

ESHRE Guideline: management of women with premature ovarian insufficiency[†]

The ESHRE Guideline Group on POI, L. Webber^{1,*}, M. Davies¹, R. Anderson², J. Bartlett³, D. Braat⁴, B. Cartwright⁵, R. Cifkova⁶, S. de Muinck Keizer-Schrama⁷, E. Hogervorst⁸, F. Janse⁹, L. Liao¹, V. Vlaisavljevic¹⁰, C. Zillikens¹¹, and N. Vermeulen¹²

¹University College London Hospital, London, UK ²University of Edinburgh, Edinburgh, UK ³The Daisy Network, Rossendale, UK

⁴Radboudumc Nijmegen, Nijmegen, The Netherlands ⁵ST5 Obstetrics and Gynaecology trainee London KSS, London, UK

⁶Center for Cardiovascular Prevention, Charles University in Prague, First Faculty of Medicine and Thomayer Hospital, Prague, Czech Republic

⁷Erasmus University Medical Center, Sophia Children's Hospital Rotterdam, Rotterdam, The Netherlands ⁸Applied Cognitive Research (SSEHS),

Loughborough, UK ⁹UMC Utrecht, Utrecht, The Netherlands ¹⁰Department of Reproductive Medicine (Slovenia), University Medical Centre,

Canterbury, UK ¹¹Erasmus MC Rotterdam, Rotterdam, The Netherlands ¹²European Society of Human Reproduction and Embryology,

Grimbergen, Belgium

*Correspondence address. E-mail: lisa.webber@uclh.nhs.uk

Submitted on December 14, 2015; resubmitted on December 14, 2015; accepted on January 11, 2016

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: 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 post-menopausal women or women with Turner Syndrome.

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

[†] ESHRE Pages content is not externally peer reviewed. The manuscript has been approved by the Executive Committee of ESHRE.

receive payment. Dr Davies reports non-financial support from Novo Nordisk, outside the submitted work; the other authors had nothing to disclose.

TRIAL REGISTRATION NUMBER: NA.

Key words: premature ovarian insufficiency / POI / European Society of Human Reproduction and Embryology / guideline / evidence based

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 I++ 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 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.

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

| Grades of recommendations | Supporting evidence |
|---------------------------|---|
| A | Meta-analysis, systematic review or multiple 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 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

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 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

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

Fragile-X premutation testing is indicated in POI women (Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada *et al.*, 2008; Bachelot *et al.*, 2009) 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: blepharophimosis–ptosis–epicanthus inversus syndrome) 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 C

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 (Chen *et al.*, 1996; Bakalov *et al.*, 2002; 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 C

In patients with a positive TPO-Ab test, thyroid stimulating hormone (TSH) should be measured every year (Kim *et al.*, 1997; Hollowell *et al.*, 2002; Goswami *et al.*, 2006) 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

Table II Summary of diagnostic workup for POI.

| 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 | |

Fra-X, fragile X; TPO-Ab, thyroid antibodies; ACA, adrenocortical antibodies.

^aNot at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).

^bPOI 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 (Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada *et al.*, 2008; Finucane *et al.*, 2012)

B

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

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 (Ossewaarde *et al.*, 2005; Amagai *et al.*, 2006; Rocca *et al.*, 2006; Hong *et al.*, 2007; 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 (Sauer *et al.*, 1994; Templeton *et al.*, 1996; Sung *et al.*, 1997; Oyesanya *et al.*, 2009)

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

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

C

Antenatal aneuploidy screening should be based on the age of the oocyte donor (Bowman and Saunders, 1994; Donnfeld *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; Wo and Viswanathan, 2009; Signorello *et al.*, 2010; Scottish Intercollegiate Guidelines Network (SIGN), 2013)

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; Karnis, 2012; Hagman *et al.*, 2013)

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

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) (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; Freriks *et al.*, 2011)

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 (Prior *et al.*, 1997; Lindsay *et al.*, 1980; Kanis *et al.*, 2013)

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 (Stevenson *et al.*, 2005; Shapiro *et al.*, 2011)

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 (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. GPP

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). B

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) C

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) C

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) (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; Schmidt *et al.*, 2011; Mann *et al.*, 2012a,b) 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.*, 2012a,b) B

What are the consequences of POI for sexuality?

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?

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) 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.*, 2014) D

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

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) 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 (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) 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 HRT

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

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) C

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) 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 HRT?

- 17- β estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement (Langrish *et al.*, 2009; Crofton *et al.*, 2010) 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 (Shifren *et al.*, 2000; Braunstein *et al.*, 2005; Buster *et al.*, 2005; Simon *et al.*, 2005; Davis *et al.*, 2006, 2008; Tamimi *et al.*, 2006; Panay *et al.*, 2010) 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 (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) C

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) B
- 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; Rebbeck *et al.*, 2005; Madalinska *et al.*, 2006) C

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 (Dunselman *et al.*, 2014) C

Women with POI and 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 (Nappi *et al.*, 2001) D

Women with POI and 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 (White, 2007; Langrish *et al.*, 2009) C

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

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) C

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) B

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 (Rada *et al.*, 2010) B

Puberty induction

(See also Table III)

How should puberty be induced?

