menopausal women can be followed.

Commencing HRT early may be particularly important for young women with POI in order to maximize peak bone mass (see Chapter 7: Bone Health). Similarly, cardiovascular risk factors may be minimized by early use of estrogen replacement (see Chapter 8: Cardiovascular Health).

### **Recommendations**

17β-estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement.	C
Women should be informed that whilst there may be advantages to micronized natural progesterone, the strongest evidence of endometrial protection is for oral cyclical combined treatment.	GPP
Patient preference for route and method of administration of each component of HRT must be considered when prescribing, as should contraceptive needs.	GPP

## 12.4. Monitoring HRT

Currently, there is no evidence regarding the optimum HRT monitoring strategy. Estrogen dosage should be titrated to achieve symptom control and adequate bone density. Serum estradiol is not helpful in clinical practice (except for monitoring HRT implants) and does not measure ethinylestradiol (in OCPs) or estrone (the predominant estrogen in some HRTs). There is no value in monitoring FSH levels, since they may not normalize ([Davies and Cartwright, 2012](#)). Regular checks, for example yearly, are recommended, with the aim to follow up on compliance, satisfaction, side effects, and possible need for change of regime or administration form. Compliance may be improved by involving the patient in the discussion of treatment choice ([Cartwright, et al., 2012](#)).

### Mammography

As was described in [section 12.2.a](#), no evidence suggests an increased risk of breast cancer in young women on HRT compared with age-matched normally menstruating women. It therefore seems safe to commence mammographic screening at the age of 45 to 50 years in HRT users as in the normal population.

### DEXA scan

The relevance of monitoring bone health in women with POI has been described in detail in section 7.3. In general, measurement of bone mineral density (BMD) with Dual-Energy X-ray Absorptiometry (DEXA) should be considered at diagnosis of POI, especially in the presence of additional risk factors for poor bone health (e.g. long duration of estrogen deficiency, history of low impact fractures).

If a diagnosis of osteoporosis is made and estrogen replacement or other therapy initiated, 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.

If the BMD is normal and adequate systemic estrogen replacement is commenced, the value of a repeat DEXA scan is low.

### Recommendations

Once established on therapy, women with POI using HRT should have a clinical review annually, paying particular attention to compliance.	GPP
No routine monitoring tests are required but may be prompted by specific symptoms or concerns.	GPP



## 12.5. POI women with special issues

### 12.5.a Women with Turner Syndrome

Hormone replacement therapy (HRT) in girls with Turner Syndrome (TS) represents a specific challenge with additional aspects that need to be taken into account, like the need for puberty induction, and potentially more severe implications of POI with respect to bone, cardiovascular and neurological health. The appropriate HRT regimens for puberty induction in girls with Turner Syndrome are discussed in detail in Chapter 13, including the transition to adult care.

In adult women with Turner Syndrome, the focus of treatment changes from growth and puberty induction to maintenance of health ([Davies, 2010](#)).

#### Bone Health

Bone health is one of the concerns for women with Turner Syndrome. A recent study showed that 12% of a group of 150 women with TS (mean age 31 years) who were undergoing systematized assessment, were found to have osteoporosis, with a further 52% having osteopenia ([Freriks, et al., 2011](#)). Although women with TS may have features other than estrogen deficiency that impact on bone health and fracture risk, adequate estrogen replacement therapy is indicated to maximize bone health. Kodama and colleagues evaluated bone mineral density (BMD) in a cohort of young TS women during continuous estrogen therapy. BMD was significantly higher in women treated with 0.625mg/day of conjugated estrogen and 10mg/day dydrogesterone, as compared to women treated with a lower dosage of estrogen. Also, HRT may be more effective if initiated at a younger age. The rate of increase in BMD plus the final BMD achieved was significantly higher in patients where treatment had been initiated before age 18 years ([Kodama, et al., 2012](#)). A longitudinal study by Khastgir reported an increase in BMD corroborated by increased cancellous bone volume with estrogen treatment (subcutaneous estradiol implants (50mg/6 months)) in women with TS (mean age 31.4 yrs.) ([Khastgir, et al., 2003](#)). Crofton and colleagues compared the effects of physiological (transdermal estradiol and vaginal progesterone) and standard (oral ethinylestradiol and norethisterone) sex steroid replacement regimens on bone mass acquisition and turnover in young women with premature ovarian failure, including women with TS. Physiological sex steroid replacement significantly improved BMD Z-scores at the lumbar spine and increased bone formation whereas standard HRT did not ([Crofton, et al., 2010](#)). In addition to estrogen therapy, women with TS may benefit from vitamin D, calcium supplements, and regular exercise. In TS women with confirmed osteoporosis, or with a high risk for fractures, medical treatment for osteoporosis may be indicated ([Bondy and Turner Syndrome Study Group, 2007](#)).

#### Cardiovascular Health

Women with TS have increased risk of congenital heart defects, but they are also twice as likely to develop coronary artery disease and/or cerebrovascular disease as the general population ([Gravholt, et al., 1998](#)). Women with TS have an excess of several cardiovascular risk factors including hypertension, obesity, impaired glucose tolerance, and hyperlipidaemia ([Turtle, et al., 2013](#)). In addition, CVD mortality was four times higher in a study of 1400 women with TS compared to healthy female controls ([Swerdlow, et al., 2001](#)). Short-term studies of HRT in adult women with Turner Syndrome have failed to show a favourable effect on lipid profile ([Gravholt, et al., 1998](#); [Elsheikh, et al., 2000](#)), or an ambulatory arterial stiffness index ([Mortensen, et al., 2009](#)). Whether HRT is cardio-protective in women with Turner Syndrome and whether it should be recommended for this indication is still unclear. To promote cardiovascular health, women with Turner Syndrome should be advised of risk factors that they can modify through behavioural change (e.g. not starting/stopping smoking, taking regular weight-bearing exercise, maintaining/achieving a healthy weight).

#### Neurological Health

An abnormal neuro-cognitive profile is well described in females with TS, which may partly be due to ovarian insufficiency and estrogen deprivation. Women with Turner Syndrome, on average, have worse emotional recognition and lower visuo-spatial, attentional, working memory and executive function compared to controls



matched for age, height, total IQ and socioeconomic status (Ross, *et al.*, 2006). Only a few studies were found evaluating the effect of estrogen replacement therapy on neuro-cognitive functioning in women with TS. Estrogen treatment would appear to improve executive ability, memory, and motor function in TS, while other features such as visuo-spatial processing, visual memory and arithmetic skills, might not improve (Downey, *et al.*, 1991; Swillen, *et al.*, 1993; Romans, *et al.*, 1998; Ross, *et al.*, 1998).

### ***Reproductive, Genito-Urinary and Psychosexual Health***

Women with TS who become pregnant, whether spontaneously or through oocyte donation, have increased obstetric risks. These risks are discussed in detail in Section 6.3. Since the uterus is an estrogen-dependent organ, maintaining its health with estrogen and progestogen replacement is likely to be as important in women with TS as in women with karyotypically normal POI. Similarly, HRT is likely to benefit the genito-urinary system and psychosexual health of women with TS. These issues are covered in [Section 10.3](#) and [9.2](#), respectively.

### **Conclusions and considerations**

Estrogen replacement treatment should probably aim to mimic the normal reproductive lifetime exposure. One guideline on diagnosis and management of Turner Syndrome describes the use of a higher estrogen dose (e.g. 100 µg patch) during young adulthood, and decreasing to 50 µg patches by age 30 to 35 years, with further reduction and cessation by age 45-50 years (Bondy, 2005). The authors also recommend progesterone rather than any progestogen derivative, with cycling on a monthly to tri-monthly basis. This guidance is based on expert opinion rather than clinical studies though. As for women with karyotypically normal POI, estrogen can also be given in the form of a combined oral contraceptive pill, if this is more acceptable to patients and thereby improves compliance. However, the risks of treatment are likely to be higher and the benefits to bone health less.

### **Recommendation**

Girls and women with POI due to Turner Syndrome should be offered HRT throughout the normal reproductive lifespan.	C
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### ***12.5.b Women with POI and a BRCA gene mutation or after breast cancer***

In the last few decades, early detection and improved treatments have led to an increase in the survival rates for young women with breast cancer. However, the chemotherapy used can induce premature ovarian insufficiency, with associated vasomotor symptoms, sexual dysfunction, and adverse effects on bone and cardiovascular health. The vasomotor symptoms in particular may be worsened by adjuvant endocrine treatments (Day, *et al.*, 1999). The impact of chemotherapy on ovarian function is dependent on the age of the patient, and the type and dosage of treatment and is difficult to predict (Wallace, 2011). Furthermore, women who are carriers of mutations in the BRCA1/2 genes may be recommended prophylactic premenopausal bilateral salpingo-oophorectomy (BSO) to reduce their risks of breast and ovarian cancers.

