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The British Menopause Society and Women's Health Concern recommendations on the management of women with premature ovarian insufficiency

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Hormone replacement therapy, premature menopause, premature ovarian insufficiency

Introduction

This guidance document by the British Menopause Society provides recommendations on the assessment and management of women with premature ovarian insufficiency (POI).

The consequences of POI are related to the decline in ovarian function and estrogen deficiency associated with the condition. These can be short-term menopausal symptoms and long-term effects on bone and cardiovascular health, cognition as well as the fertility consequences associated with POI.

Sex steroid hormone replacement (both hormone replacement therapy containing physiological estrogens (HRT) and preparations containing synthetic ethinyl estradiol such as the combined oral contraceptive pill) provides a beneficial role both in the context of symptom control, as well as minimising the long-term adverse health effects associated with the condition. The benefits of hormone replacement and its role in this context are discussed in detail in the relevant sections in the document. The risks of hormone replacement including the risk of breast cancer quoted in the Women's Health Initiative study (WHI) and other studies on naturally menopausal women over the age of 50, do not apply to women with POI. These findings should not therefore be extrapolated to this group of women and this is addressed in the relevant sections in these recommendations.

The key message from this guidance is that women with POI represent a different cohort to women who have natural menopause beyond the age of 50. Hormone replacement has a beneficial role in maintaining bone and cardiovascular health as well as cognitive function in women with POI in addition to symptom control. HRT and the combined contraceptive pill containing ethinyl estradiol would both be suitable options for hormone replacement, although HRT may be more beneficial in improving bone health and cardiovascular markers compared to the combined oral contraceptive pill. Hormone replacement should aim to achieve physiological levels of estrogen and is generally recommended at least until the natural age of the menopause.

Definition

POI refers to amenorrhoea, hypo-estrogenic status and elevated gonadotropins due to a decline of ovarian function before the age of 40. The syndrome was first described by Fuller Albright, a Harvard Endocrinologist, who used the term 'primary ovarian insufficiency' to describe the condition – 'primary'

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referring to the primary defect lying within the ovary. Numerous terms have been used to describe the condition over the years, but most current Advisory Body Statements have concluded that the term 'Premature Ovarian Insufficiency' would be a more accurate description and should be used to describe the condition.

The cut-off age of 40 used in this definition is based on this being more than two standard deviations below the age of natural menopause in the Western World. It is estimated that approximately 1% of women would become menopausal before the age of 40, while the prevalence in women under the age 30 is estimated to be 0.1%. The term 'Early menopause' refers to an onset of the menopause between the age of 40 and up to 45 years of age. In clinical practice, however, both groups (<40 and 40–45) are advised similarly regarding the bone and cardiovascular protective effects of sex steroid hormone replacement and should be advised to continue this at least until the natural age of the menopause of 51 in the absence of a contra-indication to doing so. Women who become menopausal between the ages of 45 and 50 need to be counselled in a similar way although there is less evidence to guide clinical practice regarding the preventative role of hormone replacement for women in the latter group.[1–11]

Aetiology

Idiopathic

The majority of cases of POI are idiopathic with reports estimating this to contribute to up to 85%–90% of cases of POI in a number of literature series.

Genetic

In a review of the literature, Qin et al.[12] concluded that chromosomal abnormalities were the cause of POI in approximately 10%–13% of cases, and this was noted to be higher in cases with primary amenorrhoea compared to those with secondary amenorrhoea. The majority of chromosomal abnormalities associated with POI are X chromosome abnormalities including Turner syndrome.

Cases with gonadal dysgenesis associated with the presence of Y chromosome have a high risk of gonadal dysplasia which is estimated to occur in more than a third of such cases.[13]

In summary, karyotype analysis should be considered in women with unexplained POI. Cases with gonadal dysgenesis with Y chromosome should be advised to have their gonads removed to minimise the risk of malignancy.

Whole genome analysis has been assessed in a number of studies and is likely to uncover further genetic causes for POI in the foreseeable future. However, at present there is insufficient evidence to recommend carrying whole genome analysis as part of the routine screening of women with unexplained POI.