- Puberty should be induced or progressed with 17- β 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 Pareden *et al.*, 2003; Stephure and Canadian Growth Hormone Advisory Committee, 2005) 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 (Illig *et al.*, 1990; Cisternino *et al.*, 1991; Ankarberg-Lindgren *et al.*, 2001; Piippo *et al.*, 2004; Maurus *et al.*, 2007; Nabhan *et al.*, 2009; 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

Table III 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 | 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 |

^aThe 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.

^bWith 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.

^cFor 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).

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.

Acknowledgements

The GDG 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 GDG also acknowledges the help of many clinicians and patient organizations who refereed the content of the Guideline.

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 co-ordinator 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.

Funding

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

Conflict of interest

Dr Davies reports non-financial support from Novo Nordisk, outside the submitted work; the other authors had nothing to disclose.

References

- Abdalla HI, Billelt A, Kan AK, Baig S, Wren M, Korea L, Studd JW. Obstetric outcome in 232 ovum donation pregnancies. *Br J Obstet Gynaecol* 1998; **105**:332–337.
- Absolom K, Eiser C, Turner L, Ledger W, Ross R, Davies H, Coleman R, Hancock B, Snowden J, Greenfield D *et al.* Ovarian failure following cancer treatment: current management and quality of life. *Hum Reprod* 2008; **23**:2506–2512.
- Albright F, Smith P, Fraser R. A syndrome characterized by primary ovarian insufficiency and decreased stature. *Am J Med Sci* 1942; **204**:625–648.