HRT has been shown to increase the risk of developing breast cancer in postmenopausal women (Rossouw, *et al.*, 2002; Beral, *et al.*, 2007). The HABITS randomized trial on hormone replacement after breast cancer was stopped prematurely after new breast cancer events were found in 26 patients in the HRT-group, compared to 7 patients in the non-HRT group at a median follow-up of 2.1 years (Holmberg and Anderson, 2004). A similar trial, however, found no significance difference in the number of patients with recurrence of breast cancer at median follow-up 4.1 years and 10.8 years, possibly attributable to the difference in progestogen administration in the 2 trials (von Schoultz and Rutqvist, 2005; Fahlen, *et al.*, 2013). Although the data are inconsistent, HRT is widely accepted to be contra-indicated for treatment of vasomotor symptoms in breast cancer survivors (Antoine, *et al.*, 2007).

It is not clear if the estrogen receptor status of the original tumour influences the risk of recurrence with HRT use. Following a healthy lifestyle (e.g. not starting/stopping smoking, taking regular weight-bearing exercise, achieving/maintaining a healthy weight) would be a reasonable recommendation for breast cancer survivors,

although studies are limited. These measures may improve bone and cardiovascular health in women with POI in general, may reduce vasomotor symptoms and have been shown to reduce breast cancer recurrence ([Duijts, et al., 2009](#); [Kwan, et al., 2010](#); [McTiernan, et al., 2010](#)).

Non-hormonal treatments may be an option for reducing vasomotor symptoms in women with POI after breast cancer, but evidence is scarce (see also chapter 14). A Cochrane review collected evidence on non-hormonal therapies for relieving hot flushes in women with a history of breast cancer. Selective serotonin (SSRI) and serotonin-norepinephrine (SNRI) reuptake inhibitors, clonidine and gabapentin reduced the number and severity of hot flushes. One of two studies on relaxation therapy showed a significant benefit. The other non-pharmacological therapies discussed in the review (homeopathy, vitamin E, magnetic devices and acupuncture) showed no significant benefit. In all studies, side effects were inconsistently reported ([Rada, et al., 2010](#)). Importantly, the safety of phytoestrogens in women with a history of estrogen-dependent cancer is unknown ([Dennehy, 2006](#)). A recent review on treatment of vasomotor symptoms recommended gabapentin, venlafaxine and fluoxetine for relieving vasomotor symptoms in breast cancer survivors, consistent with the Cochrane review ([Murthy and Chamberlain, 2012](#)). In some cases, when the benefits of reducing debilitating vasomotor symptoms and increasing quality of life outweigh the risks, HRT may still be an option to consider.

In BRCA1/2 mutation carriers without a previous history of cancer, prophylactic BSO before the age of natural menopause is recommended as it substantially reduces the risk of breast, ovarian and fallopian tube cancer ([Rebbeck, et al., 2009](#)). Risk-reducing salpingo-oophorectomy in young women can result in severe hot flushes, vaginal dryness, sexual dysfunction, sleep disturbances, cognitive changes and an increased risk of cardiovascular disease ([Finch, et al., 2011](#); [Finch, et al., 2012](#)).

Concerns have been raised on the effect of HRT on breast cancer risk in BRCA1/2 mutation carriers after prophylactic BSO. A study of 462 mutation carriers showed that HRT after prophylactic BSO did not significantly alter the reduction in breast cancer risk associated with BSO, as compared to BRCA1/2 mutation carriers without BSO or HRT (follow up 3.6 years) ([Rebbeck, et al., 2005](#)). Similar findings were reported in a study evaluating the effect of HRT on the life expectancy of BRCA1/2 mutation carriers after prophylactic BSO. Use of HRT was associated with small changes in life expectancy (+0.17 to -0.34 years) when treatment was stopped at age 50, while continuing HRT for life resulted in reduced life expectancy (-0.79 to -1.09 years) ([Armstrong, et al., 2004](#)). Finally, HRT was shown to significantly reduce hot flushes and night sweats in 164 women after prophylactic BSO ([Madalinska, et al., 2006](#)).

In conclusion, and in contrast to breast cancer survivors, HRT is a treatment option for BRCA1/2 carriers after prophylactic BSO without a history of breast cancer, especially due to the lack of effective non-hormonal therapies without significant side-effects.

## Recommendations

HRT is generally contra-indicated in breast cancer survivors.	B
HRT is a treatment option for women carrying BRCA1/2 mutations but without personal history of breast cancer after prophylactic bilateral salpingo-oophorectomy (BSO).	C

### 12.5.c Women with POI and endometriosis

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus. Induction of medical or surgical castration 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 salpingo-oophorectomy is not a preferred option for relieving pain symptoms in women with endometriosis and should be considered only in women who have completed their family and failed to respond to more conservative treatments (Good practice point) (Dunselman, *et al.*, 2014).

As endometriosis is an estrogen-dependent disease, the use of estrogen replacement therapy in women with endometriosis and premature ovarian insufficiency (for instance after hysterectomy and BSO) could theoretically reactivate residual disease, produce new lesions, or lead to malignant transformation of endometriosis.

The question on how to treat vasomotor symptoms in women with endometriosis has also been discussed in the “ESHRE guideline: Management of women with endometriosis” (Dunselman, *et al.*, 2014).

#### Recommendation

For women with endometriosis who required oophorectomy, combined estrogen/progestogen therapy can be effective for the treatment of vasomotor symptoms and may reduce the risk of disease reactivation.	C
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### 12.5.d Women with POI and other medical issues

Women with POI, can suffer from medical conditions, similar to healthy women. However, in women with POI these medical issues can affect the options for HRT. Although not well studied, some recommendations can be derived from the literature.

#### Migraine

The main issues to consider regarding HRT use in women with POI and migraine are the potential risk of ischaemic stroke and whether replacement treatment might affect the occurrence of migraine. The evidence on which to base recommendations for these women is, however, sparse.

Migraine with aura is a risk factor for ischaemic stroke, which may be greatest in younger women (under 50 years old) (Kurth, *et al.*, 2006). No studies were identified for the risk of stroke in women with POI and migraine, although POI itself is a risk factor (see section 8.1).

HRT use in healthy postmenopausal women may be a risk factor for stroke (Magliano, *et al.*, 2006; Sare, *et al.*, 2008) but the International Headache Society Task Force on Combined Oral Contraceptives & Hormone Replacement Therapy concluded there was insufficient evidence to support any link between stroke and HRT use by migraine-sufferers (Boussier, *et al.*, 2000). A later systematic review from 2007 did not identify any evidence to change this view (MacGregor, 2007).

Surgical menopause may be associated with an increased risk of stroke, which appears to be reduced by estrogen replacement (Parker, *et al.*, 2009; Rivera, *et al.*, 2009). These studies did not specifically consider any potential confounding effect of migraine.

Migraine without aura appears to be associated with low (or falling) levels of estrogen (“estrogen withdrawal”), whereas migraine with aura can be linked to high levels of estrogen. Surgical menopause appears to be associated with the highest prevalence of migraine when compared to natural menopause, presumably because of a sudden reduction of estrogen (see [\(Nappi, et al., 2009\)](#) for a review).

No studies were identified for the dose, type, or route of administration of HRT in women with POI and migraine. Data for normal postmenopausal women with migraine is also minimal and conflicting.

Migraine with aura remains a contraindication for combined oral contraceptive pill use for women with POI.

### Conclusion and considerations

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 sort 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 the HRT if new migraine occurs during replacement therapy.

Transdermal estrogen may have the advantage of providing a constant level of estrogen and may be associated with a lower risk of thrombosis. A small, randomised trial of oral versus transdermal estrogen in postmenopausal women showed no increase in the frequency of migraine in the transdermal group but a significant increase in the oral group [\(Nappi, et al., 2001\)](#). No equivalent studies were identified for women with POI.

Continuous combined regimens have the similar theoretical advantage of providing constant hormone levels. However, a large case control study of postmenopausal women over 45 years did not show any difference in migraine prevalence in women taking estrogen alone or estrogen with progestin [\(Misakian, et al., 2003\)](#).

### Recommendations

Migraine should not be seen as a contraindication to HRT use by women with POI.	GPP
Consideration should be given to changing dose, route of administration or regimen if migraine worsens during HRT.	GPP
Transdermal delivery may be the lowest-risk route of administration of estrogen for migraine-sufferers with aura.	D

## Hypertension

Women with POI show increased cardiovascular morbidity and mortality (see chapter 8). As hypertension is a leading risk for cardiovascular disease, heart attack, and stroke, hypertensive women with POI could be at increased risk for cardiovascular morbidity. Furthermore, hypertension is a well-accepted contraindication for combined oral contraceptives, feeding the caution on prescribing HRT to hypertensive women with POI.

No evidence was found on the effect of HRT in hypertensive POI patients. Langrish and colleagues evaluated cardiovascular health, including 24 hour ambulatory blood pressure, in POI patients receiving physiological (transdermal estradiol and vaginal progesterone) or standard (oral ethinylestradiol and norethisterone) therapy ([Langrish, et al., 2009](#)). Although none of the women were clinically hypertensive, physiological therapy was associated with a lower blood pressure ( $P<0.0001$  for both systolic and diastolic blood pressures) in comparison with the standard regimen. Differences between physiological and standard regimen were found at 3 ( $P<0.05$ ), 6 ( $P<0.05$ ), and 12 months ( $P<0.01$ ) after initiation of treatment.