Wittenberger et al.[14] reported a literature review that showed that the prevalence of POI in female carriers of Fragile X (FMR1) pre-mutation is between 13% and 26%. The review also showed that approximately 0.8% to 7.5% of women with sporadic POI were carriers of the FMR1 pre-mutation and up to 13% of women with familial POI were noted to be carriers.

Consideration should therefore be given to testing for the mutation in women with unexplained POI especially in the presence of family history of the condition.

Autoimmune

POI caused by autoimmune ovarian damage has been reported to occur in approximately 5% of cases of POI and the prevalence of autoimmune conditions is more common in women with POI compared with controls. The majority of cases with autoimmune POI have autoimmunity involving other organs, the commonest being adrenal autoimmunity, estimated to occur in approximately 60%–80% of cases with autoimmune POI. Thyroid autoimmunity is estimated to occur in approximately a fifth of cases with autoimmune POI.[15,16]

Patients with POI who have clinical manifestations of adrenal or thyroid disease or where there is suspicion of immune disease involving the latter organs, should be referred to an endocrinologist for further assessment.

Iatrogenic

POI may result following medical interventions such as chemotherapy, radiotherapy and surgery. There has been a significant improvement in the prognosis of childhood cancers over the last two decades with long-term survival rates of more than 80%.[17,18] In addition, an increasing number of premenopausal women who carry the BRCA gene mutation are undergoing risk reducing surgery including prophylactic oophorectomy. These factors have resulted in an increase in the numbers of women with iatrogenic POI. Chemotherapeutic agents can have a direct toxic effect on the ovaries. This varies with different chemotherapeutic agents and is more common with alkylating agents, which can result in POI in approximately 40% of treated cases. The risk is also influenced by the dose of medications used and the age of the woman at the time of treatment.

The toxic effects of radiotherapy are related to the site of treatment and are more common with pelvic, abdominal and whole body irradiation. In addition, the effect is also dose and age dependent.

Endometriosis involving the ovaries and its surgical treatment can increase the risk of a woman developing POI. In addition, studies have shown an increased risk of early menopause in women undergoing hysterectomy with ovarian conservation.

Other causes

There is limited evidence on the effect of smoking on the risk of POI. However, studies have suggested an association between smoking and early menopause.

Observational studies have suggested that women with HIV are at increased risk of early menopause. This may be directly related to the disease itself or an effect of anti-retroviral medications. Further research is required to assess this association.[19,20]

Diagnosis of POI

The diagnosis of POI is based on a combination of oligomenorrhoea/amenorrhoea of more than four months' duration associated with elevated gonadotropins (FSH >40 IU/l) on at least two occasions measured four to six weeks apart in women under the age of 40.

Anti-mullerian hormone (AMH), a glycoprotein produced by the granulosa cells of the early antral and antral follicles, is used as a test to assess ovarian reserve and has been shown to be a good indicator of the remnant pool of oocytes in the ovary. However, very low or undetectable levels of AMH, while suggestive of diminished ovarian reserve, are not sufficient for the diagnosis of POI especially in the presence of regular menstrual cycles.[21]

AMH should therefore not be routinely used to diagnose POI but may have a role when the diagnosis of POI is inconclusive.

Sequelae of POI

POI can result in a number of short-term and long-term sequelae related to the hypo-estrogenic status associated with the condition.

Short-term sequelae

Vasomotor symptoms (hot flushes and night sweats) are the commonest menopausal symptoms reported in women with POI. In addition, women with POI may experience insomnia, joint pain, labile mood, low energy, low libido as well as impaired memory and concentration. Sex steroid hormone replacement has been shown in observational studies to be effective for the control of menopausal symptoms in women with POI.

Symptoms related to urogenital atrophy have been reported in approximately 40%–50% of women with POI. These may present as vaginal dryness, dyspareunia, urinary frequency and urinary incontinence. Topical estrogen treatment is effective in improving symptoms related to vaginal atrophy, such as vaginal dryness, superficial dyspareunia and urinary symptoms related to urogenital atrophy. Menopausal symptoms experienced by women with POI may vary in intensity and can be intermittent due to fluctuations in ovarian activity.

