REVIEW

Premature ovarian insufficiency: an International Menopause Society White Paper

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ABSTRACT

The aim of this International Menopause Society White paper on Premature ovarian insufficiency (POI) is to provide the latest information regarding this distressing condition. The impact of POI has far-reaching consequences due to its impact on general, psychological and sexual quality of life, fertility prospects and long-term bone, cardiovascular and cognitive health. Progress in fully understanding the etiology, diagnosis and optimal management options has been slow thus far due to the complexity of the condition and fragmented research. Recent advances in epidemiological and genetic research have improved our understanding of this condition and randomized prospective trials are being planned to determine the intervention strategies, which will optimize quality of life and long-term well-being. The International Menopause Society has commissioned a number of experts at the forefront of their specialty to define the state of the art in the understanding of this condition, to advise on practical management strategies and to propose future research strategies. It is hoped that a global task force will subsequently be convened in order to formulate a consensus statement across key societies, to accelerate date collection and analysis of a global POI registry, and to facilitate progress in the key defined areas of research.

Introduction

The development and diagnosis of premature ovarian insufficiency in a young woman has potentially life-changing physical and emotional consequences for the sufferer. It is therefore surprising that there has been relatively little expenditure of global resources to fully understand what causes this condition and how to optimally manage the many sequelae of a premature cessation of ovarian activity resulting in a chronic hypoestrogenic state. There is still ongoing controversy in the nomenclature used to describe this condition. Fuller Albright, a Harvard endocrinologist, first described the condition as primary ovarian insufficiency to indicate that the ‘primary’ defect was within the ovary. The view of the International Menopause Society and others is that it should be referred to as premature ovarian insufficiency, although many still refer to it as primary ovarian insufficiency, premature ovarian failure and premature menopause. The term premature ovarian insufficiency (POI) is recommended because ‘premature’ encompasses both spontaneous and iatrogenic conditions and ‘insufficiency’, rather than failure, reflects the possibility of some intermittent ovarian activity, which can result in ovulation and even pregnancy. There has also been controversy regarding the precise diagnostic criteria and optimal management options. All of these factors often lead to a delay in the diagnosis and effective treatment of POI. The International

Menopause Society has therefore commissioned a number of experts for this White Paper to define the state of the art in the understanding of this condition and to propose practical management and future research strategies.

The topics discussed in this paper include: Demographics and etiology; Pathophysiology and causes; Presentation and diagnosis; Psychosexual and psychosocial health; Cardiometabolic health; Bone health; Cognitive health; Reproductive health; Practical management; POI registry; Executive summary; Conclusion.

Demographics and etiology of premature ovarian insufficiency

POI, or hypergonadotropic hypogonadism, refers to loss of ovarian activity that occurs under the age of 40. It may be associated with intermittent resumption of ovarian activity in over 25% of women[1] and causes amenorrhea and hypoestrogenism. The cut-off age of 40 years is used because it represents two standard deviations below the mean age of natural menopause. It has been estimated that POI occurs in approximately 1% of the population[2] but may differ between countries: in Sweden the incidence was found to be 1.9%, with 0.2% due to iatrogenic interventions[3]. A recent global prevalence study of POI and early menopause concluded that the pooled prevalence of POI was as high as 3.7% (95% confidence interval (CI) 3.1–4.3) and that the prevalence was higher in countries with a medium or low Human Development Index[4]. It occurs in 1/1000 women under the age of 30 and 1/10,000 under the age of 20[5]. The etiology is unknown in 70–90% of diagnosed women[6]. Other causes include genetic (X chromosome-related and autosomal), autoimmune, infectious, metabolic, toxin-related and iatrogenic including following chemotherapy, radiation or surgery[7,8].

Pathophysiology of premature ovarian insufficiency

Women are born with 700,000–1 million oocytes within primordial follicles. The duration of survival of this pool determines the reproductive lifespan, typically through 400 ovulated cycles. POI occurs due to loss of these follicles with subsequent infertility and the loss of ovarian estrogen production. Causes of POI could include a reduction in the primordial follicle pool via accelerated follicular atresia or destruction, or problems in support, recruitment or maturation of primordial or growing follicles. A combination of factors such as genetics, recreational drug use, autoimmune diseases, pelvic surgery or chemical exposures may ultimate precipitate the disorder[9]. ‘Resistant ovary syndrome’ is a rare disorder characterized by elevated levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) despite normal anti-Müllerian hormone (AMH) and antral follicle

counts. The ovaries are unresponsive to endogenous and exogenous FSH due to genetic or immunological inactivation of the FSH or LH receptor (see Genetic factors section)[10].

It is also possible that spontaneous POI may occur as part of an aging syndrome in some women. There is increasing evidence that epigenetic aging can begin as early as a few weeks post-conception in fetal tissues[11]. Premature aging, previously thought to be exclusively due to hormone deficiency in women with POI, may therefore only be partially correctable with hormone therapy (HT). This is a major public health issue given the well-recognized long-term sequelae of POI such as osteoporosis, cardiovascular disease and dementia. Even more concerningly, a recent study of more than 11,000 Australian women demonstrated that women with POI had almost three times higher odds of developing multi-morbidity in their sixties, adjusted for a number of chronic conditions at baseline and related risk factors[12]. The pathophysiological mechanisms of POI, including the phenomenon of epigenetic aging in developing organs such as the ovaries, therefore deserve greater forensic examination and scientific endeavor.

Genetic factors

Up to 30% of women with idiopathic POI have a family history of early menopause or POI suggesting a genetic etiology[13]. When primary amenorrhea occurs, 21% will have a karyotypic abnormality compared to 11% with secondary amenorrhea[14]. More genetic mutations have recently been discovered by whole genome sequencing[15]. Responsible genes that have been identified affect mainly the X chromosome or, less commonly, autosomal genetic variations. These may impact gonadal development and function via DNA replication and repair, meiosis, hormonal, immune or metabolic pathways[16].

X-linked chromosomal abnormalities

Turner syndrome: Turner syndrome occurs in 1 in 2500 births and involves the complete or partial loss of one X chromosome (deletions, translocations, inversions, isochromosomes and sometimes mosaicisms)[17]. The loss of X-linked genes results in X inactivation of important X-related gene products that escape inactivation by the second X[18]. These women are usually born with a normal number of primordial follicles that undergo accelerated atresia[19]. Some women with primary amenorrhea, especially those with Y material in the karyotype, may have streak gonads. Women with a mosaic X pattern are more likely to present at variable times after menarche[20]. They may have phenotypic characteristics including short stature, lymphedema, webbed neck, visual impairment, strabismus, otitis media, high arched palate,

wide-spaced nipples, shield chest, multiple nevi, cubitus valgus, short 4th metacarpal as well as cardiac (coarctation or aortic anomalies) and renal tract abnormalities. Women with Turner syndrome are best managed in multidisciplinary clinics due to possible long-term health issues including potential pregnancy risks, hearing and learning difficulties, diabetes, celiac disease, hypothyroidism, hepatic dysfunction, dyslipidemia, coronary artery disease and cerebrovascular disease[21]. If Y chromosome material is present in some cells, gonadectomy is recommended[22].

Fragile X syndrome: A premutation in the fragile X mental retardation I gene (FMR-I) carried in 1 in 250 women affects the copies of the CGG trinucleotide repeat in this gene in the 5' area of chromosome X[23]. The normal finding is 5–45 repeats. The full syndrome of mental disability and autism occurs in males with 200 repeats. When 55–200 repeats (termed a premutation) are present, there is a 20% chance of developing POI and an increased risk of ataxia with aging[24], occurring in 8–16% of carriers. Genetic screening including family members is recommended to prevent severe mental disability in male offspring as well as for affected female family members who might consider egg storage or pregnancy planning[25].

Other X-linked and autosomal mutations: Genetic mutations in the X chromosome such as in BMP-15 and DIAPH2 and autosomal defects in genes such as GDF9, ESR 1, NOBOX, FSHR, LHR, FSH, inhibin A, GALT, AIRE, NOGGIN, POLG (mitochondrial diseases), CYP19A1, FOXL2 (associated with blepharophimosis/ptosis/epicanthus inversus syndrome), FOXO3 and steroidogenic factor 1 are rare causes of POI. Some rare mutations may be associated with neurologic, syndromics and increased cancer risk and have POI as one aspect. Examples are ataxia telangiectasia (associated with cerebellar degeneration, telangiectasias, oculomotor dysfunction and immunodeficiency), and Bloom (short stature, distinctive skin rashes and premature aging) and Perrault (sensorineural hearing impairment, ovarian dysgenesis) syndromes[18]. The presence of other phenotypic abnormalities in association with POI should prompt referral to a genetic counsellor for consideration of additional genetic testing[18].

Rarely, primary hypergonadotropic hypogonadism can be caused by genetic causes of gonadotropin receptor mutations. An inactivating variant of the LH gene and steroidogenic enzyme defects (StA R mutation, CYP17 and aromatase) prevent estradiol production, resulting in low estrogen and high FSH levels despite some follicular growth.

Autoimmune cause/association

Spontaneous POI has been associated with autoimmune diseases in 4–30% of cases, such as Hashimoto's thyroiditis, type I diabetes, adrenal insufficiency, Sjögren's syndrome, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, celiac disease, myasthenia gravis and alopecia. However, there is no evidence that the apparent clustering of autoimmune diseases with POI indicates that the cause is inflammatory oocyte destruction.

