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ESHRE Guideline: management of women with premature ovarian insufficiency†

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STUDY QUESTION: What is the optimal management of women with premature ovarian insufficiency (POI) based on the best available evidence in the literature?

SUMMARY ANSWER: The guideline development group (GDG) formulated 99 recommendations answering 31 key questions on the diagnosis and treatment of women with POI.

WHAT IS KNOWN ALREADY: NA.

STUDY DESIGN, SIZE, DURATION: This guideline was produced by a multidisciplinary group of experts in the field using the methodology of the Manual for ESHRE Guideline Development, including a thorough systematic search of the literature, quality assessment of the included papers up to September 2014 and consensus within the guideline group on all recommendations. The GDG included a patient representative to ensure input from women with POI. After finalization of the draft, the European Society for Human Reproduction and Embryology (ESHRE) members and professional organizations were asked to review the guideline.

PARTICIPANTS/MATERIALS, SETTING, METHODS: NA.

MAIN RESULTS AND THE ROLE OF CHANCE: The guideline provides 17 recommendations on diagnosis and assessment of POI and 46 recommendations on the different sequelae of POI and their consequences for monitoring and treatment. Furthermore, 24 recommendations were formulated on hormone replacement therapy in women with POI, and two on alternative and complementary treatment. A chapter on puberty induction resulted in five recommendations.

LIMITATIONS, REASONS FOR CAUTION: Despite the limitations, the guideline group is confident that this document will be able to guide health care professionals in providing the best practice for managing women with POI given current evidence. Furthermore, the guideline group has formulated research recommendations on the gaps in knowledge identified in the literature searches, in an attempt to stimulate research on the key issues in POI.

WIDER IMPLICATIONS OF THE FINDINGS: Despite the limitations, the guideline group is confident that this document will be able to guide health care professionals in providing the best practice for managing women with POI given current evidence. Furthermore, the guideline group has formulated research recommendations on the gaps in knowledge identified in the literature searches, in an attempt to stimulate research on the key issues in POI.

STUDY FUNDING/COMPETING INTEREST(S): The guideline was developed and funded by ESHRE, covering expenses associated with the guideline meetings, with the literature searches and with the implementation of the guideline. The guideline group members did not...
**Introduction**

This European Society of Human Reproduction and Embryology (ESHRE) guideline on the management of women with premature ovarian insufficiency (POI) offers best practice advice on the care of women with POI, both primary and secondary. The patient population comprises women younger than 40 years (which includes Turner Syndrome patients) and women older than 40 years, but with disease onset before the age of 40.

Furthermore, this clinical guideline provides recommendations on the initial assessment and management of women with POI. The initial assessment includes diagnosis, assessment of causation and basic assessment. The management includes hormonal treatment. Since POI has consequences for health apart from gynaecological issues, these are also described. Consequences of POI and treatment options are included in the following domains: fertility and contraception, 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.

**Materials and Methods**

The guideline was developed according to a well-documented methodology, universal to ESHRE guidelines (Vermeulen et al., 2014).

In short, 31 key questions were formulated by the guideline group and structured in PICO format (Patient, Intervention, Comparison, Outcome). For each question, we searched the databases (PUBMED/MEDLINE, Cochrane library, PsycInfo) from inception to 1 April 2014. The literature searches were limited to studies written in English. Based on the evidence, and after constructing evidence tables and quality assessment, draft recommendations were written by the assigned expert guideline group member. Two additional meetings were organized to discuss the evidence and recommendations and to reach consensus on the final formulation of the recommendations.

For each recommendation, a grade (A–D) was assigned based on the strength of the supporting evidence (scored from 1+ to 4). In the case of absence of evidence, the guideline development group (GDG) could decide on writing good practice points (GPPs), based on clinical expertise (see Table I).

After finalization of the guideline draft, an invitation to review was published on the ESHRE website. In addition, an invitation to review was sent to members of the ESHRE special interest group Reproductive Endocrinology (n = 6000) and to professional organizations on human reproduction, gynaecology, endocrinology and menopause (n = 79). Three hundred and ninety-eight comments from 34 reviewers were processed by the methodological expert (N.V.) and the chair of the GDG (L.W.) either by adapting the content of the guideline and/or by replying to the reviewer. The review process was summarized in the review report, published on the ESHRE website.

The guideline will be considered for update 4 years after publication, with an intermediate assessment of the need for updating 2 years after publication.

