


# ESHRE guideline: Management of women with premature ovarian insufficiency (POI)

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| Journal: | *Human Reproduction* |
| Manuscript ID | HUMREP-15-1399 |
| Manuscript Type: | ESHRE pages |
| Date Submitted by the Author: | 14-Dec-2015 |
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| Keywords: | premature ovarian insufficiency, POI, European Society of Human Reproduction and Embryology, guideline, evidence based |
| Specialty: | Reproductive Endocrinology |
| | |

**Title:**

ESHRE guideline: Management of women with premature ovarian insufficiency (POI)

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**Word count**

Abstract: 361 words

Text (excluding abstract, acknowledgments, figure legends, and references): 3995 words

**Number of tables: 3**

**Declaration of authors' role:**

LW chaired the guideline development group and hence fulfilled a leading role in collecting the evidence, writing the manuscript and dealing with reviewer comments. NV, as methodological expert, performed all literature searches for the guideline, provided methodological support and was overall coordinator of the guideline production. MD was co-Chair of the guideline development group until December 2014. JB 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, synthesising evidence, writing the different parts of the guideline and discussing recommendations until consensus within the group was reached.

**Conflicts of interest**

DB reports research grants from MSD, Ferring and Serono. The other authors reported no conflicts of interest.

**Acknowledgements**

The Guideline development group would like to thank invited experts Frank Broekmans, Gerard Conway, Alberto Falorni, Angela Maas and Anette Tonnes Pedersen for providing helpful comments as experts on specific areas of this multidisciplinary guideline. The guideline development group also acknowledges the help of many clinicians and patient organisations who refereed the content of the Guideline.

**Funding**

The study has no external funding; all costs are covered by ESHRE.

**Key words**

premature ovarian insufficiency, POI, European Society of Human Reproduction and Embryology, guideline, evidence based

**Abstract**

**Study question:** What is the optimal management of women with premature ovarian insufficiency based on the best available evidence in the literature?

**Summary answer:** The guideline development group formulated 99 recommendations answering 31 key questions on the diagnosis and treatment of women with premature ovarian insufficiency.

**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 guideline development group included a patient representative to ensure input from women with POI. After finalisation of the draft, ESHRE members and professional organisations 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 2 on alternative and complementary treatment. A chapter on puberty induction resulted in 5 recommendations.

**Limitations, reasons for caution:** The main limitation of the guideline is that due to the lack of data, many of the recommendations are based on expert opinion, or indirect evidence from studies on postmenopausal women or women with Turner Syndrome, were possible.

**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 receive payment. All guideline group members disclosed conflicts of interest.

**Trial registration number:** NA

**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.

**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 2-day meetings were organised 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 case of absence of evidence, the Guideline Development Group (GDG) could decide on writing good practice points (GPP), based on clinical expertise ***(see table 1).***

After finalisation 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 organisations on human reproduction, gynaecology, endocrinology and menopause (n=79). Three hundred ninety-eight comments from 34 reviewers were processed by the methodological expert (NV) and the chair of the GDG (LW) 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).

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|---|---|
| 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 Premature Ovarian Insufficiency 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: (1) gynaecological surgical practice, (2) lifestyle – smoking, (3) modified treatment regimens for malignant and chronic diseases.

**DIAGNOSIS OF POI**

Summary of diagnostic workup in ***table 2.***

***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: (1) oligo/amenorrhea for at least 4 months, and (2) 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 (Bachelot, et al., 2009, Jiao, et al., 2012, Kalantari, et al., 2013, Rocha, et al., 2011). | C |
| Gonadectomy should be recommended for all women with detectable Y chromosomal material (Rocha, et al., 2011). | C |
| Fragile-X premutation testing is indicated in POI women (Bachelot, et al., 2009, Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada, et al., 2008). | 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.<br>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 (Bakalov, et al., 2002, Chen, et al., 1996, Dal Pra, et al., 2003, Husebye and Lovas, 2009) | C |
| Screening for thyroid (TPO-Ab) antibodies should be performed in women with POI of unknown cause or if an immune disorder is suspected.<br>In patients with a positive TPO-Ab test, thyroid stimulating hormone (TSH) should be measured every year (Goswami, et al., 2006, Hollowell, et al., 2002, Kim, et al., 1997). | C |
| There is insufficient evidence to recommend routinely screening POI women for diabetes (Kim, et al., 1997). | D |
| There is no indication for infection screening in women with POI (Kokcu, 2010). | 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 (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 (Finucane, et al., 2012, Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada, et al., 2008). | B |
| Relatives of women with non-iatrogenic premature ovarian insufficiency who are concerned about their risk for developing POI should be informed that: (1) 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, (2) there are no established POI preventing measures, (3) fertility preservation appears as a promising option, although studies are lacking, and (4) their potential risk of earlier menopause should be taken into account when planning a family. | GPP |