POI may occur in cases with the inherited autoimmune conditions, type I (AIRE mutation) and type II polyglandular autoimmune syndromes. Autoimmune polyendocrinopathy syndrome type I usually presents in childhood with mucocutaneous candidiasis, Addison's disease, and hypoparathyroidism. It is caused by mutations in the autoimmune regulator gene AIRE on chromosome 21. POI related to steroidogenic cell autoantibodies to multiple endocrine and other organs can result in ovarian lymphocytic oophoritis in 60% of affected individuals. Type II results in adrenal insufficiency, type 1 diabetes, hypothyroidism or Graves' disease and, less commonly, POI[17].

Women with autoimmune POI may have adrenal or 21-hydroxylase autoantibodies (approximately 4% of all women with POI). These autoantibodies initiate an immune response to ovarian tissue involving cytokines, B and T cells that has been associated with lymphocytic infiltration, destruction of follicles resulting in oophoritis[26] and, early in the disease, enlarged cystic ovaries. POI may occur prior to the development of adrenal insufficiency and therefore referral to an endocrinologist is recommended if adrenal antibodies are present[27,28].

Infectious causes

POI may rarely be associated with a history of mumps[29] or human immunodeficiency virus, either due to antiviral medications or the virus[30], as well as possibly tuberculosis, malaria, cytomegalovirus and varicella.

Toxic causes

POI has been associated with polycyclic aromatic hydrocarbon exposure, e.g. in cigarette smoke[31,32]. Exposure to phthalates and bisphenol-A found in plastic production and other environmental pollutants has been suggested as a possible cause[33].

Metabolic causes

The autosomal genetic defect known as galactosemia, caused by a deficiency of galactose-1-phosphate uridylotransferase (GALT), is associated with accumulation of galactose in organs with high GALT expression (liver, kidney, ovary and heart) and may cause oocyte toxic levels of galactose that lead to POI[34].

Iatrogenic causes

POI can occur as a result of chemotherapy, radiation or surgical therapies. The effects of chemotherapy depend on the type, previous ovarian reserve, dosage and age at administration[35,36]. The commonest responsible chemotherapies include cyclophosphamide, cisplatinum, and doxorubicin[37]. Gonadotropin releasing hormone (GnRH) analogs may provide some protection of the ovaries during chemotherapy but outcomes are often conflicting[38]. Women who have received anthracyclines and alkylating agents are at high risk and those who undergo allogeneic stem cell transplants are at very high risk of POI (> 90%)[39]. Radiation in doses as low as 1 Gy used for some childhood malignancies, either locally or external beam, can also cause POI[40]. Uterine artery embolization and pelvic surgery including treatment of torsions, endometriomas, ovarian cysts, and pelvic malignancies, or electively for genetic BRCA carriers, may also be responsible.

Presentation and diagnosis of premature ovarian insufficiency

History – key features

It is important to take a careful personal and family history. A recent position statement[41] concluded that the following were predictors of POI (particularly those in italics):

- *Genetic abnormalities*
- *Family history of premature or early menopause*
- Multiple pregnancy
- Early menarche
- Nulliparity/low parity
- Cigarette smoking (dose–response effect)
- Underweight

Symptoms and biomarkers

The presentation of POI is usually one of secondary amenorrhea or oligomenorrhea, subfertility and estrogen deficiency symptoms. However, the spontaneous POI phenotype can be extremely variable with some women presenting with few or no symptoms apart from variable degrees of amenorrhea. Multiple factors influence symptoms including the cause of POI; symptoms may be more severe and may differ qualitatively, e.g. psychosocially/psychosexually in iatrogenic POI[42-44]. Symptoms may also be more severe in POI than those experienced with menopause at the natural age.

Although these symptoms can be variable due to intermittent production of ovarian hormones, a consistent feature is the finding of low ovarian reserve associated with amenorrhea or oligomenorrhea. Most guidelines to date have recommended that this is confirmed by two elevated FSH tests, 4–6 weeks apart[5,45-47]. The most widely utilized diagnostic limit is > 40 IU/l, although the National Institute for Health and Care Excellence guideline suggests > 30 IU/l[47] and the European Society of Human Reproduction and Embryology guideline suggests a lower cut-off of > 25 IU/l[5]. If there is still some menstruation, these tests should be performed on day 2–3 of the cycle. It is important though that POI is not over-diagnosed in those with regular cycles and no history of relevant menstrual disturbance.

AMH produced by developing antral follicles in the ovaries is currently thought to be the most reliable measure of impaired ovarian reserve, particularly now that ultra-sensitive standardized assays have become more widely available. An AMH test could be performed to support the diagnosis of POI, although no diagnostic cut-off is established and AMH can be undetectable for as long as 5 years before periods cease; additionally, lack of universal availability, especially in primary care, and cost preclude this from being used routinely as a diagnostic test for POI[47].

It has been postulated that AMH could be used to predict the timing of spontaneous POI as well as natural menopause but, despite complex modelling, the utility for POI has not been confirmed[47]. On the other hand, there are data indicating that AMH can be used to diagnose and predict loss of ovarian function following iatrogenic interventions, e.g. chemotherapy for breast cancer[48]. Transvaginal ultrasound scan, as well as checking for anatomical abnormalities, can also be helpful in assessing ovarian volume and AFC. These would be expected to be low in POI and usually correlate with AMH levels[49], although occasionally relatively normal AFCs are seen despite low AMH levels. AMH appears to be a stronger predictor of ovarian response to gonadotropin therapy than AFC in assisted reproduction

treatment[50]; by extrapolation, it may therefore be a better predictor of the onset of POI, although this requires confirmation.

Other key diagnostic tests

If the diagnosis of spontaneous POI appears likely, then assessment of karyotype and the FMR1 gene premutation should be offered. Where resources are limited, women with early POI (< 30 years old), those with learning difficulties and those with a family history of POI can be prioritized for genetic testing, although ideally all women with POI would be offered this. Other genetic testing is usually in research centers. Whole genome sequencing might enable identification of novel causative genomic factors not yet identified by targeted gene sequencing.

In view of the increased incidence of autoimmune disorders in POI, autoantibody testing should be performed. To a certain extent, the tests performed will depend on personal and family history. The most clinically significant autoimmune association of POI is with adrenal insufficiency; 2.5–20% of women with POI have evidence of adrenal autoimmunity with histological evidence of autoimmune oophoritis, and 10–20% of patients with Addison's disease have POI[51]. Testing for adrenal cortex or 21-hydroxylase antibodies in peripheral blood is the most sensitive test and should be screened for in all POI patients. If positive, adrenal function tests should then be performed. Thyroid peroxidase autoantibodies and thyroid function should also be tested for due to the frequent co-existence of autoimmune thyroid disorders. Ovarian antibody testing is not recommended due to poor correlation with clinical symptoms and hormone biomarkers and high rate of false-positive results[51].

Tests of general health

Given the well characterized cardiometabolic and bone impact of POI, optimal management of this condition should involve a baseline assessment of insulin resistance, e.g. HbA1c, a lipid profile and a dual-energy X-ray absorptiometry (DXA) scan. The importance of these tests and the frequency with which they are repeated in each individual will depend on local resources and premorbid personal and family history. Although evidence for cost effectiveness is lacking, annual assessment of cardiovascular risk markers would seem logical, although this can be judged according to the individual's age and risk profile. The frequency of bone densitometry should be judged according to the presence of risk factors (in addition to POI), baseline DXA bone densitometry and the change in bone mineral density (BMD) with time (see 'Bone health' section).

Psychosexual and psychosocial health in women with premature ovarian insufficiency

POI is a life-changing diagnosis carrying a high risk of psychosexual and psychosocial consequences[52]. The early hormonal deprivation contributes to the impairment of central and peripheral components of the sexual response, resulting in hypoactive sexual desire disorder (HSDD) and symptomatic vulvovaginal atrophy (VVA)/genitourinary syndrome of menopause (GSM)[53]. Significant emotional and cognitive 'rebuilding' is required due to the multiple effects of POI including infertility, potential early aging and reduced self-esteem[54]. In women with POI, lower androgen levels alone do not account for the amount of sexual dysfunction and the poor sense of well-being and sexual satisfaction[55]. Indeed, intimacy-based stimuli also play a role[56], in spite of fewer sexual fantasies and less frequent masturbation, as well as less sexual arousal, reduced lubrication, and increased genital pain with sexual contact, possibly exacerbated by lack of androgens[55]. The absence of the vital effect of estrogens on sexual pathways[57] is likely to underpin the increased 2.8-fold increased risk of sexual dysfunction in women with POI[58]. However, systemic HT does not completely resolve sexual symptoms in women with POI[59]. Both estrogens and androgens cooperate in the brain and genitourinary physiology[60], and restoration of their deficiency should be strongly considered in the context of a biopsychosocial approach, as advised for postmenopausal women[61].

Health-care professionals should be aware that, following POI diagnosis, high levels of depression and perceived stress, and low levels of self-esteem and life satisfaction are present[62,63]. In addition, women with POI perceive lower levels of social support[64] and display a positive correlation between functional and spiritual well-being[65]. Moreover, women across different POI groups display an impairment in mood, body image, and self-confidence[43,66]. Infertility is the most disturbing aspect of POI followed by other dimensions of physical and psychological well-being[44]. In another study, women with POI reported poorer psychosocial functioning with impairment of quality of life, a high rate of emotional role limitation, less vitality, and worse mental health in comparison with typical aged menopausal women[67]. Age, experiencing hot flushes and/or night sweats and patient satisfaction predicted psychosocial functioning.

There is recent evidence that bilateral oophorectomy[68] and even hysterectomy with ovarian conservation[69] performed before the onset of natural menopause is associated with an increased long-term risk of depressive and anxiety symptoms, the latter possibly due to prematurely failing ovaries with inadequate hormone replacement.