In addition, it has been reported that approximately 12%–14% of women with POI do not experience menopausal symptoms. The latter group, while not requiring estrogen replacement for symptom control would still be advised to have hormone replacement for the prevention of the long-term sequelae of POI including bone and cardiovascular protection.

In summary, systemic sex steroid hormone replacement is effective for the management of menopausal symptoms in women with POI and topical estrogen preparations are effective for the management of symptoms related to urogenital atrophy.

Long-term sequelae

Cardiovascular disease

Observational data have shown that women with POI are at increased risk of cardiovascular disease including coronary heart disease, as well as having an increased risk of cardiovascular mortality compared to controls. However, there is limited evidence from randomised controlled trials assessing the cardiovascular effects of sex steroid hormone replacement in women with POI.

Gordon et al.[22] reported on the association of age at menopause and coronary heart disease in the Framingham Study. Postmenopausal women in their 40 s were found to have an increased incidence of cardiovascular disease compared to premenopausal age-matched controls.

Løkkegaard et al.[23] reported on the association between early menopause and the risk of ischaemic heart disease in a prospective cohort questionnaire study that included Danish female nurses above the age of 44 years. A total of 19,898 nurses completed the questionnaires. Of these, 10,533 were postmenopausal. Menopause both before the age of 40 and before the age of 45 was associated with an increased risk of ischaemic heart disease. The association was more pronounced in women who had an oophorectomy but was also noted among spontaneous menopausal women.

Women who had oophorectomy before the age of 40 had a significantly higher risk of ischaemic heart disease compared to those who had their menopause after the age of 45 (HR 8.7; 95% CI: 2.0–38.1) as did women who had spontaneous menopause before the age of 40 (HR 2.2; 95% CI 1.0–4.9, compared to women who had their menopause after the age of 45).

When the entire cohort (irrespective of the cause of menopause) was assessed, early menopause was noted to be a risk factor for ischaemic heart disease and with each year the age of the menopause increased, the risk of ischaemic heart disease decreased. Ever use of HRT in women who had oophorectomy was noted to result in a significantly lower risk of ischaemic heart disease compared to that noted in never users of HRT. This effect though was not noted in women who had spontaneous menopause. The numbers in both the latter two comparisons, however, were small and this would limit the conclusions that can be drawn from this sub-analysis of the study.

Findings from the Mayo Clinic study reported by Rocca et al.[24] showed that mortality was significantly increased in women who had bilateral oophorectomy before the age of 45 years compared to control women (HR 1·67; 95% CI: 1.16–2.40). Increased mortality was noted in women who had not received estrogen replacement up to the age of 45 years.

Ebong et al.[25] assessed the associations between age at menopause as well as that with early menopause occurring before the age of 45 years and heart failure in postmenopausal women. The review included 2947 postmenopausal women without known cardiovascular disease aged 45–84 years. The study had a median follow-up period of 8.5 years and 71 heart failure events were noted during the study period. Adjusted analysis showed that early menopause was associated with increased risk of heart failure (HR 1.66; 95% CI: 1.01–2.73), and the risk of heart failure decreased with each year of increase in age at menopause (HR 0.96; 95% CI: 0.94–0.99).

Rahman et al.[26] reported on the association of younger age at natural menopause and the risk of heart failure. The study included 22,256 postmenopausal women from the population-based Swedish Mammography Cohort and had a mean follow-up of 13 years. Early natural menopause between 40 and 45 years of age was significantly associated with an increased risk of heart failure, compared with menopause at 50–54 years of age (HR 1.40; 95% CI: 1.19–1.64).

Atsma et al.[27] reported a meta-analysis that included 18 studies that assessed the association between cardiovascular disease, postmenopausal status and age at menopause. There was a significant association between early menopause and the risk of cardiovascular disease (RR 1.38; 95% CI: 1.21–1.58). A significant association was also noted with bilateral oophorectomy (RR 4.55; 95% CI: 2.56–8.01) and the effect with the latter was more pronounced than that noted in women who had a natural menopause.