A recent review summarizing the effect of HRT regimens on blood pressure in normotensive and hypertensive older postmenopausal women, showed significant inconsistencies in studies, due to differences in HRT regimens, age of patients and time since onset of the menopause, and measurement of blood pressure ([Cannoletta and Cagnacci, 2014](#)). In hypertensive postmenopausal women, most studies showed a decrease in systolic and diastolic blood pressure after estrogen therapy, although an increase was found in some studies. Studies evaluating transdermal estradiol and measuring office BP were less conflicting and showed either a neutral or BP lowering effect. The effect of different progestins on blood pressure in hypertensive postmenopausal women is not well studied, but in general progestins do not seem to hamper the effect of estrogen on blood pressure. Recent studies have shown promising results for drospirenone, a novel progestin with aldosterone receptor antagonism, and therefore antihypertensive effects. Hormone therapy combining  $17\beta$ -estradiol with drospirenone has been shown to have a blood pressure-lowering effect in postmenopausal women with elevated blood pressure, in addition to effectively relieving symptoms of the menopause ([White, 2007](#)).

## Recommendations

Hypertension should not be seen as a contraindication to HRT use by women with POI	GPP
In hypertensive women with POI, transdermal estradiol is the preferred method of delivery	C

## History of prior venous thromboembolism (VTE)

Venous thromboembolism is the most prevalent serious adverse effect of HRT ([Canonico, et al., 2008](#)). In the WHI study, an increase in the risk of pulmonary embolism (hazard ratio 2.13, 95% CI 1.39–3.25) was confirmed in women using oral HRT compared to placebo ([Rossouw, et al., 2002](#)). HRT is contra-indicated in postmenopausal women with VTE risk factors, which include being overweight or obese, the presence of thrombophilic disorders, or a history of prior VTE.

No studies were found on the risk of VTE recurrence in women with POI and a history of prior VTE. In older postmenopausal women, 2 placebo controlled RCTs described up to a five-fold higher risk of recurrent VTE in women using oral combined HRT, as compared to placebo ([Hoibraaten, et al., 2000](#); [Cushman, et al., 2004](#)).

Tibolone and transdermal estrogen have been put forward for the treatment of severe vasomotor symptoms in postmenopausal women with a history of prior VTE. Tibolone is widely used for vasomotor symptoms and it was found to be effective in relieving these symptoms (Formoso, *et al.*, 2012). Furthermore, a case-control study showed no increased incidence of VTE in women (aged 50-79) using tibolone (RR 0.92; 95% CI: 0.77-1.10), relative to non-users (Renoux, *et al.*, 2010b). However, data on the long-term safety of tibolone are scarce but raise suspicion of increased risks for breast cancer and stroke (Formoso, *et al.*, 2012). A meta-analysis concluded that the risk for recurrent VTE is not increased in women using transdermal estrogen, as compared to non-users (Canonico, *et al.*, 2008).

The impact of the type of progestogen on VTE recurrence is not well studied, but may be relevant, as the WHI trials showed that the risk of VTE was higher in women using estrogen with medroxyprogesterone acetate, as compared to estrogen alone (Manson, *et al.*, 2013). The study of Canonico and colleagues showed no significant association of micronized progesterone or pregnane derivatives (e.g. dydrogesterone, medroxyprogesterone acetate, cyproterone acetate) with recurrent VTE, while norpregnane derivatives were associated with an increased risk of recurrent VTE (OR 3.9; 95%CI 1.5-10.0). However, these data need confirmation.

Women with POI but at significant risk of VTE may still benefit from HRT and the risks of HRT are unknown for this population. Given that increased age itself is a risk factor for VTE, extrapolation of data from the postmenopausal population may not be appropriate. However, given that no directly relevant studies were identified, it would seem a reasonable caution to seek advice from a coagulation haematologist for at risk women prior to commencing HRT, as prophylactic anticoagulation therapy may be appropriate.

## Recommendations

Women with POI and a history of prior venous thromboembolism (VTE) or thrombophilic disorder should be referred to a haematologist prior to commencing HRT.	GPP
Transdermal estradiol is the preferred route of delivery for women with POI at increased risk of VTE.	B

## Obesity

The main issue to consider regarding HRT use in women with POI who are obese or overweight is the potential risk of VTE. In addition, obesity is a risk factor for hypertension and coronary artery disease (see chapter 8), and premature death (see chapter 5). Indeed, McCarthy showed in a multivariate analysis that women who were obese at the time of interview and who had had an oophorectomy before 40 years of age were more than twice as likely to die (HR 2.23; 95%CI 1.25-3.98) particularly of cardiovascular disease (HR, 2.77; 95%CI 0.91–8.41), as compared to non-obese women with intact ovaries. (McCarthy, *et al.*, 2012).

No studies were found evaluating HRT in overweight or obese women with POI.

The risk of VTE is increased in postmenopausal women with an increased body mass index using oral estrogen therapy (pooled OR 2.6; 95%CI 2.1 to 3.3) (Canonico, *et al.*, 2008). A study on the impact of oral and transdermal estrogen on VTE risk in postmenopausal women (age 45-70 years) who were overweight (25kg/m<sup>2</sup> <BMI < 30 kg/m<sup>2</sup>) or obese (BMI > 30 kg/m<sup>2</sup>) showed that transdermal estrogen does not increase the risk of VTE in women with increased BMI. Users of transdermal estrogen with increased BMI had similar risk as non-users with increased BMI (OR 2.9; 95%CI 1.5-5.8 and OR 2.7; 95%CI 1.7-4.5, respectively for overweight; OR 5.4; 95%CI 2.1-14.1 and

OR 4.0; 95%CI 2.1-7.8, respectively for obesity). An increased VTE risk associated with the use of oral estrogen was confirmed, and compared to non-users with normal weight, the combination of oral estrogen use and being overweight or obese further enhanced VTE risk (OR 10.2; 95% CI 3.5-30.2 and OR 20.6; 95%CI 4.8-88.1, respectively) ([Canónico, et al., 2006](#)).

Throughout the current document, a healthy lifestyle, including a normal body weight or BMI, is recommended for women with POI to reduce the impact of the sequelae of POI and improve quality of life.

### Recommendation

Transdermal estradiol is the preferred method of delivery for women with POI requiring HRT who are obese or overweight.	C
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### Fibroids

Uterine fibroids (myomas or leiomyomas) are benign tumours arising from individual smooth muscle cells of the uterus. Most fibroids are asymptomatic but some women have significant symptoms including abnormal uterine bleeding, pelvic pressure (urinary frequency, constipation) and pain, and reproductive dysfunction.

The potential effect of HRT on fibroids has not been well studied, but fibroid growth could be promoted by estrogens and progestogens. No evidence was found for the effects of HRT on fibroids in women with POI.

Studies in postmenopausal women have been summarized in systematic reviews ([Ang, et al., 2001](#); [Ciarmela, et al., 2014](#)). Two randomized controlled trials compared HRT with tibolone, enrolling a total of 88 women. The trend of the results was that tibolone did not increase fibroid size significantly. Studies on the impact of HRT showed variable results. While some studies showed an increase in the number and size of fibroids, other studies did not find a significant increase in the mean volume of the fibroids before and after HRT. Both reviews stated that none of the studies reported a significant increase in clinical symptoms or adverse effects associated with fibroid growth, and more importantly, most women, even those with growth of fibroids, remained asymptomatic.

### Recommendation

Fibroids are not a contraindication to HRT use by women with POI.	B
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## 12.6. Treatment with androgens

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 major pitfall in this research area is the lack of reliable testosterone assays. Although liquid chromatography-tandem mass spectrometry 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 radioimmunoassays ([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 spontaneous 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 hypoandrogenic 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](#)).

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.

## **12.6.a Indications**

### **Sexual function**

As was noted in [chapter 10](#), 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](#)). From about 2000, a series of randomised, placebo-controlled trials of testosterone patches in oophorectomised women have been carried out, 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 naturally postmenopausal women with and without estrogen therapy ([Davis, et al., 2006](#); [Panay, et al., 2010](#)).

### **Neurological function**

No studies were identified for androgen replacement therapy in women with spontaneous or iatrogenic POI on neurological function. Only one study in girls with Turner syndrome was identified. These girls were between 10 and 14 years old and were 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](#)).

### **Bone health**

Two randomized studies were performed on the effect of adding methyltestosterone (2.5mg/d) to estrogen therapy over 2 years in women with surgical menopause. In one of these studies, spine (but not hip or radius) BMD increased in the group that received testosterone therapy, however, this was not significantly different from estrogen therapy alone ([Watts, et al., 1995](#)). In the second study, spine and hip BMD increased significantly in the androgen plus estrogen group compared with the estrogen alone group ([Barrett-Connor, et al., 1999](#)). A double blind crossover RCT investigated the effect of one year's treatment with oral methyltestosterone in 14 women with Turner Syndrome aged 17-27 who were also taking HRT ([Zuckerman-Levin, et al., 2009](#)). An increase in bone density (total body, lumbar spine, hip, pelvis, trunk) of  $+0.021 \pm 0.01 \text{ g/cm}^2$  (95%CI nor p value given) was seen with methyltestosterone, as well as an increase in lean body mass and decrease in body fat. No studies were identified on DHEA treatment and bone density outcomes for surgically menopausal women or those with spontaneous POI.