Optimizing psychosexual and psychosocial health

Women with POI should have easy access to specialist counsellors who can address their needs, including those of involuntary childlessness and implications counselling to facilitate informed choices. Basic counselling is a cornerstone of sex therapy in postmenopausal women[70] and it should be always offered to women with POI because the majority of them do not receive adequate information, especially on sexual symptoms, which are highly distressing due to the younger age[44]. Moreover, women with POI are emotionally unprepared for the diagnosis and, according to many experts and working groups, a structured intervention is desirable to overcome the multitude of consequences[71,72].

Counselling is important both prior to and post sterilizing medical and surgical procedures, especially for benign or risk-reducing indications. A good example of combining elements of cognitive behavioral therapy with sexual health education was tested successfully in women following risk-reducing salpingo-oophorectomy[73] and such intervention should be replicated in POI in order to acquire skills to manage sexual dysfunction.

Psychosexual and psychosocial symptoms in POI deserve more research in order to understand the complexity of factors involved in the burden of the condition and to establish a tailored treatment with hormonal and non-hormonal strategies in the long term[53,74]. Clinical judgment has to guide the choice of treatment with the aim of counteracting, whenever possible, androgen insufficiency[53], either by prescribing transdermal estradiol at an adequate dosage[75] and/or by using transdermal testosterone at the dosage typical of the physiological premenopausal range[76,77]. Other pharmacological and non-pharmacological treatments are identical to those used in typical postmenopausal women. Cognitive behavioral and sexual interventions should be designed according to the specific needs of women with POI[53].

Cardiometabolic health in women with premature ovarian insufficiency

It is now well recognized that POI is associated with an increased incidence of cardiovascular and cerebrovascular disease. Even basal FSH levels > 7 IU/l have been found to be associated with adverse cardiovascular risk marker changes[78]. Tao *et al.*[79] detected a 48% higher risk of ischemic heart disease in POI, compared to the risk in women whose last menstruation was 50 years of age. A meta-analysis of ten observational studies (1966–2012) of 190,588 women with 9440 events has shown that POI is an independent risk factor for ischemic heart disease and coronary vascular disease[80]. It has been well documented that untreated women with POI

have a higher mortality rate[81-83]. The Shanghai Women's Health Study of 1003 POI cases found an increased risk of mortality of 1.29 (95% CI 1.08–1.54)[84].

In the largest study to date, data were pooled from 15 observational studies across five countries and regions from 301,438 women[85]. Compared with women who had menopause at 50–51 years, the risk of cardiovascular disease (coronary heart disease or stroke) was greater in women with POI (hazard ratio [HR] 1.55, 95% CI 1.38–1.73; $p < 0.0001$) with an almost linear dose–response relationship. Each year of decrease in age at menopause was associated with a 3% increased risk of cardiovascular disease[85].

Spontaneous versus surgical premature ovarian insufficiency and cardiovascular disease

A recent study of spontaneous and surgical POI confirmed a statistically significant relationship between the age of menopause and a composite primary outcome measure of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease and venous thromboembolism (VTE)[86]. Of the 144,260 women included in the study, 4904 (3.4%) had spontaneous POI and 644 (0.4%) had surgical POI. The primary outcome occurred in 292 (6.0%) women with spontaneous POI (8.78/1000 woman-years) and 49 (7.6%) women with surgical POI (11.27/1000 woman-years) compared to 5415 (3.9%) women without POI (5.70/1000 woman-years). For the primary outcome, spontaneous and surgical POI were associated with HRs of 1.36 (95% CI 1.19–1.56; $p < 0.001$) and 1.87 (95% CI 1.36–2.58; $p < 0.001$), respectively, after adjusting for cardiovascular disease risk factors and HT usage. Two meta-analyses[86,87] have attempted to examine the difference in the risks between spontaneous and surgical POI. One of these could not demonstrate a significant difference in cardiovascular risk between these types of POI[87]. This may be because a difference did not exist, or possibly that limitations in numbers of cases studied and methodology led to a false-negative outcome. Another meta-analysis stated that, because the number of available studies in some of their analyses was small, it precluded their ability to assess the effect of type of menopause in their results[88].

Impact of hormone therapy on spontaneous and iatrogenic premature ovarian insufficiency

Hypoestrogenism exerts effects at many levels of relevance including on lipids, insulin resistance, obesity, inflammation, hypertension, vasoconstriction, endothelial dysfunction, autonomic nervous system dysfunction, nitric oxide disturbances and impaired flow-mediated dilatation[89]. The benefits of early initiation of HT have been confirmed in many recent trials

and meta-analyses of naturally and surgically menopausal women. The dose and type of hormones at initiation of therapy appear crucial for coronary heart disease benefits[90]. In women with POI, meta-analyses have shown that those who used HT for longer, especially greater than 10 years, have the lowest risk of cardiovascular disease when compared with women who do not use HT[85,91].

Estrogen reduces cholesterol levels, increases high-density lipoprotein and apolipoprotein A1, decreases low-density lipoproteins (LDL) cholesterol levels and triglycerides and upregulates the apolipoprotein B_{100} receptor. Under the influence of estrogen, small dense LDL particles which are prone to oxidative damage are cleared through a scavenger mechanism and become embedded in the subendothelial space. Oral HT, especially with drospirenone as the progestogen compound, and transdermal HT reduce the activity of angiotensin converting enzyme, thus reducing blood pressure[92]. Estrogen therapy also has antioxidative effects, by increasing levels of endothelial nitric oxide synthase and production of nitric oxide, reducing endothelin 1 and regulating blood pressure, platelet function, vascular smooth muscle proliferation and the expression of adhesion molecules. Therapy with 17β-estradiol could exert antiarrhythmic effects by inhibition of calcium channels[93].

In a study of endothelial function[94], 18 women with POI were assessed before and after 6 months of HT. Findings were compared with a control group of 20 premenopausal, regularly menstruating women. Flow-mediated dilation of the brachial artery was significantly lower in women with POI at baseline than in controls. Six months of HT in the POI group resulted in restoration of flow-mediated dilation back to that of the control group. In another study of young hypogonadal women, increasing doses of oral estradiol (1, 2 and 4 mg) resulted in a reduction of intima-media thickness[95].

Cardiovascular outcomes appear to vary according to the type of estrogen used. Women with POI were randomized to either transdermal estradiol with vaginal or oral progesterone, or to a 30 μg ethinylestradiol combined oral contraceptive (COC). Mean systolic (between-group difference 7.3 mmHg, 95% CI 2.5–12.00 mmHg) and diastolic (7.4 mmHg, 95% CI 2.5–12.00 mmHg) blood pressure, plasma angiotensin II and serum creatinine were significantly lower in the HT group than in the COC group at the end of the 12-month treatment[96].

Although some studies have shown that HT in POI women, particularly when used for more than 10 years, is associated with a lower cardiovascular risk, this was not observed in all studies[86-88]. It is difficult to fully assess the relationship of cardiovascular risk in POI with HT in cohort studies because accurate data are not always available regarding the timing of initiation, the dosage, the type, and the duration of use of HT. A long-term prospective

randomized trial would be ideal, but, in the absence of this, good-quality prospectively collated global registry data should provide useful information[71,72].

Metabolic changes

Estradiol regulates many of the key enzymes involved in mitochondrial bioenergetics, including glucose transporters, required for the regulation of glucose uptake in cells. Hypoestrogenism induces centripetal obesity, adipose tissue inflammation, fatty liver and changes of glucose uptake from the circulation, without changes in 'de novo' free fatty acid synthesis. Kuylaksizoglu *et al*. confirmed insulin resistance in POI patients with hypoestrogenism[97]. Estrogen has beneficial effects on the metabolism of glucose and insulin, thus improving insulin sensitivity[91]. Whereas stressors increase insulin and cortisol[98], metformin also has potential beneficial effects on metabolic parameters such as insulin resistance, gluconeogenesis and immune function[99-101]. In an unblinded, randomized trial of 17 women with Turner syndrome[102] in which subjects were treated with either conjugated equine estrogens 0.625 mg or 30 μg ethinylestradiol with progestogen for 6 months, it was found that both were effective at correcting hyperinsulinemia.

Bone health in women with premature ovarian insufficiency

Osteoporosis is a key concern for women with POI[43,44], with estimated prevalence rates ranging from 8% to 27% according to the definition used (BMD or fracture) and cause of POI[12,103-105]. Women with POI have significantly lower BMD[105,106] and an increased risk of osteoporosis compared to women with usual age at menopause (odds ratio 2.54; 95% CI 1.63–3.96)[12], especially in women younger than 70 years[12,105]. Underlying mechanisms for low bone mass include: insufficient peak bone mass accrual; increased bone resorption associated with estrogen deficiency; presence of co-morbidities, which increase the risk of osteoporosis; and potential defects specific to the cause of POI[107].

Identified risk factors for low BMD incorporate both generally recognized and cause-specific factors and, in women with spontaneous normal karyotype POI, include: age < 20 years at onset of irregular menses, > 1 year delay in diagnosis, low serum vitamin D concentrations, low dietary calcium, non-compliance with HT, and lack of exercise[103,106]. Women with Turner syndrome may have additional contributors to bone loss including genetically related skeletal fragility, increased risk of celiac disease and increased risk of falls secondary to hearing loss and visuospatial abnormalities[107]. Celiac disease is also associated with

autoimmune POI. Importantly, fracture risk assessment tools, such as FRAX, are not validated for women under age 40 years.