A more recent meta-analysis by Roeters Lennep et al.[28] assessed the risk of ischaemic heart disease, stroke and overall cardiovascular disease in women with POI. The analysis included 10 observational studies and had 190,588 women with a 4–37 years' follow-up period. A total of 9440 events were included with 2026 events of ischaemic heart disease, 6438 events of stroke and 976 events of total cardiovascular disease. POI was associated with an increased risk of developing or dying from ischaemic heart disease (HR 1.69; 95% CI: 1.29–2.21) and total cardiovascular disease (HR 1.61; 95% CI: 1.22–2.12). No significant association was noted with stroke in the cohort included (HR 1.03, 0.88–1.19).

Studies assessing the effects of sex steroid hormone replacement on cardiovascular markers including vascular elasticity in women with POI have reported adverse changes in cardiovascular surrogate markers in women with POI compared with controls.

Kalantaridou et al.[29] assessed endothelial function in 18 women with POI before and after six months of HRT. The findings were compared with a control group of 20 premenopausal women who were both age and body mass index matched. Brachial artery diameter was measured both during hyperaemia to assess endothelium dependent vasodilation and in response to glyceryl trinitrate to assess endothelium independent vasodilation. Flow-mediated dilation was significantly lower in women with POI at baseline than in control women while glyceryl trinitrate-induced vasodilation did not differ between the groups. After six months of HRT in women with POI, flow-mediated dilation increased by more than 2-fold and returned to normal values similar to those noted in the control group.

Langrish et al.[30] reported on the cardiovascular effects of physiological and synthetic sex steroid replacement regimens in women with POI in a randomised controlled crossover pilot trial. HRT was given as transdermal estradiol in doses of 100–150 μg a day in combination with vaginal progesterone in a dose of 400 mg a day for two weeks per month. Synthetic sex steroid replacement was given in the form of a combined oral contraceptive pill containing ethinyl estradiol 30 μg and 1·5 mg norethisterone. The study included 34 women with POI, of whom 18 completed the study. HRT resulted in significantly lower mean 24-h systolic and diastolic blood pressures throughout the 12-month treatment period compared with the combined oral contraceptive pill. No difference was noted in arterial stiffness between the two groups. In addition, HRT reduced plasma angiotensin II and serum creatinine concentrations without altering plasma aldosterone

concentrations suggesting less activation of the renin–angiotensin system with HRT and a more beneficial effect on renal function compared to the combined oral contraceptive pill.

In summary, sex steroid hormone replacement is likely to lower the long-term risk of cardiovascular disease associated with POI. HRT and the combined contraceptive pill containing ethinyl estradiol would both be suitable options for hormone replacement, although HRT may be more beneficial in improving cardiovascular markers compared to the combined oral contraceptive pill. Women with POI should be advised to take hormone replacement and to continue to do so at least until the natural age of the menopause in the absence of a contra-indication, to minimise this risk.[31]

Bone health

Estrogen has an important role in regulating and maintaining bone structure in women and estrogen deficiency associated with POI has been shown to result in a reduction in bone density and an increased risk of fractures. The evidence for the latter, however, has not been demonstrated in adequately controlled studies.[32]

Observational studies have shown that women with POI are at increased risk of having lower bone density with an estimated reduction of 2%–3% in bone mineral density at both spine and hip compared to controls when assessed at a mean interval of 2.9 years following the diagnosis of POI and 4.4 years after the onset of irregular menses. Observational data have reported the prevalence of osteoporosis in women with POI to be in the region of 8%–14%.

In addition, prospective observational data have reported a significant adverse effect on bone density related to chemotherapy exposure independent to the effect of estrogen deficiency in women with POI.

Women with POI should be given advice regarding lifestyle modification and bone health. This should include information on a balanced diet, exercise, smoking cessation as well as avoidance of excessive alcohol intake. Advice should also be given on adequate calcium and vitamin D requirements with a recommended daily intake of calcium of 1000 mg and that for vitamin D of 1000 IU a day.