## **12.6.b 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 up to 300 micrograms of testosterone per day. The 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). 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](#)).

### **Endometrial effect**

Theoretically, androgen therapy could lead to endometrial hypertrophy by peripheral aromatization of androgens to estrogen. A retrospective study on nearly 260 postmenopausal women using estrogen implants as well as testosterone implants identified an endometrial thickness of >5 mm in 17%, in which in almost two thirds an endometrial polyp was found. On the other hand, androgens are also 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 taking estrogen replacement, similar endometrial biopsy findings were identified between baseline and after 1-year use. Markedly, 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](#)).

These findings suggest that androgen replacement probably leads to an increase of endometrial atrophy. When using estrogen replacement along with testosterone treatment, it is advisable to also add progestin therapy for endometrial safety, as was discussed in section 12.2.b. 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 and Davison, 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 (relative risk 2.48; 95%CI 1.53-4.0) in women included in the Nurses' Health Study with a follow-up of 24 years ([Tamimi, et al., 2006](#)).

## **12.6.c Routes of administration, dose, duration, monitoring**

Testosterone may be administered transdermally (gel/patch/cream), orally or through an implant. No research was identified for any of these routes of administration in women with POI. A search for women who reached menopause normally, 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, 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 taken into account 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 suprphysiological levels in women for which there are no data on safety and efficacy. One study in 447 oophorectomized women aged 24-70 years 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 evidence on efficacy and safety is available after 24 months. No studies have been performed on the monitoring of androgen treatment. It seems wise to evaluate the baseline testosterone concentration before treatment is started, and continue to measure this every 3 to 6 months. Adverse effects should be assessed. The effect of the treatment should be evaluated and if no improvement of sexual function is seen, treatment should be discontinued.

## Recommendations

Women should be informed that androgen treatment is only supported by limited data, and that long-term health effects are not clear yet.	C
If androgen therapy is commenced, treatment effect should be evaluated after 3-6 months and should possibly be limited to 24 months.	GPP

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# 13. PUBERTY INDUCTION

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## Introduction

Most of the available literature on puberty induction in primary ovarian insufficiency concerns studies of girls with Turner Syndrome (TS). Five to 10% of girls with TS retain sufficient ovarian function for puberty to start spontaneously. Most girls show a progressive ovarian failure and need estrogen treatment for complete breast development and withdrawal bleeding. The attainment of an optimal adult height with growth hormone (GH) therapy is another factor to be considered. Lower estrogen doses may stimulate growth, but higher estrogen doses cause acceleration of bone maturation and result in decreased adult height ([Ross, et al., 1983](#); [Ross, et al., 1986](#)).

It is important to educate the patient that estrogen replacement is usually required until the time of normal menopause to maintain feminization and prevent osteoporosis ([Bondy and Turner Syndrome Study Group, 2007](#)). Still, recent studies have shown that a considerable percentage of TS patients discontinue therapy in adult life and are lost to follow-up ([Davies, 2010](#)). Therefore, the continuum of care through childhood and adolescence into adulthood is mandatory.

## **KEY QUESTION: HOW SHOULD PUBERTY BE INDUCED?**

### Clinical evidence

#### *When to start estrogens?*

The optimal age at which to begin remains controversial. Because estrogens accelerate bone maturation, estrogen replacement has traditionally been delayed, often until 15 or 16 years of age, to allow additional time for linear growth with growth hormone therapy ([Chernausek, et al., 2000](#)). More recently, studies have shown that beginning GH at a younger age, thus providing a longer period of estrogen-free GH treatment, may allow initiation of estrogen therapy, at a lower dose, at a more normal age (12-13 years) without loss of adult height ([Reiter, et al., 2001](#); [Massa, et al., 2003](#); [van Pareren, et al., 2003](#); [Stephure and Canadian Growth Hormone Advisory Committee, 2005](#)). Starting estrogen supplementation from the age of 12 years in the absence of a spontaneous start or progression of breast development has been recommended in several reviews on the care of girls with TS ([Kanaka-Gantenbein, 2006](#); [Bondy and Turner Syndrome Study Group, 2007](#); [Davenport, 2008](#); [Pinsker, 2012](#); [Trolle, et al., 2012](#)). This approach can be considered for other causes of delayed or absent puberty when the condition is known from an early age.

#### *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, progestins, and androgens, some of which are not found in humans and are not justified for use in children ([Davenport, 2010](#)). 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 ([Bondy and Turner Syndrome Study Group, 2007](#)). 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 and micronized estradiol have both been used for puberty induction. As oral ethinylestradiol is a synthetic estrogen that is not metabolized by the liver, it can be delivered at relatively low doses. Natural estrogens are metabolised in the liver and must be given either orally in higher doses ([Leung, et al., 2004](#)) or, to avoid the first pass effect, transdermally. Natural estrogens have less pronounced effects on coagulation factors, lipid profiles and blood pressure than synthetic estrogens ([Lobo, 1987](#)). With 17β-estradiol transdermal (TD) patches or percutaneous gel spontaneous pubertal hormonal changes are mimicked and normal pubertal

development is achieved ([Illig, et al., 1990](#); [Cisternino, et al., 1991](#); [Ankarberg-Lindgren, et al., 2001](#); [Piippo, et al., 2004](#)).

Puberty is a relatively slow process and the replacement therapy in the induction process should mimic this ([Hindmarsh, 2009](#)). 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 ([Divasta and Gordon, 2010](#)). To allow for normal breast and uterine development, it seems advisable to delay the addition of progestin at least 2 years after starting estrogen or until breakthrough bleeding occurs ([Bondy and Turner Syndrome Study Group, 2007](#); [Fritz and Speroff, 2010](#)).

Based on these principles, suggested age-specific preparations and doses of estrogen substitution therapy in adolescence are listed in table 13.1. This table is only a guide and individual tailoring of dose and timing will be required.

**Table 13.1: Estrogen substitution therapy in adolescence (adapted from ([Bondy and Turner Syndrome Study Group, 2007](#)))**

Age	Age-specific suggestions	Preparation/dose/comments
12 -13 years	If no spontaneous development and FSH elevated, start low dose estrogens	17β-estradiol (E2) Transdermal: 6.25 µg/day <sup>1</sup> E2 via patch Oral micronized E2: 5 µg/kg/day or 0.25 mg/day
12.5 - 15 years	Gradually increase E2 dose at 6-12 months interval over 2 - 3 years <sup>2</sup> 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)
14 – 16 years	Begin cyclic progestogen after 2 years of estrogen or when breakthrough bleeding occurs	Oral micronized progesterone 100-200 mg/day or dydrogesterone 5-10 mg/day during 12 – 14 days of the month <sup>3</sup>

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> for prolonged treatment progesterone, dydrogesterone or medroxyprogesterone are preferred to other progestogens because of their less negative effect on lipid metabolism and less androgenic effects ([Lobo, 1987](#)).

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 ([Davenport, 2008](#)). 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.

## 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 17 $\beta$ -estradiol in 56 GH-treated TS girls without spontaneous start of pubertal development starting at mean age 12.7 ( $\pm$  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 years delay (Bannink, *et al.*, 2009). In 15 girls with hypogonadism (mean age 18.8  $\pm$  0.9 years) with increasing doses of transdermal estradiol (treatment period up to 3 years), breast development was obtained in all up to stage 4, pubic hair ranged from stage 1 to 5 (Cisternino, *et al.*, 1991). 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). In TS, suboptimal breast development could also be due to poor development of breast anlage and widely spaced nipples (known as a “shield chest”) (Saenger, 2004).

### *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 E2 group (Nabhan, *et al.*, 2009). Four studies reported inconclusive results for uterine size after oral estrogen therapy. In the study of Bannink and colleagues uterine volume, length and shape of the TS girls were suboptimal at age 19.9 ( $\pm$ 2.2) years, after on average 7.1 ( $\pm$  2.2) years of oral estrogen therapy compared to women of the same age (Bannink, *et al.*, 2009). Similar findings were reported by 2 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 ( $\pm$  2.2) years), all girls had normal uterine length and volume at final assessment at age 17.1 ( $\pm$  2.8) years (McDonnell, *et al.*, 2003). Illig and colleagues investigated the use of low-dose transdermal 17 $\beta$ -estradiol for the induction of puberty in nine TS girls. Three girls being followed longitudinally showed normal uterine growth and maturation to the adult configuration (Illig, *et al.*, 1990).

### *Metabolic actions*

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 Turner Syndrome (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). Two studies concluded that transdermal estradiol may be preferred over oral administration for puberty induction, as the transdermal route may have less deleterious effect on hepatic metabolism and may be associated with lower total estrogen exposure and be more physiological than oral estrogen (Jospe, *et al.*, 1995) (Torres-Santiago, *et al.*, 2013).