Management of bone health in POI can be summarized as: bone health assessment including clinical risk factors, biochemistry and imaging (DXA); prompt institution of HT (unless contraindicated); appropriate lifestyle interventions; education; and ongoing monitoring (Figure 1). However, multiple factors, including consumer and clinician knowledge gaps, sub-optimal screening, confusion regarding the definition of osteoporosis in young adults, and delayed initiation and non-adherence to therapy, contribute to sub-optimal management of bone health in women with POI[97,108-112].

Women with POI demonstrate osteoporosis knowledge gaps, which negatively influence screening behaviors and calcium intake[110]. A variety of clinicians including primary-care physicians, gynecologists and endocrinologists are involved in the care of women with POI, with differing expertise in bone health[111,112].

Diagnosis of low BMD and osteoporosis in women below 40 years is challenging as the use of the DXA-derived BMD *T*-score to diagnose osteoporosis can generally not be used until peak bone mass has been achieved[113]. Additionally, BMD can be underestimated in individuals with short stature such as women with Turner syndrome[107]. However, new modalities, such as trabecular bone score measurement, may overcome this problem[114]. The 2019 International Society for Clinical Densitometry position statement recommends that *Z*-scores < -2 be used to define low bone mass in women before menopause; however, this does not specifically refer to women with POI[115].

An International Osteoporosis Foundation review of osteoporosis in young adults proposes that a *Z*-score < -2 (referring to bone density two standard deviations below the age-adjusted mean) be used to define low bone mass in young adults who have not attained peak bone mass. The term osteopenia should be avoided. However, it proposed maintaining the use of the *T*-score < -2.5 (where the bone density is 2.5 standard deviations below the young adult peak bone mass-adjusted mean) to diagnose osteoporosis in young adults suffering from chronic disorders known to affect bone metabolism, including hypogonadism, thereby encompassing POI and thus aligning with the World Health Organization definition of osteoporosis[113]. In summary, the presence of fragility fractures, especially vertebral fractures, and/or *T*-score < -2.5 (unless she is still growing) in an adolescent/woman with POI is diagnostic of osteoporosis.

A systematic appraisal of clinical guidelines for management of bone health in women with POI revealed variable quality and a paucity of high-quality evidence to guide management[116].

All guidelines agreed that HT should be initiated and continued until at least the age of usual menopause, but variation occurred in regard to screening and monitoring, with no consensus regarding the optimum HT. Although limited by small sample sizes, heterogeneous populations and methodological variation, systematic reviews of studies involving women with varying etiologies of POI demonstrate that HT maintains or increases BMD with bone loss observed in women receiving placebo[117,118]. However, the etiology of POI or type of HT influences the BMD response. Findings from randomized, controlled trials (RCTs) indicate that treatment with more 'physiological' doses of 100–150 μg transdermal or 2 mg oral estradiol may be superior to 30 μg ethinylestradiol for spine BMD accrual and bone turnover marker response[119,120]. BMD studies have not been conducted in women with POI using estradiol-containing oral contraceptive pills thus far. No difference in BMD gains over 5 years was observed in a RCT involving 20 women with Turner syndrome receiving 4 mg versus 2 mg oral estradiol, although lean mass increased with the higher dose[121]. At 1-year follow-up, a study of 60 women with POI secondary to stem cell transplant[122] reported a significant decrease in BMD with calcium/vitamin D supplementation alone, no significant BMD change with 2 mg oral estradiol, but significant increases in BMD with 35 mg weekly oral risedronate or three infusions of zoledronate.

Mixed results were obtained regarding the addition of testosterone therapy. Positive BMD effects were observed in a pilot study of 14 women with Turner syndrome treated with 1.5 mg methyltestosterone[123], whereas no benefit was observed with addition of transdermal testosterone in a RCT trial involving 145 women with idiopathic POI[124].

Management of women with POI where HT is contraindicated, such as women with breast cancer, requires specialist referral for consideration of alternative antiresorptive therapies, bisphosphonates or denosumab[5].

Repeat assessment of BMD within 5 years of initiation of HT is suggested[5] although evidence is lacking regarding the best method and frequency of monitoring. Elevations in serum bone turnover markers and response to treatment vary between studies[119,124,125] and further research is needed before recommending routine use.

Cognitive health in women with premature ovarian insufficiency

Women with a long-term hypoestrogenic state due to POI are at increased risk of cognitive impairment, stroke and Parkinson's disease; however, most of the data in this context are derived from the surgical POI population[126-129]. Appropriate HT administered at an early stage appears to modify the disease process favorably.

The link between a long-term hypoestrogenic state and cognitive impairment/dementia was reported by Rocca *et al*.[126] using data from the Mayo Clinic Study of oophorectomy and aging. In a study of 813 women with unilateral oophorectomy, 676 women with bilateral oophorectomy, and 1472 controls, they found that women who underwent surgery before the age of menopause had an increased risk of cognitive impairment or dementia compared to the controls (HR 1.46; 95% CI 1.13–1.90), with an increased risk for younger age at oophorectomy ($p < 0.0001$).

Rocca *et al*.[127] also reported an increased risk of ischemic stroke in a review of three observational studies in women who had bilateral oophorectomy compared with women who conserved their ovaries before the age of 50 years. Estrogen replacement appeared to reduce the risk in one of the studies.

Data from two longitudinal studies assessing cognitive decline (Religious Orders Study and Rush Memory and Aging Project) confirmed that age at surgical menopause was associated with cognitive decline and Alzheimer disease neuropathology[129]. Earlier age of surgical menopause was associated with faster decline in global cognition ($p = 0.0007$) including specific episodic memory ($p = 0.0003$) and semantic memory ($p = 0.002$). Earlier age at menopause was also associated with increased Alzheimer disease neuropathology ($p = 0.038$), especially neuritic plaques ($p = 0.013$). HT use for at least 10 years was associated with a reduction in cognitive decline as long as it was administered within a 5-year perimenopausal window.

Reproductive health in women with premature ovarian insufficiency

Involuntary childlessness is one of the most significant consequences for women diagnosed with POI. Not only may this adversely affect her psychological well-being but, world-wide, it may compromise a woman's status in her community and impact her economic stability[5]. Apart from those with gonadotropin receptor mutations, the infertility of POI is caused by a critically low number of ovarian oocytes, so follicle development leading to ovulation falters, despite high gonadotropin levels. However, ovarian activity can be detected in around 25%, and naturally conceived pregnancies can occur in up to 5% of women with POI[130]. Most of these pregnancies will be within 1 year of diagnosis, but may occur many years later[131] and evidence of ovarian activity at diagnosis is a positive predictive factor[132].

Treatments

There are no proven treatments to increase the rate of autologous oocyte pregnancies, as assessed by two systematic reviews published 20 years apart[132,133]. There have only been three RCTs of therapeutic interventions and all were small. Two trialled estrogen treatments that lower endogenous FSH levels, which might allow FSH receptors that have been desensitized by chronically high FSH exposure to respond to a change in level. The oldest trial randomized 37 women with POI to receive 2 mg oral estradiol or no treatment for 6 weeks in a cross-over study, with ovulation as the end-point. There was no effect of estradiol, although 46% ovulated at least once during the trial period and there were two pregnancies[134]. The other two trials were for adjunct treatments to gonadotropin stimulation. In one, 50 women with POI were randomized to receive 14 days of ethinylestradiol before gonadotropin stimulation[135]. In the other, 58 women with POI were randomized to receive 6 mg oral dexamethasone daily or placebo for 28 days during GnRH analog ovarian suppression prior to gonadotropin stimulation[136]. Although there were four pregnancies in the ethinylestradiol trial, two in the dexamethasone trial, and all the pregnancies were in the intervention arms, the differences were not statistically significant. However, neither of the trials was powered for pregnancy as the main outcome and there was a statistically significant difference in the ovulation rates in the intervention arms.

Dehydroepiandrosterone

A Cochrane systematic review concluded that dehydroepiandrosterone (DHEA) and its derivative testosterone may improve live birth rates in poor responders undergoing assisted conception, although, when the authors excluded trials with a high risk of bias, the apparent benefit was no longer seen[137]. The effect of androgens is postulated to be augmentation of follicle development at the preantral stage and in response to gonadotropins. With this in mind, 38 women with POI were recruited to an observational trial of 12 months DHEA supplementation (25 mg three times a day), the aim being to allow sufficient time for any effect on follicle recruitment to become apparent. Thirty-one women completed the study and there was no effect on markers of ovarian reserve or menstrual pattern[138].

Critique

The background pregnancy rate associated with POI, together with the small numbers of recruits to all the trials published to date, means that results must be interpreted with caution, especially the more invasive treatments. Reproductive medicine practitioners are led by a desire to help women with POI fulfil their dreams of a child, and the balance of pushing

boundaries versus false expectation can be difficult to find. These issues were explored in an editorial published recently, although the intervention under discussion was endometrial scratching[139]. This became a popular invention to improve implantation rates, based on encouraging results from small trials, but was shown to be ineffective when subjected to a large multicenter RCT.

Oocyte donation and freezing

Oocyte donation is an established fertility treatment for women with POI and the number of therapeutic cycles is increasing. It is, of course, a very different treatment than any using autologous oocytes and is not an acceptable/appealing option for everyone. In addition, access to suitable donors may be restricted by availability, cost or local recruitment restrictions.

Oocyte freezing for fertility preservation is not an option for a woman with POI. However, there have been many successful pregnancies in women with POI who stored eggs or embryos prior to their loss of fertility, usually due to iatrogenic sterilizing treatment(s). If it were possible to identify impending POI in other circumstances, then this could become an option for more women. *In vitro* maturation following aspiration of oocytes from small antral follicles may sometimes be an option. This emphasizes the importance of understanding the etiology and natural history of this distressing condition.