The Scientific Advisory Committee on Nutrition (SACN)[33] reviewed the evidence on vitamin D and health and published its updated report on the topic in July 2016. The review identified that a significant proportion of the UK population had low vitamin D concentrations. An estimated 22%–24% of the 19–64 years old age group had an annualised mean plasma vitamin D concentration below the 'population protective level' of 25 nmol/L. In addition, approximately 30%–40% of the population had a plasma vitamin D concentration less than 25 nmol/L in winter compared to 2%–13% in the summer.

The Committee report recommended a reference nutrient intake (RNI) of 10 μg (400 IU/day) of vitamin D per day, throughout the year, for everyone in the general population aged four years and older. This represents the average amount of vitamin D (from natural food sources, fortified foods or supplements) that is required to achieve a serum vitamin D concentration of 25 nmol/L or above during winter in 97.5% of the population.

Evidence from large randomised trials has shown that HRT significantly improves bone density in postmenopausal women and lowers the risk of fractures in both spine and hip. However, the evidence assessing the effect of sex steroid hormone replacement on bone density in women with POI comes from small prospective studies and observational data.

Women with POI should be counselled about the effects of estrogen deficiency on bone mineral density. Hormone replacement should be recommended at least until the natural age of the menopause, in the absence of a contra-indication to doing so, to maintain bone density and prevent osteoporosis. It is also likely to minimise the risk of osteoporosis-related fractures.[34]

Sex steroid hormone replacement should be considered the first line treatment for the prevention and management of osteoporosis in women with POI.

In a retrospective observational study that included 54 women with Turner Syndrome, Kodama et al.[35] reported that oral-conjugated equine estrogen in a dose of 0.625 mg a day combined with cyclical dydrogesterone resulted in significant increase in bone density compared to that noted in women who received low-dose-conjugated equine estrogen and controls who did not receive HRT. In addition, the age at which HRT was started was inversely related to the increment in bone density with a better response noted the earlier HRT was initiated.

Crofton et al.[36] reported a randomised controlled crossover pilot trial that compared HRT, given as transdermal estradiol in doses of 100–150 μg a day in combination with vaginal progesterone in a dose of 400 mg a day for two weeks per month, with a combined oral contraceptive pill containing oral ethinylestradiol 30 μg and 1·5 mg norethisterone in women with POI. The trial included 34 women with POI, of whom 18 completed the study. Lumbar spine bone density significantly increased with HRT as did bone formation markers compared to that noted in women who received the combined oral contraceptive pill. Bone resorption markers were suppressed with both HRT and the combined oral contraceptive pill.

Cartwright et al.[37] reported a two-year open-label randomised controlled trial that compared changes in

bone mineral density in women with POI with HRT compared to the combined oral contraceptive pill and included a non-randomised observation of women who declined treatment. The treatment arms included Nuvelle (estradiol 2 mg + levonorgestrel 75 μg) versus the combined oral contraceptive pill Microgynon 30 (ethinyl estradiol 30 μg and levonorgestrel 150 μg). Thirty-six women completed the trial (12 women in the HRT group, 9 in the combined oral contraceptive pill group and 15 women in the non-randomised observational group that received no treatment). The study showed that HRT significantly increased lumbar spine bone mineral density at two years compared to the combined oral contraceptive pill. Bone turnover markers showed similar reductions in the two treatment groups. In comparison, bone density dropped at all sites in the 'no treatment' group, and bone turnover markers remained unchanged compared women who received HRT or the combined oral contraceptive pill. The findings suggest that HRT may result in a more significant improvement in bone density compared to the combined oral contraceptive pill. However, the small sample size needs to be taken into consideration when interpreting the findings and further research is required to assess this. The study findings also suggest that both treatments were superior to expectant management.