## 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 (Amagai, et al., 2006, Hong, et al., 2007, Ossewaarde, et al., 2005, Rocca, et al., 2006, Wu, et al., 2014). | 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 |

***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 (van Kasteren and Schoemaker, 1999). | A |
| Oocyte donation is an established option for fertility in women with POI (Oyesanya, et al., 2009, Sauer, et al., 1994, Sung, et al., 1997, Templeton, et al., 1996). | C |
| Inform women considering oocyte donation from sisters that this carries a higher risk of cycle cancellation (Sung, et al., 1997) | 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 (Scottish Intercollegiate Guidelines Network (SIGN), 2013, Signorello, et al., 2012). | 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 (Abdalla, et al., 1998, Nelson and Lawlor, 2011, Pados, et al., 1994, Soderstrom-Anttila, et al., 1998, Stoop, et al., 2012). | C |
| Antenatal aneuploidy screening should be based on the age of the oocyte donor (Bowman and Saunders, 1994, Donnenfeld, et al., 2002). | 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 (Bath, et al., 1999, Larsen, et al., 2004, Scottish Intercollegiate Guidelines Network (SIGN), 2013, Signorello, et al., 2010, Wo and Viswanathan, 2009). | 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 (Bryman, et al., 2011, Hadnott, et al., 2011, Hagman, et al., 2013, Karnis, 2012). | D |
| A cardiologist 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). | 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 (Abdalla, et al., 1998). | 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 (Altena, et al., 2012, Bar, et al., 2003, Felker, et al., 2000, Gorton, et al., 2000, van Dalen, et al., 2006). . | 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 (Haddow, et al., 1999). | 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 |

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

| | |
|---|---|
| POI is associated with reduced bone mineral density (BMD) (Bachelot, et al., 2009, Bakalov, et al., 2003, Castaneda, et al., 1997, Conway, et al., 1996, Freriks, et al., 2011, Hadjidakis, et al., 1999, Han, et al., 2008, Michala, et al., 2008, Park, et al., 1999, Popat, et al., 2009, Ratcliffe, et al., 1992). | 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 (Bours, et al., 2011, Challoumas, et al., 2013). | C |
| Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture (Kanis, et al., 2013, Lindsay, et al., 1980, Prior, et al., 1997). | C |
| The combined oral contraceptive pill may be appropriate for some women but effects on BMD are less favourable (Crofton, et al., 2010) | C |
| Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies to women desiring pregnancy (Shapiro, et al., 2011, Stevenson, et al., 2005). | C |

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75 ***How should bone health be monitored in women with POI?***

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|---|---|
| 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 (Kanis, et al., 2013). | 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 | GPP |

review of estrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate.

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

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

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79 ***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 (Kalantaridou, et al., 2004, Langrish, et al., 2009, Lokkegaard, et al., 2006, Ostberg, et al., 2007). C

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81 ***Should cardiovascular risk factors be monitored?***

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| 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) (Freriks, et al., 2011). | C |

***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, Mann, et al., 2012, Schmidt, et al., 2011). | D |

***What are the Management options for reduced quality of life associated with POI?***

| | |
|---|---|
| Psychological and lifestyle interventions should be accessible to women with POI (Boivin, 2003, Duijts, et al., 2012, Mann, et al., 2012). | B |

***What are the consequences of POI for sexuality?***

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

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

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|---|---|
| Adequate estrogen replacement is regarded as a starting point for normalising sexual function. Local estrogen may be required to treat dyspareunia (Pacello, et al., 2013, Rubinow, et al., 1998, Sarrel, 1987). | 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 (Alexander, et al., 2004, Kingsberg, et al., 2008). | B |

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

| | |
|---|---|
| Local estrogens are effective in treatment of genito-urinary symptoms (Suckling, et al., 2006). | A |
| 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., 2013). | D |
| Lubricants are useful for treatment of vaginal discomfort and dyspareunia for women not using HRT (Grimaldi, et al., 2012, Le Donne, et al., 2011). | C |