Advances in reproductive health research in women with premature ovarian insufficiency

There has been considerable interest in the potential of stem cell therapy. Four pregnancies were reported after bone marrow or peripheral blood stem cell transplantation[140] and there are several mouse and rat models that have shown resumption of ovarian function after mesenchymal stem cell transfusion[141]. Platelet-rich plasma has been used for *in vitro* maturation of primordial and primary follicles[142] and there is a case report of a live birth (of twins) following single intra-ovarian injection of platelet-rich plasma in combination with gonadotropin and followed by two cycles of ovarian stimulation delivered by intravaginal injection[143].

Primordial follicle activation has also been proposed as a new treatment for POI. The key study involved 37 women, 20 of whom had remnant dormant follicles identified histologically. Their removed ovaries were treated with a phosphatase and tensin homolog inhibitor and then transplanted near the Fallopian tubes. Nine of 20 women experienced

follicular growth and three pregnancies ensued with two livebirths[144]. The safety and reproducibility of this technique requires confirmation[145].

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation (OTC) is increasingly widely used around the world to mitigate against the adverse effects of gonadotoxic cancer therapies and thus the fertility loss associated with iatrogenic POI. From initial case reports in the 1990s and the first successful live birth after transplantation in 2004, it is now used across the world, although the number of babies born remains limited, being approximately 200 at the moment[146,147]. The precise number is difficult to obtain in the absence of an international register but is certainly increasing all the time. Accurate calculation of a success rate is equally difficult, but larger centers report live birth rates in the region of 25–30%, with expected evidence of a decrease in success to low rates in women when ovarian tissue is stored in their late thirties and beyond.

While this is most widely used for girls and young women facing gonadotoxic therapy for cancer, it has wider application for those at risk of POI. Application in Turner syndrome has been considered and reported for a number of years, although there are no reports of successful transplantation of tissue with pregnancy or live birth. A recent report highlights that this is likely only to be applicable to women with X chromosome mosaicism and even then prediction of favorable ovarian histology is difficult[148]. In some young women, there may be a fairly normal population of healthy follicles, but others can show very few follicles or a high proportion of markedly abnormal follicles, with these differences not detectable endocrinologically or by ultrasound. Careful individual assessment is therefore essential, including consideration of the health of the patient in regards to her ability to successfully carry a pregnancy as this is a major risk in women with Turner syndrome.

Future research will undoubtedly extend the indications further, for example, women with genetic predispositions to POI such as mutations in the FOXL2 gene, which is associated with blepharophimosis, ptosis, and epicanthus inversus syndrome, may be appropriate candidates. While, in these women, there is not the issue of contamination of the tissue with malignant cells, as is such an issue in, for example leukemia, the question remains as to whether these conditions where the pathology resides in the ovary are an appropriate indication for successful use of this approach.

Further developments in this field will be related to whether or not OTC continues to be regarded as an experimental approach to fertility preservation. Importantly, the American

Society for Reproductive Medicine has recently concluded that OTC should be considered 'an established medical procedure with limited effectiveness that should be offered to carefully selected patients'[149]. It is important to recognize that the data are extremely limited in regard to prepubertal girls, with only two case reports in the world literature of successful pregnancies in patients where tissue was taken before or in the early stages of puberty. Both these patients had hematological rather than malignant diseases. Nevertheless, this change in the status of the procedure is an important advance, allowing its more widespread use where the need for patient funding has previously been a major limitation.

OTC was primarily developed for fertility preservation, rather than any endocrine benefit. However, one clear advantage of this approach to fertility preservation over oocyte vitrification is that replacement of ovarian tissue results in normalization of the endocrine profile, albeit for a limited and variable length of time. Its potential use specifically for hormonal benefit has been discussed, but there are no objective data on any endocrine benefit, for example, on bone density following ovarian tissue replacement. At present, it seems appropriate that the surgical collection of ovarian tissue should only be performed where the primary indication is restoration of fertility, and replacement for endocrine benefit should only be performed where fertility is no longer relevant to that patient. Importantly, the procedure requires a laparoscopy to remove the tissue and further surgery to replace it, and this is not without risk. The surgical procedures and appropriate storage require specific expertise and therefore should be only offered by centers with that laboratory and clinical expertise.

Oogonial stem cells

One of the key differences between the male and female reproductive systems is that, in the male, gametogenesis continues throughout adult life with little diminution, whereas female reproduction is characterized by its finite duration and indeed the significant reduction in gamete quality in the later reproductive years. The biological basis for this is the presence of spermatogonial stem cells within the testis, which undergo unequal division to form daughter spermatogonia but with retention of the key stem cell characteristics in one product of that division. By contrast, in the female, it is understood that all oocytes are formed during fetal life, following a wave of meiosis in the late first and early second trimesters of pregnancy. All oogonia within the ovary thus enter meiosis with subsequent arrest at prophase of meiosis I, with formation at that same time of the pool of primordial follicles, which constitutes the ovarian reserve.

The existence of a germline stem cell pool within the ovary would provide huge opportunities for the prevention and treatment of POI. The possible existence of such cells in the postnatal mammalian ovary was suggested in two papers published in 2004[150] and 2012[151], which attracted enormous controversy[152]. Subsequently, however, a number of research groups have provided further evidence that such cells, often termed 'oogonial stem cells' (OSCs), can indeed be identified and isolated from the postnatal mammalian ovary in a number of species including the human[153,154].

Most studies on their functional capacity have been performed in the mouse, with essentially minimal evidence of their developmental potential in larger species. In rodents, data have shown that, following isolation and expansion, they can be re-injected into ovaries of animals where the follicle pool has been ablated with chemotherapy, with evidence of restoration of fertility and production of healthy offspring, identified through cell-labelling technologies[155]. Much more preliminary data have been obtained in the human, with some evidence of subpopulations, which may indicate different stages of maturation[156], but there remains no evidence that these cells contribute to normal reproduction or indeed can be activated to regenerate the follicle pool.

In mice, it has been suggested that OSCs may indeed contribute to the normal follicle pool but this ability declines with age[157]. While the cells can be isolated from aging mouse ovary, they seem to no longer have the capacity to form follicles. Intriguingly, in other experiments relating to chemotherapy depletion of the follicle pool, the ability of OSCs to form new follicles diminished with increasing time since chemotherapy administration[158], with both lines of evidence suggesting that it may well not be changes in the OSCs but in their microenvironment within the ovary that compromises their endogenous development potential. However, it must be emphasized that these experimental models are a long way from any confirmation in the human and clinical application, similarly to other approaches to artificial gamete generation[159].

Practical management of women with premature ovarian insufficiency

General

POI has a multisystemic impact with profound physical and emotional ramifications; as such, its management should be by multidisciplinary teams or with multi-professional collaboration. Health-care professionals from the menopause, fertility and psychology fields should be available, ideally in a one-stop service. There should be close liaison with endocrinologists, adolescent gynecologists, oncologists, hematologists, pharmacists,

dieticians and patient advocacy groups, e.g. The Daisy Network (https://www.daisynetwork.org). The initial management of POI should ideally be in specialist centers; subsequent management will depend on expertise in the community. If this is not available, then long-term follow-up should remain within the specialist center, at least until the average age of menopause.

In view of the impact on health and well-being, it is particularly important that women who are diagnosed with POI should be advised to observe a well-balanced diet with adequate exercise, maintain a healthy weight range, whilst avoiding smoking and minimizing alcohol consumption. Although routine supplementation with calcium is not required unless there is proven deficiency, supplementation with 800–1000 IU/day of vitamin D3 can be advised in addition to calcium and vitamin D-rich foods. These approaches, combined with adequate HT, should reduce the risk of cardiovascular disease and osteoporosis, although specific clinical trial evidence is lacking.

Hormone therapy

The importance of HT in POI is multifactorial. First, it facilitates the development of secondary sexual characteristics (including uterine growth) in prepubertal girls with primary amenorrhea. Second, it effectively alleviates typical vasomotor symptoms such as hot flushes and sweats and urogenital problems due to vulvovaginal atrophy and bladder atrophy, e.g. vaginal dryness, pain on intercourse, sensory urgency and recurrent urinary tract infections. Third, it can have a beneficial effect on other symptoms which affect quality of life, e.g. mood/cognitive problems, energy levels and musculoskeletal aches and pains. Fourth, HT will create a favorable hormonal environment, which will be conducive to the replacement of embryos and might increase the chances of natural pregnancy. Finally, HT will minimize the long-term risks of POI such as cardiovascular disease and osteoporosis[160].

Principles of hormone therapy in premature ovarian insufficiency

If we assume that restoring the physiological hormonal environment as closely as possible will achieve the most optimal outcomes in POI (maximizing benefits and minimizing side effects/risks), the principles of HT should be as follows:

(1) The hormones replaced should be identical to those which are missing.
(2) Non-oral estrogen delivery routes offer advantages in regard to avoiding first-pass hepatic metabolism and thus minimizing the prothrombotic effect of oral estrogen.

(3) The estrogen doses used should be generally higher than used in natural menopause.

Hormone therapy in premature ovarian insufficiency: a pragmatic approach

In actual practice, the treatment of POI with HT varies considerably from unit to unit and country to country for the following reasons:

(1) RCT data confirming symptom and quality-of-life benefits of specific regimens in POI are few.
(2) There is still controversy as to the adequate dose of progesterone for endometrial protection with the higher doses of estrogen used in POI.
(3) The availability and cost of hormones types vary considerably from country to country (and even within countries).
(4) Patient preference for a perceived 'peer friendly' preparation such as the combined oral contraceptive pill versus 'menopausal' HT.