### *Bone*

The study of Nabhan compared the effect of oral or transdermal estrogen on bone accrual in GH-treated TS girls (Nabhan, *et al.*, 2009) and concluded that transdermal estradiol resulted in a significantly greater change in spine bone density at 12 months compared with conjugated oral estrogen (bone mineral density 0.12  $\pm$  0.01 vs. 0.06  $\pm$  0.01 g/cm<sup>2</sup>, P=0.004). However, in the study of Torres-Santiago, bone mineral density accrual after 6 and 12 months was similar between TS girls treated with oral or transdermal 17 $\beta$ -estradiol (Torres-Santiago, *et al.*, 2013). No long-term studies were found comparing the effect of oral versus transdermal estrogen on bone health during adolescence.

## Conclusion and considerations

Estrogen therapy should be started from the age of 12 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 only form of therapy to achieve natural levels of estradiol in blood and mimic normal estradiol physiology in adolescence and adulthood ([Ankarberg-Lindgren, et al., 2001](#); [Davenport, 2010](#)).

For regular withdrawal bleeding and normal breast and uterine development progestogen should be added at least 2 years after starting estrogen or when breakthrough bleeding occurs ([Bondy and Turner Syndrome Study Group, 2007](#); [Fritz and Speroff, 2010](#)).

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 ([Davenport, 2010](#)).

With increasing doses of oral and transdermal 17 $\beta$ -estradiol normal breast and pubic hair development can be achieved ([Cisternino, et al., 1991](#); [Bannink, et al., 2009](#); [Nabhan, et al., 2009](#)). With higher starting doses of E2 and/or more rapid dose escalation, breast development should be monitored for stretch marks and asymmetry.

The extent of uterine development achievable with oral estrogens is uncertain ([Paterson, et al., 2002](#); [Snajderova, et al., 2003](#); [Bannink, et al., 2009](#)), while normal uterine development after transdermal estrogen is only reported in one study with a limited sample size ([Illig, et al., 1990](#)). Short-term comparison of oral and transdermal estrogen showed a significant greater uterine growth with transdermal E2 ([Nabhan, et al., 2009](#)). No long-term studies compared the effect of oral versus transdermal estrogen on uterine growth and development, or more importantly obstetric outcomes.

There is either no effect or comparable effects of oral or transdermal estrogen on body composition and several metabolic parameters in adolescents ([Mauras, et al., 2007](#); [Nabhan, et al., 2009](#); [Torres-Santiago, et al., 2013](#)).

The short-term effect of oral or transdermal 17 $\beta$ -estradiol on bone accrual was comparable ([Torres-Santiago, et al., 2013](#)). No long-term studies exist in adolescent girls.

## Recommendations

Puberty should be induced or progressed with 17 $\beta$ -estradiol, starting with low dose at the age of 12 with a gradual increase over 2 to 3 years.	C
In cases of late diagnosis and for those girls in whom growth is not a concern, a modified regimen of estradiol can be considered.	D
Evidence for the optimum mode of administration (oral or transdermal) is inconclusive. Transdermal estradiol results in more physiological estrogen levels and is therefore preferred.	B

The oral contraceptive pill is contra-indicated for puberty induction.	D
Begin cyclical progestogens after at least 2 years of estrogen or when breakthrough bleeding occurs.	C

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# 14. COMPLEMENTARY TREATMENTS IN POI

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## Introduction

Hormone replacement therapy (HRT) is commonly used in women with POI to prevent or treat menopausal sequelae. However, some women with POI may choose against HRT, while for other women, including women with POI after breast cancer treatment, studies have shown severe adverse events and HRT may not be appropriate.

Both women and physicians have increased interest in alternatives for HRT and are interests in both pharmacological alternatives, and non-pharmacological therapies to relief vasomotor symptoms and increase quality of life.

In this section the evidence on alternative and complementary therapies for relief of symptoms in POI is summarized. Indirect evidence on women after natural menopause is added.

### **KEY QUESTION: WHAT COMPLEMENTARY TREATMENTS ARE AVAILABLE IN POI?**

## Clinical evidence

The literature search included the following alternative and complementary therapies: lifestyle changes (smoking, diet, exercise, and alcohol), traditional Chinese medicine, herbal medicine, acupuncture, phyto-estrogens, and non-hormonal therapies. The outcomes include relief of vasomotor symptoms, and infertility.

### Women with POI

We did not identify any RCTs, cohort or case-control studies evaluating alternative and complementary treatments in women with POI, as defined in chapter 2.

A pilot study assessed 31 women with POI (mean age 35 years) with a mean history of amenorrhea of 8 months (SD 6; range, 4-25) before and after acupuncture once every other day for three months. Compared to baseline, participants showed a significant reduction in the average serum FSH, LH and E2 levels at the end of treatment. No serious adverse events were reported ([Chen, et al., 2014](#)).

Some case reports have been published. Chao reported ovulation after the administration of Chinese herbal medicine for 3 months in a women with POI and secondary amenorrhea for 8 years ([Chao, et al., 2003](#)). Letur-Konirsch reported that combined pentoxifylline (PTX) and tocopherol (Vitamin E) reduces fibroatrophic uterine lesions and improves the uterine response to HRT, thus allowing embryo implantation and ongoing pregnancy in 3 women with POF and uterine resistance to HRT ([Letur-Konirsch and Delanian, 2003](#)).

It is important to stress that these studies represent very low quality evidence, and that indications for efficacy could be influenced by the fluctuating character of POI.

### Women with vasomotor symptoms / infertility

#### *Lifestyle changes (smoking, diet, exercise, alcohol)*

We found no studies investigating the effects of smoking cessation or a healthy diet on the relief of vasomotor symptoms in women with POI, or after natural menopause.

The evidence of the effect of exercise on vasomotor symptoms is limited, as most studies evaluated the effect of exercise on bone health. In a study of Duijts and colleagues, physical exercise had a beneficial effect on vasomotor symptoms in women with breast cancer treatment induced menopause ([Duijts, et al., 2012](#)). Three studies compared exercising with sedentary postmenopausal women. Kemmler and colleagues reported that exercise



had a positive effect on bone health, physical fitness, insomnia and mood, but not on other vasomotor symptoms ([Kemmler, et al., 2004](#)). Chan and colleagues found a beneficial effect of Tai Chi-Chun exercise on bone loss ([Chan, et al., 2004](#)). Gauthier reported a beneficial effect of exercise limited to bone structure submitted to sufficient mechanical force ([Gauthier, et al., 1992](#)). It is important to mention that all studies investigated women between 45 and 60 years of age.

#### *Non-hormonal therapies*

Not surprisingly, all studies on non-hormonal therapies for vasomotor symptoms are performed on breast cancer survivors.

In a randomized controlled trial, venlafaxine was compared with clonidine for the relief of hot flushes in women after breast cancer treatment. Both therapies had similar efficacy - with a 50% reduction in hot flushes in 2/3 of the women – and were both well tolerated. The authors concluded that both venlafaxine and clonidine are good alternatives to HRT for the prevention of hot flushes in women after breast cancer treatment ([Buijs, et al., 2009](#)).

A Cochrane review collected evidence on non-hormonal therapies (selective serotonin (SSRI) and serotonin-norepinephrine (SNRI) reuptake inhibitors (6RCTs), clonidine (2 RCTs), gabapentin (1 RCT), relaxation therapy (2 RCTs) homeopathy (2 RCTs), vitamin E (1 RCT), magnetic devices (1 RCT), acupuncture (1 RCT)) for relieving hot flushes in women with a history of breast cancer. They reported that three of the pharmacological treatments (SSRIs and SNRIs, clonidine and gabapentin) reduced the number and severity of hot flushes. One of two studies on relaxation therapy showed a significant benefit. None of the other non-pharmacological therapies had a significant benefit and side-effects were inconsistently reported ([Rada, et al., 2010](#)).

Non-hormonal lubricants and moisturizers are discussed in [section 10.3](#): treatment of genito-urinary symptoms

#### *Phyto-estrogens: soy and red clover*

Phyto-estrogens are plant substances that have similar effects to estrogen. Two groups of phyto-estrogens, isoflavones and lignans, can be found in soybeans-red clover, and flaxseed, respectively.

In observational studies, higher intake of soy was associated with lower fracture risk, especially early menopause ([Zhang, et al., 2005](#)). A systematic review found no clear benefit of soy foods, soy extracts, or red clover extracts on hot flushes and other vasomotor symptoms ([Krebs, et al., 2004](#)). One recent study showed a beneficial effect of soy isoflavones as compared to placebo on hot flushes, and other menopausal women with limited side effects in postmenopausal women over the age of 45 ([Ye, et al., 2006](#)). Mittal and colleagues reported a positive effect of soy isoflavones as compared to placebo on urogenital symptoms, but not on thyroid profile or vasomotor symptoms in oophorectomised women under the age of 55 years ([Mittal, et al., 2011](#)). The safety of phyto estrogens in women with a history of estrogen- dependent cancer is unknown ([Dennehy, 2006](#)).