- Alexander JL, Kotz K, Dennerstein L, Kutner SJ, Wallen K, Notelovitz M. The effects of postmenopausal hormone therapies on female sexual functioning: a review of double-blind, randomized controlled trials. *Menopause* 2004;**11**:749–765.
- Altena R, Gietema JA, van Veldhuisen DJ, Reyniers AK. Pregnancy unbosoms the heart of breast cancer survivors. *Ann Oncol* 2012;**23**:2206–2208.
- Amagai Y, Ishikawa S, Gotoh T, Kayaba K, Nakamura Y, Kajii E. Age at menopause and mortality in Japan: the Jichi Medical School Cohort Study. *J Epidemiol* 2006;**16**:161–166.
- Ang WC, Farrell E, Vollenhoven B. Effect of hormone replacement therapies and selective estrogen receptor modulators in postmenopausal women with uterine leiomyomas: a literature review. *Climacteric* 2001;**4**:284–292.
- Ankarberg-Lindgren C, Elfving M, Wikland KA, Norjavaara E. Nocturnal application of transdermal estradiol patches produces levels of estradiol that mimic those seen at the onset of spontaneous puberty in girls. *J Clin Endocrinol Metab* 2001;**86**:3039–3044.
- Antoine C, Liebens F, Carly B, Pastijn A, Neusy S, Rozenberg S. Safety of hormone therapy after breast cancer: a qualitative systematic review. *Hum Reprod* 2007;**22**:616–622.
- Armstrong K, Schwartz JS, Randall T, Rubin SC, Weber B. Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. *J Clin Oncol* 2004;**22**:1045–1054.
- Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause* 2006;**13**:265–279.
- Baba Y, Ishikawa S, Amagi Y, Kayaba K, Gotoh T, Kajii E. Premature menopause is associated with increased risk of cerebral infarction in Japanese women. *Menopause* 2010;**17**:506–510.
- Bachelot A, Rouxel A, Massin N, Dulon J, Courtillot C, Matuchansky C, Badachi Y, Fortin A, Paniel B, Lecuru F et al. Phenotyping and genetic studies of 357 consecutive patients presenting with premature ovarian failure. *Eur J Endocrinol* 2009;**161**:179–187.
- Bakalov VK, Vanderhoof VH, Bondy CA, Nelson LM. Adrenal antibodies detect asymptomatic auto-immune adrenal insufficiency in young women with spontaneous premature ovarian failure. *Hum Reprod* 2002;**17**:2096–2100.
- Bakalov VK, Axelrod L, Baron J, Hanton L, Nelson LM, Reynolds JC, Hill S, Troendle J, Bondy CA. Selective reduction in cortical bone mineral density in Turner syndrome independent of ovarian hormone deficiency. *J Clin Endocrinol Metab* 2003;**88**:5717–5722.
- Bar J, Davidi O, Goshen Y, Hod M, Yaniv I, Hirsch R. Pregnancy outcome in women treated with doxorubicin for childhood cancer. *Am J Obstet Gynecol* 2003;**189**:853–857.
- Bath LE, Critchley HO, Chambers SE, Anderson RA, Kelnar CJ, Wallace WH. Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: response to sex steroid replacement. *Br J Obstet Gynaecol* 1999;**106**:1265–1272.
- Benetti-Pinto CL, Soares PM, Magna LA, Petta CA, Dos Santos CC. Breast density in women with premature ovarian failure using hormone therapy. *Gynecol Endocrinol* 2008;**24**:40–43.
- Betterle C, Volpato M, Rees Smith B, Furmaniak J, Chen S, Greggio NA, Sanzari M, Tedesco F, Pedini B, Boscaro M et al. Adrenal cortex and steroid 21-hydroxylase autoantibodies in adult patients with organ-specific autoimmune diseases: markers of low progression to clinical Addison's disease. *J Clin Endocrinol Metab* 1997;**82**:932–938.
- Boivin J. A review of psychosocial interventions in infertility. *Soc Sci Med* 2003;**57**:2325–2341.
- Bondy CA. Congenital cardiovascular disease in Turner syndrome. *Congenit Heart Dis* 2008;**3**:2–15.