For these reasons, a pragmatic approach to HT in POI is currently required, which is likely to still confer benefits within appropriate margins of safety. A detailed integrated, patient-based hormonal approach for women with POI, from puberty to late reproductive age, has been proposed in a recent review[71]. Realistically, only a large, global POI registry analyzing outcomes with different regimens will provide conclusive evidence of the optimal approach[71,72].

Estrogen

A typical 'physiological' estrogen regimen might consist of estradiol 75–100 μg patches or three to four metered 0.75 mg doses of estrogel (Table 1). Oral estradiol (2–4 mg/day) can be safely used in non-obese women thought not to be at increased risk of thrombosis. These doses achieve relatively physiological levels of estradiol of 200–400 pmol/l. The rationale for recommending higher doses of HT is that, as well as symptom relief, there appears to be a dose–response effect regarding cardiovascular and bone benefits, although there are few dose–response trials of HT in POI[95,96,119,121] (see 'Cardiometabolic health' and 'Bone health' sections). Although higher doses of estrogen are physiological in younger women, some may not be able to tolerate these due to problems such as mastalgia or migraine, in which case the dose should be individualized to their requirements, carefully balancing benefits, risks and side effects. In practice, lower doses may need to be started initially to test tolerance and the

dose built up to the optimum levels. Routine monitoring of estrogen levels is not required, but it can be helpful to evaluate inadequate symptom relief or adverse effects. Transdermal estrogen delivery facilitates a greater degree of monitoring accuracy than oral, due to more stable pharmacokinetics.

If genitourinary symptoms persist, e.g. VVA causing vaginal dryness/pain despite systemic HT, then low-dose vaginal estrogen or prasterone can be added to the regimen without fear of overdose and adverse effects. VVA symptoms can be very severe in young women with POI following treatment for malignancy, particularly whilst using aromatase inhibitors after breast cancer. Even ultra-low-dose vaginal estrogen is contraindicated in women on aromatase inhibitors. Women with breast cancer on tamoxifen can use estrogen off-label due to blockage of estrogen receptors by tamoxifen[163]. Vaginal estrogen can also be used off-label in women with a history of other malignancies but caution must be exercised where these have been estrogen receptor-positive. Prasterone has not yet been sufficiently studied in women with a history of breast cancer or other malignancies to make specific recommendations.

Non-estrogenic VVA treatments include bio-adhesive moisturizers that are hydrophilic and rehydrate vaginal tissues, providing a reasonable alternative to vaginal estrogen. They are a more physiological way of replacing vaginal secretions than vaginal gels/lubricants such as KY. Lubricants and moisturizers should have similar osmolality and pH to those of physiological vaginal secretions[164]. Other non-hormonal treatments for VVA such as ospemifene and vaginal laser have not been formally evaluated in women with POI but may provide alternative solutions.

Progesterone/progestogens

A ‘physiological’ endometrial protection regimen in non-hysterectomized women can be achieved with 200 mg micronized progesterone administered orally or vaginally for 12 days per cycle (Table 1). Data from naturally menopausal women suggest that there are advantages to using micronized progesterone in combined HT; the metabolic benefits of estrogen are maintained, the combination is not pro-thrombotic and there appears to be a lower risk of breast cancer in natural menopause[165]. However, micronized progesterone in standard doses may be insufficient to provide adequate long-term endometrial protection[161]. Progesterone doses of greater than 200 mg may therefore be required, particularly with the higher doses of estrogen typically used in women with POI. Due to its similarity to micronized progesterone, dydrogesterone has similar metabolic and breast advantages, although, once again, data are

derived mainly from naturally menopausal women and require confirmation in women with POI[165].

Endometrial protection appears assured with adequate doses and durations of androgenic progestogens such as norethisterone acetate or medroxyprogesterone acetate[162]; typical regimens are presented in Table 1. Although HT regimens with micronized progesterone appear to have metabolic advantages compared to those with androgenic progestogens[166], it is possible that these benefits are not significantly attenuated by androgenic progestogens when higher doses of estrogen are used in POI. Published data are expected soon from a study comparing progesterone to medroxyprogesterone acetate in women with POI, although with standard-dose transdermal estradiol[167].

Women with POI can switch to no-bleed continuous combined regimens after a couple of years if they wish, or start immediately if they have presented with > 1 year amenorrhea. Although continuous combined HT is associated with greater endometrial safety[162], sequential HT may be associated with lower breast cancer risk[168]. Women should be advised to use a sequential HT regimen if pregnancy is desired or if they are planning to have oocyte donation fertility treatment in the near future. The dose of micronized progesterone will need to be increased above 100 mg in women using continuous combined regimens with higher doses of estrogen. If a lower dose or duration of progesterone is being used due to intolerance, or if there are episodes of unscheduled bleeding, endometrial surveillance is advised with ultrasound and hysteroscopy with/without biopsy if the endometrium is thickened post withdrawal bleed on sequential HT or at any time on continuous HT. If contraception is required or if there are vaginal bleeding problems, a levonorgestrel intrauterine system releasing 20 μg/day can be used in combination with transdermal or oral estrogen, providing up to 5 years' endometrial protection, even with higher doses of estrogen. The lower-dose levonorgestrel intrauterine systems have not yet been assessed for endometrial protection although, used off-label with ultrasound monitoring, they can provide an option for progestogen-intolerant women.

Combined oral contraceptive pill as hormone therapy

The COC containing ethinylestradiol has been extensively used for puberty induction and hormone therapy in POI. The COC is generally cheap, easily accessible, familiar to women and health-care professionals and provides contraception if required. It is particularly popular with young women requiring hormonal support for POI. However, its use has been driven largely by practicalities rather than science[169]. Ethinylestradiol is a very potent estrogen and

has a long hepatic half-life even when delivered transdermally, which makes it potentially pro-thrombotic and hypertensive. Despite its potency, there is evidence that ethinylestradiol does not result in optimum breast and uterine development and should therefore not be used for puberty induction[5]. There is also increasing evidence that its metabolic and bone profile make it less beneficial to women with POI who require HT for primary prevention purposes, not just for symptom relief[102,119,120] (see 'Cardiometabolic health' and 'Bone health' sections). Also, if it is given in a conventional 21/7 or 24/4 regimen, symptoms can recur during the hormone-free interval and valuable treatment time for primary prevention is lost. Modern COC regimens now can be used which are continuous or have reduced hormone-free intervals. Some deliver 17β-estradiol rather than ethinylestradiol; although logical treatment options for women with POI, these have not been formally tested and there are concerns that the dose of the current options may not be high enough. The contraceptive ring is another option that can be used continuously.

Use of all these regimens in POI for HT rather than contraception is off-label and requires further research. With the aim of gathering better-quality data, a large, long-term, prospective, multicenter POI study of HT vs. COC (Premature Ovarian Insufficiency Study of Effectiveness of hormonal therapy, POISE) has been funded by the National Institute of Health in the UK and should commence in late 2020. Although the primary outcome measure will be BMD, many aspects of the health of women with POI will be studied including physical and emotional quality of life and cardiometabolic risk markers. It is hoped that, after 5 years, this will convert into a long-term observational study so that long-term outcomes such as fracture rates, cardiovascular disease and breast cancer can be studied.

Contraception

A diagnosis of POI does not exclude the possibility of ovarian activity and ovulation, with approximately a 5% chance of natural conception. Use of HT might actually increase the chance of pregnancy slightly through suppression of high FSH and LH levels, which may otherwise downregulate ovarian receptors and cause premature luteinization of follicles, thus facilitating ovulation of any remaining oocytes[170,171]. It is therefore important that adequate contraception is used if pregnancy is not desired. As previously discussed, this can be achieved with an oral COC or estrogen with a levonorgestrel intrauterine system. Eventually, the COC regimen can be switched to HT when the risk of unwanted pregnancy is highly unlikely, typically > 2 years post diagnosis.

Duration of treatment

Advisory guidelines[5,41,45-47] recommend that treatment of POI with HT should continue at least until the average age of menopause (51 years). Until this age, this constitutes genuine replacement of hormones, which would have naturally been produced if the ovaries were working normally, in contrast to replacement following natural menopause. Data already discussed in this paper demonstrate that women receiving shorter courses or no HT have a greater risk of cardiovascular, bone and cognitive pathology.

Risks of treatment

Breast cancer: Women with POI generally have a lower risk of breast cancer than the general age-matched population according to observational trials, probably due to reduced exposure to estrogen. Wu *et al*. reported data from 1003 women with POI within a total cohort of 36,402 women; the incidence of breast cancer was significantly lower in the POI group (odds ratio 0.59; 95% CI 0.38–0.91)[84]. The risk of breast cancer with long-term HT usage in POI is not thought to be any higher than that of the age-matched non-POI population[84,172]. Recent data suggested that women with POI mainly using older types of HT may have a higher risk for breast cancer compared to those women with POI who had not used HT[168]. However, it would have been more appropriate if premenopausal women of a similar age were used as the comparator group. Given the methodological problems of this study[173] and the considerable benefits of HT used in POI for quality of life, bone, cardiovascular and cognitive health, the pros usually far outweigh the cons for HT to be used long term, at least until the average age of menopause.

The benefits of prophylactic risk-reducing bilateral salpingo-oophorectomy in women carrying the BRCA1 or BRCA2 genes do not appear to be mitigated when HT is added back as long as the individual does not have a past history of hormone receptor-positive breast cancer[174]. However, the breast cancer risk does appear to be lower in women using estrogen alone compared to those on combined therapy. The decision whether to continue beyond the average age of menopause will depend on individualized benefits and risks, taking into account factors such as quality of life, bone, cardiovascular, cognitive health and breast cancer.