#### *Black cohosh*

Black Cohosh is a plant native to North America widely used for the relief of vasomotor symptoms. Studies have been performed in women with vasomotor symptoms. A Cochrane review reports no significant improvement in black cohosh versus placebo in the frequency of hot flushes, or menopausal symptom scores ([Leach Matthew and Moore, 2012](#)). Another review stated a potential role of black cohosh for relieving hot flushes, vaginal atrophy, and psychological symptoms ([Dennehy, 2006](#)). Side effects are limited, although hepatotoxicity has been reported ([Huntley and Ernst, 2003](#)) and safety of black cohosh in cancer survivors is still in question. Black cohosh is approved by the German Commission E, which recommends limiting the use to 6 months due to the lack of long-term safety data. ([Dennehy, 2006](#))

#### *Other supplements*

Other supplements that have been recommended for reducing vasomotor symptoms include evening primrose oil (*Oenothera biennis*), dong quai (*Angelica sinensis*), Panax ginseng, wild yam (*Dioscorea villosa*), and vitamin E. Limited studies on these herbs did not show clear benefit for relieving vasomotor symptoms ([Kronenberg and](#)

[Fugh-Berman, 2002](#); [Huntley and Ernst, 2003](#)). One study did show a modest reduction in hot flushes in breast cancer survivors taking vitamin E (800 IU/day for 1 month) compared with placebo ([Kronenberg and Fugh-Berman, 2002](#)).

## Conclusion and considerations

Alternative and complementary therapies appeal to women with POI as these therapies are perceived as being natural with fewer side effects than hormone replacement treatment.

As alternative therapies are marketed as food supplements rather than medical treatments, they are not subject to rules of standardisation (of for instance the formula and constitution of the herbal preparation), or the need for studies supporting their efficacy and safety.

We could not find any RCTs, cohort or case-control studies on the efficacy and safety of alternative and complementary treatments on fertility and vasomotor symptoms in women with POI.

Indirect evidence for menopausal women indicates a potential benefit of non-hormonal treatments (SSRIs and SNRIs, clonidine and gabapentin), and black cohosh for relieving hot flushes. However, due to the lack of safety data, caution is warranted with alternative treatments in women with a history of estrogen- dependent cancer.

With regard to lifestyle, evidence is again limited. However, a healthy lifestyle, including a balanced diet, weight-bearing exercise, maintaining a healthy body weight, cessation of smoking and moderation of alcohol intake is believed to have a beneficial effect on general health and on the sequelae of POI, particularly the effects of POI on bone and cardiovascular health, and therefore maintaining a healthy lifestyle is advised in the corresponding chapters.

## Recommendations

Women with POI should be advised of risk factors that they can modify through behavioural change (e.g. stopping smoking, taking regular weight-bearing exercise, healthy weight).	GPP
Women should be informed that for most alternative and complementary treatments evidence on efficacy is limited and data on safety are lacking.	B

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# APPENDIX 1: ABBREVIATIONS

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17 $\alpha$ -OH-Ab	17 $\alpha$ -hydroxylase antibodies
21OH-Ab	21-hydroxylase antibodies
Ab	Antibodies
ACA	Adrenocortical antibodies
ACTH	Adrenocorticotrophic hormone
AD	Alzheimer's disease
AMH	Anti-Müllerian hormone
APS	Autoimmune polyendocrine syndrome
ART	Assisted reproductive technology
ASI	Aortic size index
ASRM	American Society for reproductive medicine
BMD	Bone mineral density
BMI	Body mass index
BP	Blood pressure
BSO	Bilateral salpingo-oophorectomy
CBT	Cognitive behavioural therapy
CEE	Conjugated equine estrogens
CHD	Coronary heart disease
CI	Confidence interval
COCP	Combined oral contraceptive pill
CT	Computed tomography
CVD	Cardiovascular disease
DEXA	Dual energy X-ray absorptiometry
DHEA	Dehydroepiandrosteron
E2	17 $\beta$ -estradiol
ECG	Electrocardiogram
EE	Ethinylestradiol
FISH	Fluorescent in Situ Hybridization
FRAX	WHO fracture risk assessment tool
FSH	Follicle stimulating hormone
FXTAS	Fragile-X-associated tremor/ataxia syndrome
GDG	Guideline development group
GH	Growth hormone
GIN	Guidelines international network
GnRH <sub>a</sub>	Gonadotrophin releasing hormone analogue
GPP	Good practice point
HDL	High-density lipoprotein
HFEA	Human Fertilisation and Embryology Authority
HFNS	Hot flushes and night sweats
HLA	Human leukocyte antigen
HR	Hazard ratio
HRQOL	Health-related quality of life

HRT	Hormone replacement therapy
HSDD	Hypoactive sexual desire disorder
ICSI	Intracytoplasmic sperm injection
IU	International units
IUGR	Intrauterine growth restriction
IVF	In vitro fertilization
LDL	Low-density lipoprotein
LH	Luteinising hormone
MAR	Medically assisted reproduction
MPA	Medroxyprogesterone acetate
MRI	Magnetic resonance imaging
NETA	Norethisterone acetate
OCP	Oral contraceptive pill
oGTT	Oral glucose tolerance test
OR	Odds ratio
P450SCC	Cytochrome P450 side-chain cleavage enzyme
PCR	Polymerase chain reaction
POI	Premature ovarian insufficiency
pSSR	Physiological sex steroid replacement
QCT	Quantitative computed tomography
QOL	Quality of life
QUS	Quantitative ultrasound
RCT	Randomized controlled trial
RNI	Recommended nutritional intake
RR	Relative risk
SCA	Steroid-cell autoantibodies
SERMs	Selective estrogen receptor modulators
SLE	Systemic lupus erythematosus
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TD	Transdermal
TPO	Thyroid peroxidase
TPO-Ab	Thyroid peroxidase autoantibodies
TS	Turner syndrome
TSH	Thyroid stimulating hormone
VTE	Venous thromboembolism
WHI	Women's health initiative
WHO	World health organisation

## APPENDIX 2: GLOSSARY

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**Amenorrhea:** Absence or suppression of the menstrual discharge ([Oxford English Dictionary](#)).

**Cancelled cycle:** an ART cycle in which ovarian stimulation or monitoring has been carried out with the intention to treat, but did not proceed to follicular aspiration or, in the case of a thawed embryo, to embryo transfer.

**Clinical pregnancy rate:** The number of clinical pregnancies expressed per 100 initiated cycles, aspiration cycles or embryo transfer cycles ([Zegers-Hochschild, et al., 2009](#)).

**Full-term birth:** A live birth or stillbirth that takes place between 37 completed and 42 completed weeks of gestational age ([Zegers-Hochschild, et al., 2009](#)).

**Galactosaemia:** A group of inherited enzyme deficiencies which feature elevations of galactose in the blood. This condition may be associated with deficiencies of galactokinase; udpglucose-Hexose-1-Phosphate Uridyltransferase; or udpglucose 4-epimerase. The classic form is caused by udpglucose-Hexose-1-Phosphate Uridyltransferase deficiency, and presents in infancy with failure to thrive, vomiting and intracranial hypertension. Affected individuals also may develop mental retardation, jaundice; hepatosplenomegaly; ovarian failure (POI); and cataracts. ([Menkes, 1995](#))

**Hypopituitarism:** Diminution or cessation of secretion of one or more hormones from the anterior pituitary gland (including LH; FSH; somatotropin; and corticotropin). This may result from surgical or radiation ablation, non-secretory pituitary neoplasms, metastatic tumors, infarction, pituitary apoplexy, infiltrative or granulomatous processes, and other conditions ([MESH database, 2015](#)).

**Hypothyroidism:** A condition in which the level of thyroxine in the blood is abnormally low resulting in a decreased metabolic rate and which when severe causes cretinism (i.e. imperfect mental and physical development) (if the condition was congenital) and myxœdema (i.e. the symptoms of which include mental slowness, muscle weakness, reduced body temperature, hair loss, and a firm oedematous thickening of the skin) (if acquired) ([Oxford English Dictionary](#)).

**In vitro fertilization (IVF):** An ART procedure that involves extracorporeal fertilization ([Zegers-Hochschild, et al., 2009](#)).

**Infertility (clinical definition):** A disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse ([Zegers-Hochschild, et al., 2009](#)).

**Live birth rate:** The number of deliveries that resulted in at least one live born baby expressed per 100 initiated cycles, aspiration cycles or embryo transfer cycles. When delivery rates are given, the denominator (initiated, aspirated, or embryo transfer cycles) must be specified ([Zegers-Hochschild, et al., 2009](#)).

**Low birth weight:** Birth weight less than 2,500 grams ([Zegers-Hochschild, et al., 2009](#)).

**Medically assisted reproduction (MAR):** reproduction brought about through ovulation induction, controlled ovarian stimulation, ovulation triggering, ART procedures, and intrauterine, intracervical, and intravaginal insemination with semen of husband/partner or donor ([Zegers-Hochschild, et al., 2009](#)).

**Neoplasia:** The development or presence of a neoplasm ([Oxford English Dictionary](#)).

**Neoplasms:** A new and abnormal growth of tissue in the body, specifically one resulting from uncontrolled proliferation of cells; a benign or malignant tumour ([Oxford English Dictionary](#)).