- Bondy CA, Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007;**92**:10–25.
- Bours SP, van Geel TA, Geusens PP, Janssen MJ, Janzing HM, Hoffland GA, Willems PC, van den Bergh JP. Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture. *J Clin Endocrinol Metab* 2011;**96**:1360–1367.
- Bove R, Secor E, Chibnik LB, Barnes LL, Schneider JA, Bennett DA, De Jager PL. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. *Neurology* 2014;**82**:222–229.
- Bowman MC, Saunders DM. Rates of aneuploidy in oocytes of older women: are equivocal findings of concern for postmenopausal embryo recipients? *Hum Reprod* 1994;**9**:1200–1201.
- Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA, Bachman G, Aguirre OA, Lucas JD, Rodenberg C et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med* 2005;**165**:1582–1589.
- Bryman I, Sylven L, Berntorp K, Innala E, Bergstrom I, Hanson C, Oxholm M, Landin-Wilhelmsen K. Pregnancy rate and outcome in Swedish women with Turner syndrome. *Fertil Steril* 2011;**95**:2507–2510.
- Buster JE, Kingsberg SA, Aguirre O, Brown C, Breaux JG, Buch A, Rodenberg CA, Wekselman K, Casson P. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005;**105**:944–952.
- Canonica M, Oger E, Conard J, Meyer G, Levesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY et al. Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. *J Thromb Haemost* 2006;**4**:1259–1265.
- Canonica M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *Br Med J* 2008;**336**:1227–1231.
- Castaneda S, Carmona L, Carvajal I, Arranz R, Diaz A, Garcia-Vadillo A. Reduction of bone mass in women after bone marrow transplantation. *Calcif Tissue Int* 1997;**60**:343–347.
- Challoumas D, Cobbold C, Dimitrakakis G. Effects of calcium intake on the cardiovascular system in postmenopausal women. *Atherosclerosis* 2013;**231**:1–7.
- Chen S, Sawicka J, Betterle C, Powell M, Prentice L, Volpato M, Rees Smith B, Furmaniak J. Autoantibodies to steroidogenic enzymes in autoimmune polyglandular syndrome, Addison's disease, and premature ovarian failure. *J Clin Endocrinol Metab* 1996;**81**:1871–1876.
- Ciarmela P, Ciavattini A, Giannubilo SR, Lamanna P, Fiorini R, Tranquilli AL, Christman GM, Castellucci M. Management of leiomyomas in perimenopausal women. *Maturitas* 2014;**78**:168–173.
- Cisternino M, Nahoul K, Bozzola M, Grignani G, Perani G, Sampaolo P, Roger M, Severi F. Transdermal estradiol substitution therapy for the induction of puberty in female hypogonadism. *J Endocrinol Invest* 1991;**14**:481–488.
- Conway GS, Kaltsas G, Patel A, Davies MC, Jacobs HS. Characterization of idiopathic premature ovarian failure. *Fertil Steril* 1996;**65**:337–341.
- Cooper GS, Sandler DP. Age at natural menopause and mortality. *Ann Epidemiol* 1998;**8**:229–235.
- Crofton PM, Evans N, Bath LE, Warner P, Whitehead TJ, Critchley HO, Kelnar CJ, Wallace WH. Physiological versus standard sex steroid replacement in young women with premature ovarian failure: effects on bone mass acquisition and turnover. *Clin Endocrinol* 2010;**73**:707–714.
- Dal Pra C, Chen S, Furmaniak J, Smith BR, Pedini B, Moscon A, Zanchetta R, Betterle C. Autoantibodies to steroidogenic enzymes in patients with premature ovarian failure with and without Addison's disease. *Eur J Endocrinol* 2003;**148**:565–570.
- Davenport ML. Moving toward an understanding of hormone replacement therapy in adolescent girls: looking through the lens of Turner syndrome. *Ann N Y Acad Sci* 2008;**1135**:126–137.