Venous thromboembolism: Limited data suggest that oral HT use in POI as well as late menopause can be associated with an increased risk of VTE. Canonico *et al*.[175] reported a U-shaped relationship between age at menopause and risk of VTE which persisted after

multivariable analysis ($p < 0.01$). Compared to women aged 40–49 years at menopause, those with early menopause (age < 40 years) or with late menopause (age > 55 years) had a significant increased non-procedural VTE risk (HR 1.8; 95% CI 1.2–2.7, and HR 1.5; 95% CI1.0–2.4, respectively). It is therefore important that estrogen therapy should be delivered transdermally in women thought to be at increased risk, given that a number of observational and case-controlled studies have confirmed a neutral impact if first-pass hepatic effects are avoided, albeit mainly in women with natural menopause[176].

Androgen therapy

In addition to estrogen and progesterone/progestogen therapy, women with POI may benefit from androgen replacement. There is increasing evidence that women with POI have lower androgen levels compared to age-matched controls. This might have an adverse effect on sexual desire, arousal and orgasm and contribute to other health problems such as tiredness, loss of stamina, osteopenia and sarcopenia. A systematic review and meta-analysis of testosterone levels performed in different types of spontaneous POI included 529 women compared to 319 controls[177]. It showed that women with POI (spontaneous and iatrogenic) had significantly lower total serum testosterone levels than the control group (weighted mean difference [95% CI] -0.38 (-0.55 to -0.22) nmol/l and -0.29 [-0.39 to -0.18] nmol/l, respectively). Apart from some data in women with early surgical menopause, as yet there have been no prospective RCTs to assess the impact of testosterone replacement on the sexuality of women with POI. This is an area that requires urgent research in view of the impact that androgen deficiency can have on women with POI. A new trial (T Bone), which is being planned by Professor S. Davis, President of the International Menopause Society, and collaborators to study the impact of testosterone supplementation on bone density, will also examine the impact on sexual and general quality of life.

A recent Global Consensus Statement[76] coordinated by the International Menopause Society, formulated mainly from a systematic review and meta-analysis of all the relevant RCT data[77], concluded that naturally and surgically menopausal women receiving physiological doses of testosterone could achieve a significant improvement in sexual desire without any adverse effects apart from excess hair growth or acne. The problem is the global lack of licensed female treatment options to achieve the required physiological dose of 5 mg/day (compared to 50 mg/day in men). This currently requires the off-label down-titration of male gels or use of a 1% testosterone cream with a female indication (Androfeme), both at a dose of 0.5

ml/day. The consensus concluded that there were insufficient data to make a recommendation for the use of oral DHEA to improve female sexual desire[76].

Complementary therapies

There are no good data for the use of complementary therapies in POI; HT should be first-line treatment unless there are specific contraindications or according to the woman's wishes, having made an evidence-based decision after being fully counselled. A network meta-analysis undertaken by the NICE UK menopause guideline group showed that St John's Wort and some isoflavone preparations may be effective for vasomotor symptoms in natural menopause, but more research is required to confirm efficacy and safety[47]. There are no hard data on major long-term outcome measures such as coronary heart disease and fractures or on long-term endometrial safety in either natural menopause or POI.

Pharmacological alternatives

Non-hormonal pharmacological options, e.g. paroxetine, venlafaxine, gabapentin, oxybutynin and clonidine, should only be advised for the alleviation of vasomotor symptoms where HT is contraindicated, e.g. hormone receptor-positive breast cancer or if the individual wishes to avoid HT despite adequate counselling on risks and benefits[178,179].

Bisphosphonates should be avoided in this young population in view of the potential desire for pregnancy and possible requirement for long-term usage with the associated reduction of bone turnover. However, bisphosphonates may be necessary if HT is contraindicated or if BMD is not improving with HT alone, despite an increase in dosage of HT.

Premature ovarian insufficiency registry

In order to fully understand the scale of the POI problem and to avoid fragmented research, a global POI registry will facilitate disease characterization and analysis of long-term outcomes[71,72]. The registry can be used to create a global biobank for genetic studies and to define and characterize the various presentations of POI. This is particularly important for relatively rare conditions such as POI where large-scale, prospective RCTS are unlikely to happen, e.g. iatrogenic induced POI for treatment of malignancy. Registrations of centers globally and data collection have already commenced using the resources at https://poiregistry.net set up by investigators at Imperial College London, UK. At the time of writing, data of more than 1000 POI patients have been anonymously uploaded to the registry, with a substantial contribution from colleagues in Capital Medical University,

Beijing. It is hoped that, through the collaboration of a global task force, data entry and analysis can be accelerated over the next few years, leading to results which will help to formulate evidence-based guidelines and optimize clinical practice.

Executive summary

Demographics/etiology/pathophysiology of premature ovarian insufficiency

- Terminology and diagnostic criteria should be standardized to avoid confusion about diagnosis.
- Major known genetic etiologies of spontaneous POI include Turner syndrome and fragile X; idiopathic still the largest category.
- The proportion of iatrogenic POI cases is increasing due to survival of childhood and young adult malignancies.
- Full understanding of etiology/pathophysiology will facilitate efficient diagnosis and management, e.g. global registry/biobank.
- Global, ethnic and cultural variations in prevalence and presentation require clarification.

Diagnosis of premature ovarian insufficiency

- Taking a full history, e.g. menstrual health, is important in making the diagnosis.
- The diagnosis should not be made on the basis of only one FSH level.
- AMH testing is only required if there is diagnostic uncertainty.
- Investigations (including karyotype, fragile X and adrenal antibody status) regarding the cause of spontaneous POI are recommended.
- A baseline DXA scan should be offered to all women diagnosed with POI.

Psychosexual/psychosocial impact of premature ovarian insufficiency

- Women with POI have a high incidence of psychosexual and psychosocial problems.
- Multidisciplinary teams should routinely offer counselling regarding psychosexual and psychological health issues.
- VVA/GSM symptoms should be enquired about openly and addressed effectively.
- Androgen replacement should be considered where sexual desire is low.

Cardiometabolic health in premature ovarian insufficiency

- Women should be informed about risk factors for cardiovascular disease and the importance of lifestyle changes (stopping smoking, regulating body weight, moderating alcohol, etc.).
- Estrogen deficiency, lipid and insulin resistance should be emergently diagnosed and treated individually and effectively.
- HT is strongly recommended at least until the average age of menopause to reduce cardiovascular morbidity and mortality.

Bone health in premature ovarian insufficiency

- Women with POI are at increased risk of osteoporosis.
- Comprehensive risk evaluation, education and HT are recommended.
- Specialist advice is needed for women where HT is contraindicated or who sustain fragility fractures while taking HT.
- Evidence gaps persist regarding optimum regimen, monitoring and fracture outcomes, highlighting need for further research.

Cognitive health/dementia in premature ovarian insufficiency

- It is important that the data from studies in much older women such as the Women's Health Initiative cognitive study are not extrapolated to women with POI.
- A window of opportunity for cognitive benefit of HT when initiated within the perimenopause appears to exist in POI as it does for cardiovascular disease.
- The findings and outcomes in women after bilateral oophorectomy may differ from those with non-surgical POI.
- Prospective RCTs of dementia risk in women with POI are unlikely to be conducted due to the need for very large numbers and long-term follow-up.

Fertility in premature ovarian insufficiency

- Infertility is one of the most disturbing aspects of POI and there are no proven treatments to increase the rate of pregnancy with autologous oocytes.
- When counselling women with POI about fertility options, it is of paramount importance that they are given correct information to empower them to make evidence-based choices.
- Oocyte donation currently offers the best chance of achieving a pregnancy in POI.
- Stem cell therapies, platelet-rich plasma and primordial follicle activation all require further research and confirmation of efficacy and safety.

- Women should be counselled about the possibility of oocyte, embryo and ovarian tissue cryopreservation pre-gonadotoxic and sterilizing therapies.

Management of premature ovarian insufficiency

- Management of women with POI should be multidisciplinary.
- Patient advocacy groups should be involved in producing protocols.
- Lifestyle, weight, diet and exercise should be optimized.
- HT at least until the average age of menopause should be first-line treatment unless contraindicated or if rejected by the woman after careful counselling.
- There are very few data for the benefits and risks of complementary and alternative medicines and non-hormonal bone-sparing agents in POI.
- Replacement can be with the COC initially if contraception is required or because of personal preference, but in the long term HT is recommended to optimize bone and metabolic health.

Key research priorities in premature ovarian insufficiency

- Global POI registry collaboration/expansion/biobanking.
- Further determination of etiologies of POI, especially genetic.
- Discovery of reliable biomarkers for predicting and diagnosing POI.
- Impact of hormonal interventions (e.g. HT versus COC, types of HT/COC) on quality of life, psychological/psychosexual aspects, and bone, cardiovascular and cognitive health.
- Defining adequate dose of progesterone to protect endometrium at higher levels of estrogen in HT.
- Role of androgen supplementation for quality of life, cardiovascular, bone, cognitive health and fertility.
- Differential impact and management of iatrogenic and spontaneous POI.
- POI as part of an aging syndrome versus aging following POI due to hormone deficiency.
- Confirmation of efficacy and safety of fertility-enhancing techniques.
- Further clarification of role and potential of human oogonial stem cells.