**Oligomenorrhea** : Abnormally light menstrual flow; infrequent menstruation; prolongation of the length of the menstrual cycle ([Oxford English Dictionary](#))

**Osteopenia**: T scores between 1 and 2.5 SDs below the average for the reference population were classified as osteopenia ([World Health Organization, 1994](#)).

**Osteoporosis**: A disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Measurements 2.5 SDs or more below the young adult mean were classified as osteoporosis ([World Health Organization, 1994](#)).

**Placenta Accreta/Percreta**: Abnormal placentation in which all or parts of the placenta are attached directly to the myometrium due to a complete or partial absence of decidua. It is associated with postpartum haemorrhage because of the failure of placental separation ([MESH database, 2015](#)).

**T-score**: T scores are used to express the BMD of a patient as compared to a reference population. T score = BMD of participant – mean BMD of reference population/SD of BMD of reference population. Bone density (normal, osteopenia, osteoporosis) are defined in relation to T scores by the WHO as follows:

BMD-based definitions of bone density ( <a href="#">World Health Organization, 1994</a> )	
Normal	T-score above (i.e. better than) or equal to – 1.0
Low bone mass (Osteopenia)	T-score between – 1.0 and – 2.5
Osteoporosis	T-score below (i.e. worse than) or equal to – 2.5

**Turner Syndrome**: A syndrome of defective gonadal development in phenotypic females associated with the karyotype 45,X (or 45,XO). Patients generally are of short stature with undifferentiated gonads (streak gonads), sexual infantilism, hypogonadism, webbing of the neck, cubitus valgus, elevated gonadotropins, decreased estradiol level in blood, and congenital heart defects. ([MESH database, 2015](#)). Turner syndrome (TS) occurs in phenotypic females missing all or part of one sex chromosome, with the most common karyotypes as follows: 45,X; 45,X/46XX or XY mosaics; 46,XiXq; 46,XdelXp; 46,XrX; and many of these latter groups have a 45,X cell line as well ([Bondy, 2005](#)).

**Venous Thromboembolism**: Obstruction of a vein or veins (embolism) by a blood clot (thrombus) in the blood stream ([MESH database, 2015](#)).

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## APPENDIX 3: GUIDELINE GROUP

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This guideline was developed by a guideline development group (GDG) set up by the ESHRE Special Interest Group reproductive endocrinology. The GDG constituted clinicians with special interest in women with premature Ovarian Insufficiency, including an expert in bone health, cardiology, psychology and neurology, a literature methodology expert and a patient representative.

### Chair of the GDG

Lisa Webber University College London Hospital (UK)

Melanie Davies University College London Hospital (UK)  
(Co-chair until December 2014)

### GDG members

Richard Anderson University of Edinburgh (UK)

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### Invited experts

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Anette Tonnes Pedersen Department of Gynaecology, Rigshospitalet Copenhagen (Denmark)

### Patient representative

Jane Bartlett The Daisy Network (UK)

### Methodology expert

Nathalie Vermeulen European Society of Human Reproduction and Embryology



## Declarations of interest

All members of the guideline development group were asked to declare possible conflicts of interest by means of the disclosure forms (see ESHRE manual for guideline development).

Name	Conflict of interest
Lisa Webber	<i>None declared.</i>
Melanie Davies	<i>None declared.</i>
Richard Anderson	<i>None declared</i>
Didi Braat	<i>Research grants from MSD, Ferring and Serono.</i>
Beth Cartwright	<i>None declared</i>
Renata Cifkova	<i>None declared</i>
Sabine de Muinck Keizer-Schrama	<i>None declared.</i>
Eef Hogervorst	<i>None declared</i>
Femi Janse	<i>None declared</i>
Lih-Mei Liao	<i>None declared.</i>
Veljko Vlaisavljevic	<i>None declared.</i>
Carola Zillikens	<i>None declared.</i>
Jane Bartlett	<i>None declared.</i>
Nathalie Vermeulen	<i>None declared.</i>

To further minimise potential conflicts of interest, the synthesis of the evidence was performed by the expert GDG member and the methodology expert (with no conflicts of interest). The possible influence of conflicts of interest was taken into account in the division of key questions among GDG members. Conflicts of interest were further limited by the discussion of the evidence and draft recommendations in the GDG, until consensus of the GDG was reached.

## APPENDIX 4: RESEARCH RECOMMENDATIONS

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During the literature searches and discussion of the availability and strength of the evidence, several topics were found for which there is insufficient evidence to answer the key questions. For the benefit of women with POI, the GDG recommends that future research in the field of POI is focussed on these research gaps and that researchers attempt to perform high-quality randomized controlled trials and/or cohort studies. Research recommendations were formulated on the different topics described in this document:

### Diagnosis

Studies should be set-up to determine the accuracy of biochemical markers (e.g. FSH, AMH) in the diagnosis of POI, and establish appropriate cut-off values.

### Life expectancy

Prospective studies are needed on long-term health outcomes of POI, examining contributory factors such as smoking, and the effect of long-term HRT.

### Fertility

Although several issues of fertility in women with POI have been studied, high-quality evidence is lacking on treatments for increasing ovarian activity with live birth rate as the main outcome measure. Also, studies are needed on obstetric complications after oocyte donation and in women with Turner Syndrome.

### Bone health

Evidence on bone health in women with POI is largely derived from studies in older postmenopausal women. Studies are needed that assess the lifetime risk of fracture in women with POI, and the potential of hormonal and non-hormonal interventions to decrease the risk.

### Cardiovascular health

Studies are needed on cardiovascular risk factors in women with POI, especially on known cardiovascular risk factors (autoimmune comorbidities (SLE), previous radiation exposure, distress, anxiety and depression) and whether these need to be evaluated as additional risk factors in women with POI. Furthermore, development of specific screening tools to assess cardiovascular risk in women with POI and women with Turner Syndrome is recommended.

### Psychological health, wellbeing and quality of life

Multi-centre, multi-disciplinary, longitudinal studies (in nations that share broadly similar health service structures) are required to elicit information from socio-culturally and socio-economically representative samples of women with POI established on normative age-appropriate hormonal profiles. Endpoint measurements should include wellbeing (e.g. QOL) and distress (e.g. depression) equally. However, research should not just measure endpoints but its most likely predictors – medical (e.g. surgical menopause for various reasons in younger and older age groups) and psychological (e.g. stigma, ([Slade, et al., 2007](#)); or role disengagement and reengagement, see for example ([Wrosch, et al., 2003](#)).

Regarding interventions to reduce the impact of POI on quality of life and psychological health, very little evidence was retrieved in the literature studies. New studies in POI should aim at developing and evaluating interventions that focus on limiting the negative effects of social stigma, renegotiate identity and overcome obstacles to relationships and other life goals, and on treating mental health problems that emerge upon the diagnosis and/or

stress of treatment. Also, tools that assess mental health risk where distress appears to be extreme should be developed and evaluated in women with POI.

### **Sexual function**

The strategic development of an inter-disciplinary framework is recommended for evaluating the complex relationships between POI and multiple dimensions of psychosexual wellness and sexual function using both quantitative and qualitative methods with surgical and spontaneous POI samples across age, social, economic and ethnic groups.

### **Neurological function**

Data suggest an increased risk of neurological disorders in untreated POI after oophorectomy with hysterectomy, this effect may be most apparent on global cognitive and verbal memory tests, as well as on brain scans and other markers of Alzheimer's disease. Further better quality research in women with POI and cognitive function/risk for dementia needs to be done including that using models of POI using GnRH agonists. Women with breast cancer undergoing treatment also need to be better assessed for cognitive decline.

### **Hormone replacement therapy**

Data indicate that HRT has beneficial effects for women with POI, although the effects on life expectancy, quality of life, and neurological function are inconclusive. Furthermore, transdermal estradiol is suggested to be superior to oral estrogens, especially in women with underlying medical conditions, but both treatments should be compared in RCTs evaluating efficacy, patient's satisfaction and side effects, before firm conclusion can be drawn. Finally, evidence on androgen therapy is scarce, and studies should be performed to clarify whether there is a role for androgens in the treatment of women with POI.

### **Puberty induction**

Long-term studies are needed to identify optimal therapy for puberty induction and maintenance in adolescent girls with POI.

### **Complementary treatments**

Although used and marketed, there are virtually no high quality studies evaluating the efficacy and safety of complementary treatments in women with POI. Such studies are necessary for these treatments to be perceived as a valid and safe alternative to HRT in women with POI.

### **Other topics**

Studies should be organised to clarify the optimal approach for oncological patients, a growing group of POI patients. Currently the management of these patients weight the lack of hormones against the risk of a secondary neoplasia.

Collection of good quality prospective observational data on women with POI could clarify several of the above research recommendations, especially on the topics where long term RCT data are not available.