- Davenport ML. Approach to the patient with Turner syndrome. *J Clin Endocrinol Metab* 2010;**95**:1487–1495.
- Davis SR, van der Mooren MJ, van Lunsen RH, Lopes P, Ribot C, Rees M, Moufारेग A, Rodenberg C, Buch A, Purdie DW. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Menopause* 2006;**13**:387–396.
- Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, Braunstein GD, Hirschberg AL, Rodenberg C, Pack S *et al*. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med* 2008;**359**:2005–2017.
- de Kleijn MJ, van der Schouw YT, Verbeek AL, Peeters PH, Banga JD, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. *Am J Epidemiol* 2002;**155**:339–345.
- Donnenfeld AE, Icke KV, Pargas C, Dowman C. Biochemical screening for aneuploidy in ovum donor pregnancies. *Am J Obstet Gynecol* 2002;**187**:1222–1225.
- Downey J, Elkin EJ, Ehrhardt AA, Meyer-Bahlburg HF, Bell JJ, Morishima A. Cognitive ability and everyday functioning in women with Turner syndrome. *J Learn Disabil* 1991;**24**:32–39.
- Duijts SF, van Beurden M, Oldenburg HS, Hunter MS, Kieffer JM, Stuijver MM, Gerritsma MA, Menke-Pluymers MB, Plaisier PW, Rijna H *et al*. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. *J Clin Oncol* 2012;**30**:4124–4133.
- Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A *et al*. ESHRE guideline: management of women with endometriosis. *Hum Reprod* 2014;**29**:400–412.
- Elsheikh M, Bird R, Casadei B, Conway GS, Wass JA. The effect of hormone replacement therapy on cardiovascular hemodynamics in women with Turner's syndrome. *J Clin Endocrinol Metab* 2000;**85**:614–618.
- Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000;**342**:1077–1084.
- File SE, Heard JE, Rymer J. Trough oestradiol levels associated with cognitive impairment in post-menopausal women after 10 years of oestradiol implants. *Psychopharmacology (Berl)* 2002;**161**:107–112.
- Finucane B, Abrams L, Cronister A, Archibald AD, Bennett RL, McConkie-Rosell A. Genetic counseling and testing for FMRI gene mutations: practice guidelines of the national society of genetic counselors. *J Genet Couns* 2012;**21**:752–760.
- Freriks K, Timmermans J, Beerendonk CC, Verhaak CM, Netea-Maier RT, Otten BJ, Braat DD, Smeets DF, Kunst DH, Hermus AR *et al*. Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. *J Clin Endocrinol Metab* 2011;**96**:E1517–E1526.
- Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev* 2012;**8**:CD000402.
- Gallagher LG, Davis LB, Ray RM, Psaty BM, Gao DL, Checkoway H, Thomas DB. Reproductive history and mortality from cardiovascular disease among women textile workers in Shanghai, China. *Int J Epidemiol* 2011;**40**:1510–1518.
- Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada, Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists, Chitayat D, Wyatt PR, Wilson RD, Johnson JA, Audibert F, Allen V, Gagnon A, Langlois S *et al*. Fragile X testing in obstetrics and gynaecology in Canada. *J Obstet Gynaecol Can* 2008;**30**:837–846.
- Gorton H, Wilson R, Robinson A, Lyons G. Survivors of childhood cancers: implications for obstetric anaesthesia. *Br J Anaesth* 2000;**85**:911–913.
- Goswami R, Marwaha RK, Goswami D, Gupta N, Ray D, Tomar N, Singh S. Prevalence of thyroid autoimmunity in sporadic idiopathic hypoparathyroidism in comparison to type I diabetes and premature ovarian failure. *J Clin Endocrinol Metab* 2006;**91**:4256–4259.
- Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. *J Clin Epidemiol* 1998;**51**:147–158.
- Grimaldi EF, Restaino S, Inglese S, Foltran L, Sorz A, Di Lorenzo G, Guaschino S. Role of high molecular weight hyaluronic acid in postmenopausal vaginal discomfort. *Minerva Ginecol* 2012;**64**:321–329.
- Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE *et al*. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999;**341**:549–555.
- Hadjidakis D, Kokkinakis E, Sfakianakis M, Raptis SA. The type and time of menopause as decisive factors for bone mass changes. *Eur J Clin Invest* 1999;**29**:877–885.
- Hadnott TN, Gould HN, Gharib AM, Bondy CA. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the U.S. National Institutes of Health experience. *Fertil Steril* 2011;**95**:2251–2256.
- Hagman A, Loft A, Wennerholm UB, Pinborg A, Bergh C, Aittomaki K, Nygren KG, Bente Romundstad L, Hazekamp J, Soderstrom-Anttila V. Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study. *Hum Reprod* 2013;**28**:1598–1609.
- Han TS, Goswami D, Trikudanathan S, Creighton SM, Conway GS. Comparison of bone mineral density and body proportions between women with complete androgen insensitivity syndrome and women with gonadal dysgenesis. *Eur J Endocrinol* 2008;**159**:179–185.
- Hogervorst E, Bandelow S. Sex steroids to maintain cognitive function in women after the menopause: a meta-analysis of treatment trials. *Maturitas* 2010;**66**:56–71.
- Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002;**87**:489–499.
- Hong JS, Yi SW, Kang HC, Jee SH, Kang HG, Bayasgalan G, Ohrr H. Age at menopause and cause-specific mortality in South Korean women: Kangwha Cohort Study. *Maturitas* 2007;**56**:411–419.
- Hu FB, Grodstein F, Hennekens CH, Colditz GA, Johnson M, Manson JE, Rosner B, Stampfer MJ. Age at natural menopause and risk of cardiovascular disease. *Arch Intern Med* 1999;**159**:1061–1066.
- Husebye ES, Lovas K. Immunology of Addison's disease and premature ovarian failure. *Endocrinol Metab Clin North Am* 2009;**38**:389–405. ix.
- Illig R, DeCampo C, Lang-Muritano MR, Prader A, Torresani T, Werder EA, Willi U, Schenkel L. A physiological mode of puberty induction in hypogonadal girls by low dose transdermal 17 beta-oestradiol. *Eur J Pediatr* 1990;**150**:86–91.
- Jacobsen BK, Knutsen SF, Fraser GE. Age at natural menopause and total mortality and mortality from ischemic heart disease: the Adventist Health Study. *J Clin Epidemiol* 1999;**52**:303–307.
- Jacobsen BK, Heuch I, Kvale G. Age at natural menopause and all-cause mortality: a 37-year follow-up of 19,731 Norwegian women. *Am J Epidemiol* 2003;**157**:923–929.
- Jacobsen BK, Heuch I, Kvale G. Age at natural menopause and stroke mortality: cohort study with 3561 stroke deaths during 37-year follow-up. *Stroke* 2004;**35**:1548–1551.
- Jiao X, Qin C, Li J, Qin Y, Gao X, Zhang B, Zhen X, Feng Y, Simpson JL, Chen ZJ. Cytogenetic analysis of 531 Chinese women with premature ovarian failure. *Hum Reprod* 2012;**27**:2201–2207.