**Key questions and recommendations**

The current document summarizes the key questions and the recommendations for clinical practice. Further background information and the supporting evidence for each recommendation can be found in the full version of the guideline available at http://www.eshre.eu/Guidelines-and-Legal/Guidelines.

### What should this condition be called?

Primary ovarian insufficiency was first described in 1942 and has, since then, been described with different names and definitions (Albright et al., 1942). The term ‘premature ovarian insufficiency’ should be used to describe GPP this condition in research and clinical practice.

### How should POI be defined?

POI is a clinical syndrome defined by loss of ovarian activity before the age of 40 years. POI is characterized by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotrophins and low estradiol.

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**Table I** Interpretation of the grades of recommendations for the initial assessment and management of women with POI (Vermeulen et al., 2014).

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

The grade 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 weighted it against the benefits and harms, and the preferences of clinicians and patients.
What is the prevalence of POI in the general population?

The prevalence of POI is ~ 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: (i) gynaecological surgical practice, (ii) lifestyle—smoking, (iii) modified treatment regimens for malignant and chronic diseases.

Diagnosis of POI

Summary of diagnostic workup in Table II.

What are the symptoms of POI?

Clinicians should enquire about symptoms of estrogen deficiency in women presenting with oligomenorrhea or amenorrhea GPP P

POI needs to be excluded in women with amenorrhea/oligomenorrhea or estrogen-deficiency symptoms below the age of 40 years GPP P

What investigations should be performed for diagnosis of POI?

The diagnosis POI 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: (i) oligo/amenorrhea for at least 4 months, and (ii) an elevated FSH level > 25 IU/l on two occasions > 4 weeks apart GPP P

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

Chromosomal analysis should be performed in all women with non-iatrogenic POI (Bachelot et al., 2009; Rocha et al., 2011; Jiao et al., 2012; Kalantari et al., 2013) C

Gonadectomy should be recommended for all women with detectable Y chromosomal material (Rocha et al., 2011) C

Table II Summary of diagnostic workup for POI.

<table>
<thead>
<tr>
<th>Test</th>
<th>Implications</th>
<th>Positive test</th>
<th>Negative test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic/chromosomal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karyotyping (for diagnosis of Turner syndrome)</td>
<td>Refer to endocrinologist, cardiologist and geneticist</td>
<td>Discuss gonadectomy with the patient GPP P</td>
<td>A second analysis of the karyotype in epithelial cells (in case of high clinical suspicion) GPP P</td>
</tr>
<tr>
<td>Test for Y-chromosomal material</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fra-X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Autosomal genetic testinga</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA/21OH antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPO-Ab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fra-X, fragile X, TPO-Ab, thyroid antibodies; ACA, adrenocortical antibodies.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aNot at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bPOI of unknown cause or if an immune disorder is suspected.</td>
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</table>

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 (Betterle et al., 1997) C
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 (Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada et al., 2008; Finucane et al., 2012).

Relatives of women with non-iatrogenic POI who are concerned about their risk for developing POI should be informed that: (i) currently there is no proved predictive test to identify women that will develop POI, unless a mutation known to be related to POI was detected, (ii) there are no established POI preventing measures, (iii) fertility preservation appears as a promising option, although studies are lacking and (iv) their potential risk of earlier menopause should be taken into account when planning a family.

Sequelae of POI

What are the consequences of POI for life expectancy?

Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease (Ossewaarde et al., 2005; Amagai et al., 2006; Rocca et al., 2006; Hong et al., 2007; Wu et al., 2014).

Women with POI should be advised on how to reduce cardiovascular risk factors by not smoking, taking regular exercise and maintaining a healthy weight.

What are the consequences of POI for fertility?

Women with POI should be informed that there is a small chance of spontaneous pregnancy.

Women with POI should be advised to use contraception if they wish to avoid pregnancy.

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 (van Kasteren and Schoemaker, 1999).

Oocyte donation is an established option for fertility in women with POI (Sauer et al., 1994; Templeton et al., 1996; Sung et al., 1997; Oyesanya et al., 2009).

Inform women considering oocyte donation from sisters that this carries a higher risk of cycle cancellation (Sung et al., 1997).

In women with established POI, the opportunity for fertility preservation is missed.

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 (Signorello et al., 2012; Scottish Intercollegiate Guidelines Network (SIGN), 2013).

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 (Pados et al., 1994; Abdalla et al., 1998; Soderstrom-Anttila et al., 1998; Nelson and Lawlor, 2011; Stoop et al., 2012).