Bisphosphonates work by inhibiting the activity of osteoclasts and thus reducing bone resorption. Randomised trials have demonstrated that bisphosphonates significantly increase bone mineral density at both spine and hip in postmenopausal women. They have also been shown to reduce the risk of vertebral fractures by approximately 50% and to reduce the risk for non-vertebral fractures, including hip fracture by approximately 25%.[38]

Bisphosphonates can remain incorporated in bone matrix for a long period of time and there is limited evidence assessing the long-term reproductive implications associated with their use. Caution should therefore be taken with their use in women of the reproductive age group particularly those who wish to achieve a pregnancy. In addition, a theoretical concern exists over possible over-suppression of bone turnover with long-term bisphosphonate treatment, resulting in brittle skeleton and atypical fractures. Reports and case series have indicated a higher prevalence of fractures in the subtrochanteric region of the femur and osteonecrosis of the jaw in patients on long-term treatment with bisphosphonates. The latter is generally associated with dental extraction.[39,40] Therefore, in women with POI, bisphosphonates should not be first line treatment and should only be considered after discussion with an osteoporosis specialist.

In summary, sex steroid hormone replacement should be considered the treatment of choice for the prevention and treatment of osteoporosis in women with POI. Bisphosphonates should not be first line treatment in women with POI and should only be considered after discussion with an osteoporosis specialist. HRT and the combined contraceptive pill containing ethinyl estradiol would both be suitable options for hormone replacement, although HRT may be more beneficial in improving bone health compared to the combined oral contraceptive pill.

Assessment of bone mineral density using dual energy X-ray absorptiometry (DEXA) should be considered at the time of diagnosis of POI.

The frequency of repeat bone mineral density assessment should be guided by findings from the initial assessment, the woman's risk factors and compliance with HRT.

Consideration should be given to repeat bone mineral density assessment in women with osteoporosis within two to three years of the diagnosis.

If bone density on initial assessment is normal and HRT is continued, the benefit of repeat bone mineral density assessment is limited and further assessment should then be guided by the patient's clinical risk factors.

Fertility

Van Kasteren and Schoemaker[41] reported a systematic review on reproductive outcomes of women with POI. The study included 52 case reports, 8 observational studies, 9 uncontrolled studies and 7 controlled studies. Due to the high heterogeneity of the controlled studies, it was not possible to combine the data to perform a meta-analysis. The combined data from observational studies, both controlled and uncontrolled, showed that approximately 5%–10% of women with POI achieved a spontaneous pregnancy after their diagnosis. Of the group of women who achieved a pregnancy, approximately 80% had a livebirth, while the miscarriage rate was 20%, similar to that in the general population. The mean age of the women included in the studies was 31–34 years, and the median age within these studies was 30–35 years.

More recently, Bidet et al.[42] reported a mixed retrospective and prospective study that included a total of 358 consecutive women with idiopathic POI during the period 1997–2010. A total of 86 (24%) women demonstrated features of resumption of ovarian activity (defined as at least two consecutive menstrual cycles or a pregnancy). The majority of women, 77 (88%) showed this within the first year of diagnosis. A total of 21 spontaneous pregnancies were noted in 15 (4.4%) women. These resulted in 16 births and five miscarriages. Logistic regression analysis showed that secondary amenorrhoea, the presence of follicles on pelvic ultrasound scan, family history of POI and higher

serum estradiol levels were positively predictive of resumption of ovarian activity, while AMH levels and autoimmune disease did not have a significant association.

In summary, women with POI can have intermittent ovarian activity and have a chance of natural conception, although this is likely to decrease with increasing durations of amenorrhoea.

The likelihood of natural conception in women with POI is low and is estimated to be in the region of 5%–10%.

HRT is not contraceptive and women with POI who are keen to avoid pregnancy should be advised to use contraception.

Assisted reproduction techniques including ovulation induction and IVF are unlikely to be successful in women with POI as they are unlikely to respond to ovarian stimulation due to the very low ovarian pool of oocytes.[43]

Spontaneous pregnancies in women with idiopathic POI or that associated with most forms of chemotherapy are unlikely to be associated with a higher risk of miscarriage or obstetric and neonatal complications than age-matched controls. However, women with POI who have had previous pelvic radiotherapy are at increased risk of adverse pregnancy outcomes.