The use of ovarian stem cells in women with POI

### **References**

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# APPENDIX 5: METHODOLOGY

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## Guideline development

European Society of Human Reproduction and Embryology (ESHRE) guidelines are developed based on the Manual for ESHRE guideline development (W.L.D.M. Nelen, C. Bergh, P. de Sutter, K.G. Nygren, J.A.M. Kremer Manual for ESHRE guideline development 2009), which can be consulted at the ESHRE website ([www.eshre.eu](http://www.eshre.eu)). The principal aim of this manual is to provide stepwise advice on ESHRE guideline development for members of ESHRE guideline development groups. Additionally, the expectation is that this approach will improve the methodological quality of ESHRE guidelines and will have a positive impact on the quality of European reproductive healthcare delivery. The manual has been developed by the Special Interest Group Safety and Quality in ART and has been approved by the Executive Committee. This manual describes a 12-step procedure for writing clinical management guidelines by the guideline development group, supported by the ESHRE methodological expert:

1. guideline topic selection
2. formation of the guideline development group
3. scoping of the guideline
4. formulation of the key questions
5. search of evidence
6. synthesis of evidence
7. formulation of recommendations
8. writing the guideline's draft version
9. consultation and review
10. guideline dissemination
11. guideline implementation and evaluation and
12. guideline updating.

The current guideline was developed and funded by ESHRE, which 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, online web tool, publication costs). Except for reimbursement of their travel expenses, GDG members did not receive any payment for their participation in the guideline development process.

A small initial guideline group started on the scope of the guideline. Based on the scope and the content of the guideline, clinical experts in POI in different fields were searched over Europe. We strived towards a balance in gender and location within Europe, but must admit that the final guideline development group is skewed towards clinicians from the UK. After defining the scope of the guideline, Dr M. Davies and Dr L. Webber, outlined a first set of provisional key questions that needed to be addressed in the guideline. A meeting of the guideline development group was set up to discuss these provisional questions and redefine them through the PICO process (patients – interventions – comparison – outcome). This resulted in a final list of 31 key questions. Based on the defined key words, literature searches were performed by the methodological expert (Dr. 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 to 1 April 2014.

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 randomized controlled trials, and further to cohort studies and case reports, following the hierarchy of the levels of evidence. Preliminary searches were pre-

sifted by the methodological expert based on title and abstract. An expert GDG member, to whom a specific question was assigned, continued with sifting the literature search results, based on title, abstract and his knowledge of the existing literature. If necessary, additional searches were performed in order to get the final list of papers. For selected questions, an additional search in PsycInfo was added. The quality of the selected papers was assessed by means of the quality assessment checklist, defined in the ESHRE guideline manual. Furthermore, the evidence was collected and summarized in an evidence table according to GIN format (<http://www.g-i-n.net/activities/etwg>). The quality assessment and evidence tables were constructed by the expert GDG members and reviewed by the methodological expert.

Based on the collected evidence, draft recommendations were written by the assigned expert GDG member in collaboration with the methodological expert. Two 2-day GDG meeting were organized to discuss the draft recommendations and the supporting evidence and to reach consensus on the final formulation of the recommendations. The guideline chairs and methodological expert collected all recommendations and combined them into the ESHRE guideline entitled: “Management of women with premature ovarian insufficiency”

## Grades of recommendations

All included studies were assessed to determine the quality of evidence. Based on the study type and quality, studies were scored from 1++ to 4. The combined evidence to answer a specific clinical key questions was scored from high (A) to very low quality (D), based on the included studies and their quality. Finally, the recommendations were formulated based on a standard phrasing, so they reflect the strength of the evidence. It is important to note that the grade of a recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation. This information is summarized in the table below:

Grades of recommendations	Supporting evidence
<b>A</b>	Meta-analysis, systematic review or multiple randomized controlled trials (RCTs) (high quality)
<b>B</b>	Meta-analysis, systematic review or multiple RCTs (moderate quality) Single RCT, large non-randomized trial, case-control or cohort studies (high quality)
<b>C</b>	Single RCT, large non-randomized trial, case-control or cohort studies (moderate quality)
<b>D</b>	Non-analytical studies, case reports or case series (high or moderate quality)
<b>GPP</b>	Expert opinion

## Strategy for review of the Guideline draft

After finalisation of the guideline draft, the review process was started.

As POI is a multidisciplinary disease, the guideline development group sent the individual chapters to experts in the topic for review and comments.

Also, the draft guideline was published on the ESHRE website, accompanied by the reviewers' comments form and a short explanation of the review process. The guideline was open for review between 1 June 2015 and 15 August 2015.

To notify interested clinicians, an invitation to review the guideline was sent by email to all members of the ESHRE SIG of Reproductive endocrinology.

Selected reviewers were invited personally by email. These reviewers included:

- Coordinators and deputies of the ESHRE SIG of Reproductive endocrinology and the ESHRE SIG Quality and Safety in ART.
- Contact persons of patient organisations across Europe.
- Contact persons of international and national societies on POI, reproductive endocrinology, or menopause across Europe.

All reviewers that submitted comments are listed in appendix 6. The Reviewer comments processing report, including further information on the review and a list of all comments per reviewer with the response formulated by the GDG will be published on the ESHRE website.

## Guideline Implementation strategy

The standard dissemination procedure for all ESHRE guidelines comprises publishing (3 steps) and announcement (6 steps).

Each guideline is published on the ESHRE Website and in Human Reproduction. The announcement procedure includes an announcement in "Focus on Reproduction", a newsflash on the ESHRE website homepage and a news item in the digital ESHRE newsletter. All participants in the annual ESHRE meeting will be informed about the development and release of new guidelines; all related national societies and patient organisations are separately informed about the guideline release.

Patient versions of the guideline will be developed by a subgroup of the GDG together with patient representatives. This is a translation of the recommendations in everyday language, with emphasis on questions important to patients. It aims to help patients understand the guideline's recommendations and facilitates clinical decision-making.

To further enhance implementation of the guideline, the members of the GDG, as experts in the field, will be asked to select recommendations for which they believe implementation will be difficult. They will be asked to elaborate on the barriers to implementation for each selected recommendation (variance in practice, costs, need for resources, contradictory evidence) and make suggestions for tailor-made implementation interventions (e.g. option grids, flow-charts, additional recommendations, addition of graphic/visual material to the guideline). Based on this, 2 or 3 tools for implementation tailored to the specific guideline may be developed.

## Schedule for updating the guideline

Guidelines should be kept up to date. They should be considered for revision four years after publication. Two years after publication, a search for new evidence will be performed by the methodology expert. In the case of important new findings, the methodology expert will contact the chair of the GDG and decide the necessity of an updated version of the guideline.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found at [www.eshre.eu/guidelines](http://www.eshre.eu/guidelines).

## Reference

Scottish Intercollegiate Guidelines Network EH, 8-10 Hillside Crescent, Edinburgh EH7 5EA. [www.sign.ac.uk](http://www.sign.ac.uk). 2010.

## APPENDIX 6: REVIEWERS OF THE GUIDELINE DRAFT

As mentioned in the methodology, the guideline draft was open for review for 6 weeks, between 24 June and 6 August 2015. All reviewers, their comments and the reply of the guideline development group are summarized in the review report, which is published on the ESHRE website as supporting documentation to the guideline. The list of representatives of professional organisation, and of individual experts that provided comments to the guideline are summarized below.

Representative	Professional organisation
Nick Panay	<i>British Menopause Society</i>
Jan Bosteels	<i>CEBAM, the Belgian centre for EBM</i>
Philippe Bouchard	<i>European Society of Endocrinology</i>
Andrea Lenzi	<i>Italian Endocrine Society</i>
Mostafa Metwally	<i>Royal College of Obstetricians and Gynaecologists</i>
Stephen Franks	<i>Society for Endocrinology</i>
Katharina Schiessl	<i>Swiss Menopause Society</i>
Kate Maclaran	<i>The Daisy Network</i>

Reviewer	Country
Michael Feichtinger	<i>Austria</i>
Beatriz Alvaro Mercadal	<i>Belgium</i>
Cristina Laguna Benetti-Pinto	<i>Brazil</i>
Zdravka Veleva	<i>Finland</i>
Sophie Christin-Maitre	<i>France</i>
George Basios	<i>Greece</i>
Stratis Kolibianakis	<i>Greece</i>
Nidhi Sharma Chauhan	<i>India</i>
Mary Wingfield	<i>Ireland</i>
Gianluca Di Luigi	<i>Italy</i>
Giampaolo Mainini	<i>Italy</i>
Daniela Romualdi	<i>Italy</i>
Mukhri Hamdan	<i>Malaysia</i>
Inger Overlie	<i>Norway</i>
Michał Kunicki	<i>Poland</i>
Fernanda Águas	<i>Portugal</i>
Ioana Rugescu	<i>Romania</i>
Manuel Puig Domingo	<i>Spain</i>
Roberto Matorras	<i>Spain</i>
Patsama Vichinsartvichai	<i>Thailand</i>
Annemieke Hoek	<i>The Netherlands</i>
Adam Balen	<i>UK</i>
Arianna d'Angelo	<i>UK</i>
B Mallikarjuna Kirthi	<i>UK</i>
Nivedita Reddy	<i>UK</i>
Joe Leigh Simpson	<i>US</i>



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