Antenatal aneuploidy screening should be based on the age of the oocyte donor (Bowman and Saunders, 1994; Donnenfeld et al., 2002).

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 (Bath et al., 1999; Larsen et al., 2004; Wo and Viswanathan, 2009; Signorello et al., 2010; Scottish Intercollegiate Guidelines Network (SIGN), 2013).

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 (Bryman et al., 2011; Hadnott et al., 2011; Karnis, 2012; Hagman et al., 2013).

A cardiology should be involved in care of pregnant women who have received anthracyclines and/or cardiac irradiation (Mulrooney et al., 2009; Scottish Intercollegiate Guidelines Network (SIGN), 2013).

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 (Abdalla et al., 1998).

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 (Felker et al., 2000; Gorton et al., 2000; Bar et al., 2003; van Dalen et al., 2006; Ailino et al., 2012).

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.

Women with POI should have their blood pressure, renal function and thyroid function assessed prior to pregnancy (Haddow et al., 1999).

Pregnancy in some women can be of such high risk that clinicians may consider oocyte donation to be life threatening and therefore inappropriate.

What are the consequences of POI for bone health?

POI is associated with reduced bone mineral density (BMD) (Ratcliffe et al., 1992; Hadjidakis et al., 1999; Park et al., 1999; Conway et al., 1996; Castaneda et al., 1997; Bakalov et al., 2003; Han et al., 2008; Michala et al., 2008; Bachelot et al., 2009; Popat et al., 2009; Frenkis et al., 2011).

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.

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.

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 (Bours et al., 1999; Challoumas et al., 2013).

Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture (Prior et al., 1997; Lindsay et al., 1980; Kanis et al., 2013).

The combined oral contraceptive pill may be appropriate for some women but effects on BMD are less favourable (Crofton et al., 2010).

Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies to women desiring pregnancy (Stevenson et al., 2005; Shapiro et al., 2011).
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.

Measurement of BMD at initial diagnosis of POI should be considered for all women, but especially when there are additional risk factors (Kanis et al., 2013).

If BMD is normal and adequate systemic estrogen replacement is commenced, the value of repeated DXA scan is low.

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.

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) (van der Schouw et al., 1996; Cooper and Sandler, 1998; Hu et al., 1999; Jacobsen et al., 1999, 2003, 2004; de Kleijn et al., 2002; Mondul et al., 2005; Atsma et al., 2006; Lokkegaard et al., 2006; Hong et al., 2007; Baba et al., 2010; Gallagher et al., 2011; Perk et al., 2012).

All women diagnosed with Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease (Gravholt et al., 1998; Bondy, 2008; Sharma et al., 2009).

Is estrogen replacement cardio-protective?

Despite lack of longitudinal outcome data, hormone replacement therapy (HRT) 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 (Kalantaridou et al., 2004; Lokkegaard et al., 2006; Ostberg et al., 2007; Langrish et al., 2009).

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.

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) (Frenkis et al., 2011).

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 (Liao et al., 2000; Schmidt et al., 2011; Mann et al., 2012a,b).

What are the consequences of POI for sexuality?

Routinely inquire about sexual wellbeing and sexual function in women with POI.

What are the management options for the effects of POI on sexuality?

Adequate estrogen replacement is regarded as a starting point for normalizing sexual function. Local estrogen may be required to treat dyspareunia (Sarrel, 1987; Rubinow et al., 1998; Pacello et al., 2013).

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 (Alexander et al., 2004; Kingsberg et al., 2008).

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

Local estrogens are effective in treatment of genito-urinary symptoms (Suckling et al., 2006).

Clinicians should be aware that despite seemingly adequate systemic HRT, women with POI may experience genito-urinary symptoms. Local estrogens may be given in addition to systemic HRT (Pacello et al., 2014).

Lubricants are useful for treatment of vaginal discomfort and dyspareunia for women not using HRT (Le Donne et al., 2011; Grimaldi et al., 2012).

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 (Rocca et al., 2007; Rocca et al., 2008; Vearncombe and Pachana, 2009; Phung et al., 2010; Bove et al., 2014).

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 (Sherwin, 1988; Phillips and Sherwin, 1992; Sherwin, 1994; File et al., 2002; Kritz-Silverstein and Barrett-Connor, 2002; Hogervorst and Bandelow, 2010; Bove et al., 2014).

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.

Treatment

Indications for HRT

HRT is indicated for the treatment of symptoms of low estrogen in women with POI (Piccioni et al., 2004; Madalinska et al., 2006; Absalom et al., 2008).

