



Management of women with premature ovarian insufficiency

SUMMARY

Guideline of the European Society of Human
Reproduction and Embryology

POI Guideline Development Group

December 2015

Disclaimer

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

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However, adherence to these clinical practice guidelines does not guarantee a successful or specific outcome, nor does it establish a standard of care. Clinical practice guidelines do not override the healthcare professional's clinical judgment in diagnosis and treatment of particular patients. Ultimately, healthcare professionals must make their own clinical decisions on a case-by-case basis, using their clinical judgment, knowledge, and expertise, and taking into account the condition, circumstances, and wishes of the individual patient, in consultation with that patient and/or the guardian or carer.

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INTRODUCTION

This ESHRE guideline on the management of women with premature ovarian insufficiency 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.

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.

Summary document

This summary document contains all recommendations, as formulated by the guideline development group based on clinical evidence, taking into consideration the preferences of patients and clinicians, and benefits and harms.

For background information, a summary of the clinical evidence and the methodology, the full version of the guideline can be consulted at the ESHRE website (www.eshre.eu/guidelines)

Interpretation on the grades of recommendations 1

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

RECOMMENDATIONS

Premature Ovarian Insufficiency (POI)

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

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.	
<p>Although proper diagnostic accuracy in POI is lacking, the GDG recommends the following diagnostic criteria:</p> <ul style="list-style-type: none"> • oligo/amenorrhea for at least 4 months, and • an elevated FSH level > 25 IU/l on two occasions > 4 weeks apart. 	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. ²⁻⁵	C
Gonadectomy should be recommended for all women with detectable Y chromosomal material. ³	C
Fragile-X premutation testing is indicated in POI women. ^{6;2}	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
<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.⁷⁻¹⁰</p>	C
<p>Screening for thyroid (TPO-Ab) antibodies should be performed in women with POI of unknown cause or if an immune disorder is suspected.</p> <p>In patients with a positive TPO-Ab test, thyroid stimulating hormone (TSH) should be measured every year. ¹¹⁻¹³</p>	C

There is insufficient evidence to recommend routinely screening POI women for diabetes. ¹¹	D
There is no indication for infection screening in women with POI. ¹⁴	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?

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. ¹⁵	C
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Test	Implications	
	Positive test	Negative test
Genetic/Chromosomal		
Karyotyping (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)
Test for Y-chromosomal material	Discuss gonadectomy with the patient	
Fra-X	Refer to geneticist	
Autosomal genetic testing^a		
Antibodies^b		
ACA/21OH antibodies	Refer to endocrinologist	Re-test in case of clinical signs or symptoms
TPO-Ab	Test TSH every year	

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

^b 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. ^{6; 16}	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">• 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• there are no established POI preventing measures• fertility preservation appears as a promising option, although studies are lacking, and• their potential risk of earlier menopause should be taken into account when planning a family.	GPP

Sequelae of POI

LIFE EXPECTANCY

What are the consequences of POI for life expectancy?

Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease. ¹⁷⁻²¹	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. ²²	A
Oocyte donation is an established option for fertility in women with POI. ²³⁻²⁶	C
Inform women considering oocyte donation from sisters that this carries a higher risk of cycle cancellation. ²⁵	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. ^{27; 28}	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. ²⁹⁻³³	C
Antenatal aneuploidy screening should be based on the age of the oocyte donor. ^{34; 35}	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. ^{36-39; 28}	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. ⁴⁰⁻⁴³	D
A cardiologist should be involved in care of pregnant women who have received anthracyclines and/or cardiac irradiation. ^{44; 28}	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. ³⁰	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. ⁴⁵⁻⁴⁹	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. ⁵⁰	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). ^{51-58; 2; 59; 60}	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. ^{61; 62}	C
Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture. ⁶³⁻⁶⁵	C
The combined oral contraceptive pill may be appropriate for some women but effects on BMD are less favourable. ⁶⁶	C
Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies to women desiring pregnancy. ^{67; 68}	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. ⁶⁵	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). ^{69-78; 20; 79-81}	B
All women diagnosed with Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease. ⁸²⁻⁸⁴	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. ^{85; 78; 86; 87}	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) ⁶⁰	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. ⁸⁸⁻⁹⁰	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. ⁹¹⁻⁹³	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. ⁹⁴⁻⁹⁶	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. ^{97; 98}	B

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

Local estrogens are effective in treatment of genito-urinary symptoms. ⁹⁹	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. ⁹⁶	D
Lubricants are useful for treatment of vaginal discomfort and dyspareunia for women not using HRT. ^{100; 101}	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. ¹⁰²⁻¹⁰⁶	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. ^{107-112; 106}	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. ¹¹³⁻¹¹⁵	C
Women should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection. ^{63; 64; 85; 78; 86; 87; 65}	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. ^{116; 117; 21}	D
Progestogen should be given in combination with estrogen therapy to protect the endometrium in women with an intact uterus. ¹¹⁸	B

What are the options for hormone replacement therapy?

17 β -estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement. ^{87; 66}	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

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

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. ^{119; 120; 82; 121-125; 66; 126}	C
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BRCA gene mutation or after breast cancer

HRT is generally contra-indicated in breast cancer survivors. ¹²⁷	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). ^{128; 129; 114}	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. ¹³⁰	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. ¹³¹	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. ^{132; 87}	C

History of prior 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. ¹³³	B

Obesity

Transdermal estradiol is the preferred method of delivery for women with POI requiring HRT who are obese or overweight. ¹³⁴	C
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Fibroids

Fibroids are not a contraindication to HRT use by women with POI. ^{135; 136}	B
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Androgens

Women should be informed that androgen treatment is only supported by limited data, and that long-term health effects are not clear yet. ¹³⁷⁻¹⁴⁴	C
If androgen therapy is commenced, treatment effect should be evaluated after 3-6 months and should possibly be limited to 24 months.	GPP

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. ¹⁴⁵	B

PUBERTY INDUCTION

How should puberty be induced?

Puberty should be induced or progressed with 17 β -estradiol, starting with low dose at the age of 12 with a gradual increase over 2 to 3 years. ¹⁴⁶⁻¹⁴⁸	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. ¹⁴⁹	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. ¹⁵⁰⁻¹⁵⁶	B
The oral contraceptive pill is contra-indicated for puberty induction. ^{157; 158}	D
Begin cyclical progestogens after at least 2 years of estrogen or when breakthrough bleeding occurs. ^{157; 118}	C

Table 13.1: Estrogen substitution therapy in adolescence (adapted from ¹⁵⁷)

Age	Age-specific suggestions	Preparation/dose/comments
12 -13 years	If no spontaneous development and FSH elevated, start low dose estrogens	17 β -estradiol (E2) Transdermal: 6.25 μ g/day ^a E2 via patch Oral micronized E2: 5 μ g/kg/day or 0.25 mg/day
12.5 - 15 years	Gradually increase E2 dose at 6-12 months interval over 2 - 3 years ^b to adult dose	Transdermal E2: 12.5, 25, 37.5, 50, 75, 100 μ g/day. (Adult dose: 100-200 μ g/day) Oral E2: 5, 7.5, 10, 15 μ g/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 ^c

^a the lowest dose commercially available E2 transdermal patches deliver 25 or 50 μ g/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.

^b 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.

^c 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 ¹⁵⁹.

GUIDELINE GROUP

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.

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