- Kalantari H, Madani T, Zari Moradi S, Mansouri Z, Almadani N, Gourabi H, Mohseni Meybodi A. Cytogenetic analysis of 179 Iranian women with premature ovarian failure. *Gynecol Endocrinol* 2013;**29**:588–591.
- Kalantaridou SN, Naka KK, Papanikolaou E, Kazakos N, Kravariti M, Calis KA, Paraskevaides EA, Sideris DA, Tsatsoulis A, Chrousos GP et al. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. *J Clin Endocrinol Metab* 2004;**89**:3907–3913.
- Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. Scientific Advisory Board of the European Society for C, Economic Aspects of O, Osteoarthritis, the Committee of Scientific Advisors of the International Osteoporosis F. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2013;**24**:23–57.
- Karnis MF. Catastrophic consequences of assisted reproduction: the case of Turner syndrome. *Semin Reprod Med* 2012;**30**:116–122.
- Khastgir G, Studd JW, Fox SW, Jones J, Alagband-Zadeh J, Chow JW. A longitudinal study of the effect of subcutaneous estrogen replacement on bone in young women with Turner's syndrome. *J Bone Miner Res* 2003;**18**:925–932.
- Kim TJ, Anasti JN, Flack MR, Kimzey LM, Defensor RA, Nelson LM. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. *Obstet Gynecol* 1997;**89**:777–779.
- Kingsberg SA, Simon JA, Goldstein I. The current outlook for testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. *J Sex Med* 2008;**5**(Suppl 4):182–193; quiz 193.
- Kodama M, Komura H, Kodama T, Nishio Y, Kimura T. Estrogen therapy initiated at an early age increases bone mineral density in Turner syndrome patients. *Endocr J* 2012;**59**:153–159.
- Kokcu A. Premature ovarian failure from current perspective. *Gynecol Endocrinol* 2010;**26**:555–562.
- Kritz-Silverstein D, Barrett-Connor E. Hysterectomy, oophorectomy, and cognitive function in older women. *J Am Geriatr Soc* 2002;**50**:55–61.
- Langrish JP, Mills NL, Bath LE, Warner P, Webb DJ, Kelnar CJ, Critchley HO, Newby DE, Wallace WH. Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure. *Hypertension* 2009;**53**:805–811.
- Larsen EC, Schmiegelow K, Rechnitzer C, Loft A, Muller J, Andersen AN. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. *Acta Obstet Gynecol Scand* 2004;**83**:96–102.
- Le Donne M, Caruso C, Mancuso A, Costa G, Lemmo R, Pizzimenti G, Cavallari V. The effect of vaginally administered genistein in comparison with hyaluronic acid on atrophic epithelium in postmenopause. *Arch Gynecol Obstet* 2011;**283**:1319–1323.
- Liao KL, Wood N, Conway GS. Premature menopause and psychological well-being. *J Psychosom Obstet Gynaecol* 2000;**21**:167–174.
- Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomised women. *Lancet* 1980;**2**:1151–1154.
- Lobo RA. Absorption and metabolic effects of different types of estrogens and progestogens. *Obstet Gynecol Clin North Am* 1987;**14**:143–167.
- Lokkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Pedersen AT. The association between early menopause and risk of ischaemic heart disease: influence of Hormone Therapy. *Maturitas* 2006;**53**:226–233.
- Madalinska JB, van Beurden M, Bleiker EM, Valdimarsdottir HB, Hollenstein J, Massuger LF, Gaarenstroom KN, Mourits MJ, Verheijen RH, van Dorst EB et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. *J Clin Oncol* 2006;**24**:3576–3582.
- Mann E, Singer D, Pitkin J, Panay N, Hunter MS. Psychosocial adjustment in women with premature menopause: a cross-sectional survey. *Climacteric* 2012a;**15**:481–489.
- Mann E, Smith MJ, Hellier J, Balabanovic JA, Hamed H, Grunfeld EA, Hunter MS. Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial. *Lancet Oncol* 2012b;**13**:309–318.
- Mauras N, Shulman D, Hsiang HY, Balagopal P, Welch S. Metabolic effects of oral versus transdermal estrogen in growth hormone-treated girls with turner syndrome. *J Clin Endocrinol Metab* 2007;**92**:4154–4160.
- Michala L, Goswami D, Creighton SM, Conway GS. Swyer syndrome: presentation and outcomes. *BJOG* 2008;**115**:737–741.
- Mondul AM, Rodriguez C, Jacobs EJ, Calle EE. Age at natural menopause and cause-specific mortality. *Am J Epidemiol* 2005;**162**:1089–1097.
- Mortensen KH, Hansen KW, Erlandsen M, Christiansen JS, Gravholt CH. Ambulatory arterial stiffness index in Turner syndrome: the impact of sex hormone replacement therapy. *Horm Res* 2009;**72**:184–189.
- Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robison LL et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *Br Med J* 2009;**339**:b4606.
- Nabhan ZM, Dimeglio LA, Qi R, Perkins SM, Eugster EA. Conjugated oral versus transdermal estrogen replacement in girls with Turner syndrome: a pilot comparative study. *J Clin Endocrinol Metab* 2009;**94**:2009–2014.
- Nappi RE, Cagnacci A, Granella F, Piccinini F, Polatti F, Facchinetti F. Course of primary headaches during hormone replacement therapy. *Maturitas* 2001;**38**:157–163.
- Nelson SM, Lawlor DA. Predicting live birth, preterm delivery, and low birth weight in infants born from in vitro fertilisation: a prospective study of 144,018 treatment cycles. *PLoS Med* 2011;**8**:e1000386.
- Ossewaarde ME, Bots ML, Verbeek AL, Peeters PH, van der Graaf Y, Grobbee DE, van der Schouw YT. Age at menopause, cause-specific mortality and total life expectancy. *Epidemiology (Cambridge, Mass)* 2005;**16**:556–562.
- Ostberg JE, Storry C, Donald AE, Attar MJ, Halcov JP, Conway GS. A dose-response study of hormone replacement in young hypogonadal women: effects on intima media thickness and metabolism. *Clin Endocrinol* 2007;**66**:557–564.
- Oyesanya OA, Olufowobi O, Ross W, Sharif K, Afnan M. Prognosis of oocyte donation cycles: a prospective comparison of the in vitro fertilization-embryo transfer cycles of recipients who used shared oocytes versus those who used altruistic donors. *Fertil Steril* 2009;**92**:930–936.
- Pacello PC, Yela DA, Rabelo S, Giraldo PC, Benetti-Pinto CL. Dyspareunia and lubrication in premature ovarian failure using hormonal therapy and vaginal health. *Climacteric* 2014;**17**:342–347.
- Pados G, Camus M, Van Steirteghem A, Bonduelle M, Devroey P. The evolution and outcome of pregnancies from oocyte donation. *Hum Reprod* 1994;**9**:538–542.
- Panay N, Fenton A. Premature ovarian insufficiency: working towards an international database. *Climacteric* 2012;**15**:295–296.
- Panay N, Al-Azzawi F, Bouchard C, Davis SR, Eden J, Lodhi I, Rees M, Rodenberg CA, Rymer J, Schwenkhaugen A et al. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. *Climacteric* 2010;**13**:121–131.
- Park KH, Lee SJ, Kim JY, Kim JY, Bai SW, Kim JW. A concomitant decrease in cortical and trabecular bone mass in isolated hypogonadotropic hypogonadism and gonadal dysgenesis. *Yonsei Med J* 1999;**40**:444–449.
- Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, Albus C, Benlian P, Boysen G, Cifkova R et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice

- (constituted by representatives of nine societies and by invited experts). *Int J Behav Med* 2012;**19**:403–488.
- Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology* 1992;**17**:485–495.
- Phung TK, Waltoft BL, Laursen TM, Settnes A, Kessing LV, Mortensen PB, Waldemar G. Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. *Dement Geriatr Cogn Disord* 2010;**30**:43–50.
- Piccioni P, Scirpa P, D'Emilio I, Sora F, Scarciglia M, Laurenti L, De Matteis S, Sica S, Leone G, Chiusolo P. Hormonal replacement therapy after stem cell transplantation. *Maturitas* 2004;**49**:327–333.
- Piippo S, Lenko H, Kainulainen P, Sipilä I. Use of percutaneous estrogen gel for induction of puberty in girls with Turner syndrome. *J Clin Endocrinol Metab* 2004;**89**:3241–3247.
- Popat VB, Calis KA, Vanderhoof VH, Cizza G, Reynolds JC, Sebring N, Troendle JF, Nelson LM. Bone mineral density in estrogen-deficient young women. *J Clin Endocrinol Metab* 2009;**94**:2277–2283.
- Prior JC, Vigna YM, Wark JD, Eyre DR, Lentle BC, Li DK, Ebeling PR, Atley L. Premenopausal ovariectomy-related bone loss: a randomized, double-blind, one-year trial of conjugated estrogen or medroxyprogesterone acetate. *J Bone Miner Res* 1997;**12**:1851–1863.
- Rada G, Capurro D, Pantoja T, Corbalán J, Moreno G, Letelier Luz M, Vera C. Non-hormonal interventions for hot flushes in women with a history of breast cancer. *Cochrane Database Syst Rev* 2010:CD004923.
- Ratcliffe MA, Lanham SA, Reid DM, Dawson AA. Bone mineral density (BMD) in patients with lymphoma: the effects of chemotherapy, intermittent corticosteroids and premature menopause. *Hematol Oncol* 1992;**10**:181–187.
- Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, Isaacs C, Olopade OI, Neuhausen SL, van't Veer L *et al.* Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2005;**23**:7804–7810.
- Reiter EO, Blethen SL, Baptista J, Price L. Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab* 2001;**86**:1936–1941.
- Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol* 2006;**7**:821–828.
- Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, Melton LJ 3rd. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology* 2007;**69**:1074–1083.
- Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, Melton LJ 3rd. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. *Neurology* 2008;**70**:200–209.
- Rocha VB, Guerra-Junior G, Marques-de-Faria AP, de Mello MP, Maciel-Guerra AT. Complete gonadal dysgenesis in clinical practice: the 46,XY karyotype accounts for more than one third of cases. *Fertil Steril* 2011;**96**:1431–1434.
- Romans SM, Stefanatos G, Roeltgen DP, Kushner H, Ross JL. Transition to young adulthood in Ullrich–Turner syndrome: neurodevelopmental changes. *Am J Med Genet* 1998;**79**:140–147.
- Ross JL, Roeltgen D, Feuillan P, Kushner H, Cutler GB Jr. Effects of estrogen on nonverbal processing speed and motor function in girls with Turner's syndrome. *J Clin Endocrinol Metab* 1998;**83**:3198–3204.
- Rubinow DR, Schmidt PJ, Roca CA. Estrogen-serotonin interactions: implications for affective regulation. *Biol Psychiatry* 1998;**44**:839–850.
- Sarrel PM. Sexuality in the middle years. *Obstet Gynecol Clin North Am* 1987;**14**:49–62.
- Sauer MV, Paulson RJ, Ary BA, Lobo RA. Three hundred cycles of oocyte donation at the University of Southern California: assessing the effect of age and infertility diagnosis on pregnancy and implantation rates. *J Assist Reprod Genet* 1994;**11**:92–96.
- Schmidt PJ, Luff JA, Haq NA, Vanderhoof VH, Koziol DE, Calis KA, Rubinow DR, Nelson LM. Depression in women with spontaneous 46, XX primary ovarian insufficiency. *J Clin Endocrinol Metab* 2011;**96**:E278–E287.
- Scottish Intercollegiate Guidelines Network (SIGN). *Long Term Follow up of Survivors of Childhood Cancer*. Edinburgh: SIGN, 2013. (SIGN publication no 132) 2013; Available from URL: <http://www.sign.ac.uk>.
- Shapiro CL, Halabi S, Hars V, Archer L, Weckstein D, Kirshner J, Sikov W, Winer E, Burstein HJ, Hudis C *et al.* Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: final results from CALGB trial 79809. *Eur J Cancer* 2011;**47**:683–689.
- Sharma J, Friedman D, Dave-Sharma S, Harbison M. Aortic distensibility and dilation in Turner's syndrome. *Cardiol Young* 2009;**19**:568–572.
- Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology* 1988;**13**:345–357.
- Sherwin BB. Estrogenic effects on memory in women. *Ann N Y Acad Sci* 1994;**743**:213–230; discussion 230–211.
- Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR *et al.* Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;**343**:682–688.
- Signorello LB, Mulvihill JJ, Green DM, Munro HM, Stovall M, Weathers RE, Mertens AC, Whitton JA, Robison LL, Boice JD Jr. Stillbirth and neonatal death in relation to radiation exposure before conception: a retrospective cohort study. *Lancet* 2010;**376**:624–630.
- Signorello LB, Mulvihill JJ, Green DM, Munro HM, Stovall M, Weathers RE, Mertens AC, Whitton JA, Robison LL, Boice JD Jr. Congenital anomalies in the children of cancer survivors: a report from the childhood cancer survivor study. *J Clin Oncol* 2012;**30**:239–245.
- Simon J, Braunstein G, Nachtigall L, Utian W, Katz M, Miller S, Waldbaum A, Bouchard C, Derzko C, Buch A *et al.* Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005;**90**:5226–5233.
- Soares PM, Cabello C, Magna LA, Tinois E, Benetti-Pinto CL. Breast density in women with premature ovarian failure or postmenopausal women using hormone therapy: analytical cross-sectional study. *Sao Paulo Med J* 2010;**128**:211–214.
- Soderstrom-Anttila V, Tiitinen A, Foudila T, Hovatta O. Obstetric and perinatal outcome after oocyte donation: comparison with in-vitro fertilization pregnancies. *Hum Reprod* 1998;**13**:483–490.
- Stephure DK, Canadian Growth Hormone Advisory Committee. Impact of growth hormone supplementation on adult height in turner syndrome: results of the Canadian randomized controlled trial. *J Clin Endocrinol Metab* 2005;**90**:3360–3366.
- Stevenson M, Jones ML, De Nigris E, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. *Health Technol Assess* 2005;**9**:1–160.
- Stoop D, Baumgarten M, Haentjens P, Polyzos NP, De Vos M, Verheyen G, Camus M, Devroey P. Obstetric outcome in donor oocyte pregnancies: a matched-pair analysis. *Reprod Biol Endocrinol* 2012;**10**:42.
- Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2006:CD001500.
- Sung L, Bustillo M, Mukherjee T, Booth G, Karstaedt A, Copperman AB. Sisters of women with premature ovarian failure may not be ideal ovum donors. *Fertil Steril* 1997;**67**:912–916.