***What are the consequences of POI on neurological function?***

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

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

**TREATMENT**

***Indications for hormone replacement therapy (HRT)***

| | |
|---|---|
| Hormone replacement therapy is indicated for the treatment of symptoms of low estrogen in women with POI (Absolom, et al., 2008, Madalinska, et al., 2006, Piccioni, et al., 2004). | C |
| Women should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection (Kalantaridou, et al., 2004, Kanis, et al., 2013, Langrish, et al., 2009, Lindsay, et al., 1980, Lokkegaard, et al., 2006, Ostberg, et al., 2007, Prior, et al., 1997). | 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 (Benetti-Pinto, et al., 2008, Soares, et al., 2010, Wu, et al., 2014). | D |
| Progestogen should be given in combination with estrogen therapy to protect the endometrium in women with an intact uterus (Furness, et al., 2012). | B |

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

| | |
|---|---|
| 17-β estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement (Crofton, et al., 2010, Langrish, et al., 2009). | 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 (Braunstein, et al., 2005, Buster, et al., 2005, Davis, et al., 2008, Davis, et al., 2006, Panay, et al., 2010, Shifren, et al., 2000, Simon, et al., 2005, Tamimi, et al., 2006) | 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 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 (Crofton, et al., 2010, Downey, et al., 1991, Elsheikh, et al., 2000, Gravholt, et al., 1998, Khastgir, et al., 2003, Kodama, et al., 2012, Mortensen, et al., 2009, Romans, et al., 1998, Ross, et al., 1998, Swillen, et al., 1993). | C |

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

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|---|---|
| HRT is generally contra-indicated in breast cancer survivors (Antoine, et al., 2007). | 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) (Armstrong, et al., 2004, Madalinska, et al., 2006, Rebbeck, et al., 2005). | C |

Women with POI and endometriosis

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|---|---|
| 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 (Dunselman, et al., 2014). | C |

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116 Women with POI and migraine

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|---|---|
| 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 (Nappi, et al., 2001). | D |

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118 Women with POI and hypertension

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|---|---|
| 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 (Langrish, et al., 2009, White, 2007). | C |

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

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|---|---|
| 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 (Canonico, et al., 2008). | B |

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Women with POI and obesity

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

Women with POI and fibroids

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

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

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|---|---|
| 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 (Rada, et al., 2010). | B |

**PUBERTY INDUCTION *(see also table 3).***

***How should puberty be induced?***

| | |
|---|---|
| Puberty should be induced or progressed with 17β-estradiol, starting with low dose at the age of 12 with a gradual increase over 2 to 3 years (Reiter, et al., 2001, Stephure and Canadian Growth Hormone Advisory Committee, 2005, van Pareren, et al., 2003). | 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 (Davenport, 2008). | 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 (Ankarberg-Lindgren, et al., 2001, Cisternino, et al., 1991, Illig, et al., 1990, Mauras, et al., 2007, Nabhan, et al., 2009, Piippo, et al., 2004, Torres-Santiago, et al., 2013). | B |
| The oral contraceptive pill is contra-indicated for puberty induction (Bondy and Turner Syndrome Study Group, 2007, Davenport, 2010). | D |
| 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). | C |

131

132

## Discussion

The ESHRE guideline on the management of women with premature ovarian insufficiency comprises 95 recommendations and 4 statements on the diagnosis, sequelae and treatment of premature ovarian insufficiency. 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 good practice point. 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: (1) the accuracy of biochemical markers (e.g. FSH, AMH) in the diagnosis of POI, (2) long-term health outcomes of POI, examining contributory factors such as smoking, and the effect of long-term HRT (3) fertility treatment and associated obstetric risks in women with POI (4) lifetime risk of fracture in women with POI, and the impact of interventions (5) cardiovascular risk factors in women with POI (6) impact of POI on wellbeing and quality of life, including interventions (7) comparisons of the efficacy, patient's satisfaction and side effects of the different options for HRT, and (8) 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 colleagues (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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540

**Table 1**

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

| 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)<br>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.

**Table 2**

**Summary of diagnostic workup**

| 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.*

**Table 3**

***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)<br>Transdermal: 6.25 µg/day[a] E2 via patch<br>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[b] to adult dose** | Transdermal E2: 12.5, 25, 37.5, 50, 75, 100µg/day. (*Adult dose: 100-200 µg/day*)<br>Oral E2: 5, 7.5, 10, 15 µg/kg/day.<br>*(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 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.*

[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 (Lobo, 1987).*