Women should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection (Lindsay et al., 1980; Prior et al., 1997; Kalantaridou et al., 2004; Lokkegaard et al., 2006; Ostberg et al., 2007; Langrish et al., 2009; Kanis et al., 2013).
**What are the risks of HRT?**

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 (Benetti-Pinto et al., 2008; Soares et al., 2010; Wu et al., 2014)

Progestogen should be given in combination with estrogen therapy to protect the endometrium in women with an intact uterus (Furness et al., 2012)

**What are the options for HRT?**

- 17β-estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement (Langrish et al., 2009; Crofton et al., 2010)
- 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
- Patient preference for route and method of administration of each component of HRT must be considered when prescribing, as should contraceptive needs

**Monitoring HRT**

Once established on therapy, women with POI using HRT should have a clinical review annually, paying particular attention to compliance

No routine monitoring tests are required but may be prompted by specific symptoms or concerns

**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 (Shifren et al., 2000; Braunstein et al., 2005; Buster et al., 2005; Simon et al., 2005; Davis et al., 2006, 2008; Tamini et al., 2006; Paray et al., 2010)

If androgen therapy is commenced, treatment effect should be evaluated after 3–6 months and should possibly be limited to 24 months

**HRT in POI women with special issues**

### Women with Turner Syndrome

Girls and women with POI due to Turner Syndrome should be offered HRT throughout the normal reproductive lifespan (Downey et al., 1991; Swillen et al., 1993; Gravholt et al., 1998; Romans et al., 1998; Ross et al., 1998; Elsheikh et al., 2000; Khastgir et al., 2003; Mortensen et al., 2009; Crofton et al., 2010; Kodama et al., 2012)

### Women with POI and a BRCA gene mutation or after breast cancer

HRT is generally contra-indicated in breast cancer survivors (Antoine et al., 2007)

HRT is a treatment option for women carrying BRCA1/2 mutations but without personal history of breast cancer after prophylactic bilateral salpingo-oophorectomy (Armstrong et al., 2004; Rebeck et al., 2005; Madalinska et al., 2006)

### Women with POI and 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 (Dunsian et al., 2014)

### Women with POI and migraine

Migraine should not be seen as a contraindication to HRT use by women with POI

### Consideration should be given to changing dose, route of administration or regimen if migraine worsens during HRT

Transdermal delivery may be the lowest-risk route of administration of estrogen for migraine sufferers with aura (Nappi et al., 2001)

**Women with POI and hypertension**

Hypertension should not be considered a contraindication to HRT use by women with POI

In hypertensive women with POI, transdermal estradiol is the preferred method of delivery (White, 2007; Langrish et al., 2009)

**Women with POI and a history of prior venous thromboembolism (VTE)**

Women with POI and a history of prior VTE or thrombophilic disorder should be referred to a haematologist prior to commencing HRT

Transdermal estradiol is the preferred route of delivery for women with POI at increased risk of VTE (Canonico et al., 2008)

**Women with POI and obesity**

Transdermal estradiol is the preferred method of delivery for women with POI requiring HRT who are obese or overweight (Canonico et al., 2006)

**Women with POI and fibroids**

Fibroids are not a contraindication to HRT use by women with POI (Ang et al., 2001; Ciarmela et al., 2014)

**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)
- Women should be informed that for most alternative and complementary treatments evidence on efficacy is limited and data on safety are lacking (Rada et al., 2010)

### Puberty induction

(See also Table III)

How should puberty be induced?

- Puberty should be induced or progressed with 17β-estradiol, starting with a low dose at the age of 12 years with a gradual increase over 2–3 years (Reiter et al., 2001; van Pareren et al., 2003; Stephure and Canadian Growth Hormone Advisory Committee, 2005)
- In cases of late diagnosis and for those girls in whom growth is not a concern, a modified regimen of estradiol can be considered (Davenport, 2008)
- Evidence for the optimum mode of administration (oral or transdermal) is inconclusive. Transdermal estradiol results in more physiological estrogen levels and is therefore preferred (Illig et al., 1990; Cisternino et al., 1991; Ankarcrona-Lindgren et al., 2001; Pippo et al., 2004; Mauras et al., 2007; Nabhan et al., 2009; Torres-Santiago et al., 2013)
- The oral contraceptive pill is contra-indicated for puberty induction (Bondy and Turner Syndrome Study Group, 2007; Davenport, 2010)
- Begin cyclical progestogens after at least 2 years of estrogen or when breakthrough bleeding occurs (Bondy and Turner Syndrome Study Group, 2007; Furness et al., 2012)
Table III  Estrogen substitution therapy in adolescence (adapted from (Bondy and Turner Syndrome Study Group, 2007)).