- Swillen A, Fryns JP, Kleczkowska A, Massa G, Vanderschueren-Lodeweyckx M, Van den Berghe H. Intelligence, behaviour and psychosocial development in Turner syndrome. A cross-sectional study of 50 pre-adolescent and adolescent girls (4–20 years). *Genet Couns* 1993;**4**:7–18.
- Tamimi RM, Hankinson SE, Chen WY, Rosner B, Colditz GA. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. *Arch Intern Med* 2006;**166**:1483–1489.
- Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. *Lancet* 1996;**348**:1402–1406.
- Torres-Santiago L, Mericq V, Taboada M, Unanue N, Klein KO, Singh R, Hossain J, Santen RJ, Ross JL, Mauras N. Metabolic effects of oral versus transdermal 17beta-estradiol (E(2)): a randomized clinical trial in girls with Turner syndrome. *J Clin Endocrinol Metab* 2013;**98**:2716–2724.
- van Dalen EC, van der Pal HJ, van den Bos C, Kok WE, Caron HN, Kremer LC. Clinical heart failure during pregnancy and delivery in a cohort of female childhood cancer survivors treated with anthracyclines. *Eur J Cancer* 2006;**42**:2549–2553.
- van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. *Lancet* 1996;**347**:714–718.
- van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. *Hum Reprod Update* 1999;**5**:483–492.
- van Pareren YK, de Muinck Keizer-Schrama SM, Stijnen T, Sas TC, Jansen M, Otten BJ, Hoorweg-Nijman JJ, Vulmsa T, Stokvis-Brantsma WH, Rouwe CW *et al*. Final height in girls with turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *J Clin Endocrinol Metab* 2003;**88**:1119–1125.
- Vearncombe KJ, Pachana NA. Is cognitive functioning detrimentally affected after early, induced menopause? *Menopause* 2009;**16**:188–198.
- Vermeulen N, D'Angelo A, de Sutter P, Nelen WLDM. Manual for ESHRE Guideline Development 2014, www.eshre.eu.
- White WB. Drospirenone with 17beta-estradiol in the postmenopausal woman with hypertension. *Climacteric* 2007;**10**(Suppl 1):25–31.
- Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. *Int J Radiat Oncol Biol Phys* 2009;**73**:1304–1312.
- Wu X, Cai H, Kallianpur A, Li H, Yang G, Gao J, Xiang YB, Ji BT, Yu T, Zheng W *et al*. Impact of Premature Ovarian Failure on Mortality and Morbidity among Chinese Women. *PloS one* 2014;**9**:e89597.