Conclusion

POI is a concerning condition for many reasons. Women with spontaneous and surgical POI and early menopause are at significantly greater risk of cardiovascular, bone, cognitive and

other chronic conditions than women going through menopause at the average age of 51 years. It must also not be forgotten that there is an increasing cohort of children and young women surviving following cancer treatments who will live the whole of their lives with iatrogenic POI[180]. Given all these serious health issues, POI should be a public health priority so that women with POI are supported and informed, and health-care professionals are given adequate education and resources to identify, manage and research women at risk of POI at the earliest possible stage, ideally from childhood, or even birth. Preventive measures such as optimizing lifestyle, diet and exercise and advice regarding long-term hormone replacement for this endocrine deficiency disorder, at least until the age of natural menopause, will have the greatest impact if instituted at the earliest stage possible.

Potential conflicts of interest Nick Panay has lectured and/or acted in an advisory capacity for Abbott, Besins, Lawley, Mithra, Mylan, Novo Nordisk, Roche Diagnostics, SeCur, Shionogi and Theramex. Richard Anderson has undertaken consultancy work for Merck, IBSA, Roche Diagnostics, KaNDY Therapeutics, Sojournix Inc. Rossella Nappi had past financial relationships (lecturer, member of advisory boards and/or consultant) with Boehringer Ingelheim, Ely Lilly, Endoceutics, Gedeon Richter, HRA Pharma, Procter & Gamble Co, TEVA Women's Health Inc, and Zambon SpA. At present, she has an on-going relationship with Astellas, Bayer HealthCare AG, Exceltis, Fidia, Merck Sharpe & Dohme, Novo Nordisk, Palatin Technologies, Pfizer Inc, Shionogi Limited and Theramex. Amanda Vincent has received grant funding, speaker honorarium or travel support from Besins, Amgen and Merck. Svetlana Vujovic has no declarations relevant to this manuscript. Lisa Webber has no declarations relevant to this manuscript. Wendy Wolfman has undertaken advisory board work for Pfizer, Searchlight and BioSyent.

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MANAGEMENT ALGORITHM FOR BONE HEALTH IN WOMEN WITH PREMATURE OVARIAN INSUFFICIENCY (POI)

Women with diagnosed Premature Ovarian Insufficiency

Initial Bone Health Assessment

Potential risk factors for low BMD with POI
- Primary amenorrhea.
- Longer duration of POI.
- >1yr delay in diagnosis.
- Age <20 years at onset of irregular menses
- Childhood cancer survivors

General risk factors for low BMD†

Non-modifiable
- Age.
- Prior fragility fracture.
- Family history of osteoporosis.
- Parental history of fracture.

Modifiable and lifestyle
- Multiple falls.
- Low physical activity or immobility.
- Low body weight.
- Low muscle mass and strength.
- Poor balance.
- Vitamin D insufficiency.
- Protein or calcium undernutrition.
- Smoking.
- Alcohol >2 standard drinks/day.

Diseases associated with low BMD +/- POI
- Rheumatoid arthritis.
- Hyperthyroidism.
- Hyperparathyroidism.
- Chronic kidney disease.
- Celiac disease or malabsorption.
- Diabetes mellitus.
- Myeloma or MGUS
- Organ transplant.
- Bone marrow transplant.
- HIV infection.
- Depression.

Medications associated with low BMD
- Glucocorticoids.
- Excess thyroid hormone replacement.
- Aromatase inhibitors.

Blood and urine tests
- Serum UEC, CMP, LFT, TSH, 25-hydroxy vitamin D
- Bone turnover markers: not currently recommended for routine use.
- If reduced bone mass is present, also consider the following: serum PTH, celiac serology, and 24-hour urine calcium excretion.

Imaging
- **DXA:** Indicated at initial diagnosis for all women with POI, **'Low bone mass'** (*Z* score< -2) is the preferred term instead of osteopenia in this setting. *T* scores < -2.5 may be used to define osteoporosis[$]
- **Plain imaging:** Vertebral fracture assessment should be considered on an individual basis particularly if concerns regarding height loss, back pain, chronic diseases associated with low BMD and current or past glucocorticoid use.

Management*

Maintain healthy lifestyle
- Weight-bearing exercise.
- Avoidance of smoking.
- Maintenance of normal body weight.
- Balanced diet containing the recommended intake of calcium and vitamin D – dietary supplements may be required if inadequate intake.
- Avoid excess alcohol.

Hormone replacement therapy
- Offer estrogen replacement therapy to all women diagnosed with POI unless contraindicated.
- Both HT and COC are appropriate but COC may have less favorable effects on bone density. 17β-estradiol is preferred for estrogen replacement.
- Give combined treatment with progesterone/progestogen to women with intact uterus.
- Consider patient preference for route and method of administration as well as contraceptive needs.
- Continue hormone replacement until at least the time of anticipated natural menopause (approx. 50/51yo), then reassess.

Anti-resorptive therapy
- Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist.

Education
- Provide information
- Freely available co-designed fact sheet and infographic

Ongoing monitoring

Subsequent assessment of bone health
- If BMD is normal and adequate systemic estrogen replacement is commenced, the value of repeated DXA scan is low.
- If a diagnosis of low bone mass is made and estrogen replacement or other therapy initiated, repeat DXA in 2-3 years.

Specialist referral
- A decrease in BMD on subsequent scans (bone loss >5% and/or >0.05g/cm^2) should prompt review of estrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate.
- Development of a fragility fracture should prompt referral to an osteoporosis specialist.

Figure 1. Algorithm for management of bone health in premature ovarian insufficiency (POI). This figure was originally published in *Maturitas* 2019;128:70–80[116] (©Elsevier, 2019); used with permission. HT, hormone therapy; COC, combined oral contraceptive pill; BMD, bone mineral density; DXA, dual X-ray absorptiometry; MGUS, monoclonal gammopathy of undetermined significance; CMP, calcium, magnesium, phosphate; UEC, urea, electrolytes, creatinine; LFT, liver function tests; TSH, thyroid stimulating hormone.
†Fracture risk calculators (e.g. FRAX, Garvan) are not validated for use in women < 40 years old.

[$]Controversy exists regarding diagnosing low BMD in women with POI: the International Society for Clinical Bone Densitometry recommends use of *Z*-score <-2.0 to define low bone mass for age in women < 50 years old[16]; other guidelines have suggested the use of *T*-score <-2.5 to diagnose osteoporosis[14,26].
*Management is based on existing low- to moderate-quality evidence.
https://www.monash.edu/medicine/sphpm/mchri/research/themes/womens-and-childrens-public-health/early-menopause-research.

Table 1. Hormone therapy (HT) options: standard and 'premature ovarian insufficiency (POI)' regimens.

The table does not show all available options globally. Licensed (in at least one country) types/doses/regimens of HT shown in bold; other regimens are achieved off-label by halving/doubling/combining regimens.

Notes:

- Higher doses of estradiol usually required in POI but, to assess tolerance or in case of adverse effects, lower doses may be used initially.
- Variation globally as to what doses perceived as low, medium and high, e.g. North America 0.5 mg E2 is low dose, 1 mg E2 is standard dose, and 2 mg E2 is high dose.
- Sequential regimens require 12 days progesterone/progestogen per cycle for endometrial protection – this may need modification depending on tolerance.
- Endometrial safety is less assured with micronized progesterone used for > 5 years[161].
- Progesterone/progestogen doses shown are the minimum effective for endometrial protection given current data[162].
- Endometrial safety data lacking for the minimum effective dose of progestogen/progesterone with higher estrogen doses.

*A 1 mg dose of norethisterone acetate is adequate for standard-dose continuous combined HT, but not available separately from E2, hence 1.25–2.5 mg doses (0.25–0.5 of a 5 mg tablet).

HT type	*Sequential combined HT*		*Continuous combined HT*	
	Low/standard doses	*Higher 'POI' doses*	*Low/standard doses*	*Higher 'POI' doses*
Estradiol type				
Patch (transdermal, µg)	**25–50**	**75–100**	**25–50**	**75–100**
Gel sachet (transdermal, mg)	**0.5–1.0**	**1.5–2.0**	**0.5–1.0**	**1.5–2.0**
Gel pump (1 metered dose = 0.75 mg)	**1–2**	**3–4**	**1–2**	**3–4**
Oral (mg)	**1.0–2.0**	3.0–4.0	**1.0–2.0**	3.0–4.0
Progesterone/progestogen				
Micronized progesterone (oral/per vagina, mg)	**100–200**	≥ 200 (e.g. 300–400)	**100**	≥ 200
Dydrogesterone (oral, mg)	**10**	**20**	**5.0**	**10**
Medroxyprogesterone acetate (oral, mg)	**5.0**	**10**	**2.5**	**5.0**
Norethisterone acetate (oral, mg)	2.5–**5.0**	2.5–**10**	1.25–2.5*	**5.0**
E2/progesterone combined regimens				
E2/micronized progesterone (oral, mg)	1.0–2.0/100–200	> 2.0/> 200	**1.0**–2.0/**100**–200	3.0–4.0/300–400
E2/norethisterone acetate (transdermal) µg/24 h	25–**50**/85–**170**	75–100/255–340	25–**50**/85–**170**	75–100/255–340
E2/dydrogesterone (oral, mg)	**1.0–2.0/10**	3.0–4.0/20	**0.5–1.0/2.5–5.0**	3.0–4.0/7.5–10
E2/norethisterone acetate (oral, mg)	**1.0–2.0/1.0**	3.0–4.0/2.0–4.0	**0.5–2.0/0.1–1.0**	3.0–4.0/1.5–2.0
Levonorgestrel intrauterine system	n/a	n/a	**20 µg/day** sufficient for higher POI doses	