<table>
<thead>
<tr>
<th>Age</th>
<th>Age-specific suggestions</th>
<th>Preparation/dose/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–13 years</td>
<td>If no spontaneous development and FSH elevated, start low-dose estrogens</td>
<td>17β-estradiol (E2) Transdermal: 6.25 μg/day&lt;sup&gt;a&lt;/sup&gt; E2 via patch</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral micronized E2: 5 μg/kg/day or 0.25 mg/day</td>
</tr>
<tr>
<td>12.5–15 years</td>
<td>Gradually increase E2 dose at 6 – 12 months interval over 2 – 3 years&lt;sup&gt;b&lt;/sup&gt; to adult dose</td>
<td>Transdermal E2: 12.5, 25, 37.5, 50, 75, 100 μg/day (Adult dose: 100 – 200 μg/day)</td>
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<tr>
<td></td>
<td></td>
<td>Oral E2: 5, 7.5, 10, 15 μg/kg/day (Adult dose: 2 – 4 mg/day)</td>
</tr>
<tr>
<td>14–16 years</td>
<td>Begin cyclic progestogen after 2 years of estrogen or when breakthrough bleeding occurs</td>
<td>Oral micronized progesterone 100 – 200 mg/day or dydrogesterone 5 – 10 mg/day during 12 – 14 days of the month&lt;sup&gt;c&lt;/sup&gt;</td>
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<sup>a</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>b</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>c</sup>For prolonged treatment progestogen, dydrogesterone or medroxyprogesterone are preferred to other progestogens because of their less negative effect on lipid metabolism and less androgenic effects (Lobo, 1987).

Discussion

The ESHRE guideline on the management of women with POI comprises 95 recommendations and four statements on the diagnosis, sequelae and treatment of POI. The recommendations have been formulated by a multidisciplinary group of experts based on the best available evidence, and they have been reviewed by relevant stakeholders. Based on the assessment of the current literature on POI during the development of the guideline it is clear that evidence is limited. Of the 95 recommendations, 33 (34.7%) were based on expert opinion, and graded as a GPP. Only 15 of the 31 key questions were regarding treatment and management options, while the other questions dealt with diagnosis, monitoring and sequelae of POI. From the 61 recommendations on interventions (not including monitoring), 12 (19.7%) could be based on good quality evidence (level A or B), 35 (57.4%) were based on moderate quality evidence (C or D) and 14 (22.9%) were formulated as GPP.

The lack of sufficient high-quality evidence on the interventions available for women was the most significant limitation for the current guideline, and has led to a number of topics for future research: (i) the accuracy of biochemical markers (e.g. FSH, anti-Mullerian hormone) in the diagnosis of POI, (ii) long-term health outcomes of POI, examining contributory factors such as smoking, and the effect of long-term HRT, (iii) fertility treatment and associated obstetric risks in women with POI, (iv) lifetime risk of fracture in women with POI, and the impact of interventions, (v) cardiovascular risk factors in women with POI, (vi) impact of POI on wellbeing and quality of life, including interventions, (vii) comparisons of the efficacy, patient’s satisfaction and side effects of the different options for HRT and (viii) the optimal approach for oncological POI patients.

One of the options explored for the collection of long-term data is a POI registry, as suggested by Panay and Fenton (2012).

Despite the limitations of guidelines in general, and the limitations in the evidence supporting the current guideline, the guideline group is confident that this document will help best practice in the management of women with POI. Efforts will be undertaken to ensure adequate dissemination and implementation of the guideline.

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Authors’ roles

L.W. chaired the GDG and hence fulfilled a leading role in collecting the evidence, writing the manuscript and dealing with reviewer comments. N.V., as methodological expert, performed all the literature searches for the guideline, provided methodological support and was overall coordinator of the guideline production. M.D. was co-chair of the GDG until December 2014. J.B. represented the patient perspective in the guideline group. All other authors, listed in alphabetical order, as guideline group members, contributed equally to the manuscript, by drafting key questions, synthesizing evidence, writing the different parts of the guideline and discussing recommendations until consensus within the group was reached.

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Guideline for managing premature ovarian insufficiency


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