Oocyte donation remains the realistic option and the treatment of choice for the majority of women with POI who are unable to achieve a pregnancy naturally.

The success rate with oocyte donation and the risk of aneuploidy are related to the age of the oocyte donor while the age of the oocyte recipient has minimal effect on the chances of success. An analysis of 15,037 egg donation cycles from the Society for Assisted Reproductive Technology showed live birth rates in excess of 50% per embryo transfer with the average age of the donors being 25.4 years.[45–47]

However, oocyte donation appears to be independently associated with a higher risk of obstetric complications including pregnancy-induced hypertension, preeclampsia and may be associated with lower foetal birthweight.

Women with POI undergoing egg donation treatment should therefore undergo pre-conception medical assessment to ascertain their medical fitness and evaluate their cardiovascular status. Women with POI undergoing egg donation treatment should also undergo counselling regarding the issues related to child bearing and the long-term effects that may be associated with it. They should also have an evaluation to ensure welfare of any resulting children and that adequate support is in place to do so.

Pregnant women with POI who have had previous pelvic radiation, those with Turner syndrome and women who achieved a pregnancy through oocyte donation are at high risk of obstetric complications and should be managed in obstetric settings that have the facilities to manage this. In addition, women with POI who have Turner syndrome should undergo cardiology assessment and pre-conception counselling.

Fertility preservation techniques including oocyte/embryo cryopreservation or ovarian tissue cryopreservation are unlikely to be successful in women with established POI.

However, fertility preservation and in particular oocyte/embryo cryopreservation would be a suitable option for women at risk of POI including those due to undergo chemotherapy or radiotherapy that may diminish their ovarian function or women with a strong family history of POI. The advantages and disadvantages of fertility preservation should be discussed to allow women at risk of POI to make an informed decision regarding this.

A guidance document by The Practice Committee of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology[48] reviewed the published literature assessing fertility outcomes with oocyte cryopreservation. It concluded that both fertilisation and pregnancy rates with IVF using cryopreserved oocytes was similar to that noted with fresh oocytes. The concluding recommendation from the document was that the technique should no longer be considered experimental. Cobo et al.[49] reported the largest series to date on fertility outcomes with oocyte cryopreservation. The review included a total of 1468 women who underwent oocyte cryopreservation with the indication being the woman's age or an associated medical condition other than cancer. The mean age at oocyte cryopreservation was 37.2 years. A total of 137 women returned to use their cryopreserved oocytes at a mean age of 39.2 and the oocyte thaw-survival rate was 85%. The clinical pregnancy rate per cycle was 37% while the clinical pregnancy rate per embryo transfer was 45%. The live birth rate per patient was 29%. Pregnancy rates were noted to be age-dependent and the authors concluded that at least 8–10 metaphase II oocytes are necessary to achieve reasonable success.

Ovarian tissue banking, where ovarian cortical biopsies are cryopreserved offers an alternative to oocyte cryopreservation. The clinical application of this technique at present, however, is limited. In-vitro maturation of oocytes from ovarian tissue biopsies has not yet been successfully achieved and re-implantation of the cryopreserved ovarian tissue remains the only feasible option in current clinical practice but with a relatively small number of live births reported.[50,51]

Other techniques, like activation of dormant ovarian follicles with PTEN inhibitor following by re-implantation of treated ovarian tissue samples have been recently explored.[52] These could in the future provide

an option for fertility treatment in women with POI, but further research is required to assess their feasibility, safety and efficacy.

Cognition

Observational studies have shown an increased risk of cognitive impairment and dementia in women with early onset of menopause.

The Mayo Clinic Cohort Study of Oophorectomy and Aging included 813 women who had unilateral oophorectomy, 676 women who had bilateral oophorectomy before the onset of the menopause, and 1472 age-matched controls. Women who underwent either unilateral or bilateral oophorectomy before the onset of the menopause had an increased risk of cognitive impairment or dementia compared to controls (HR = 1.46; 95% CI: 1.13–1.90). The risk increased with younger age at oophorectomy ($p < 0.0001$). These findings were similar regardless of the indication for oophorectomy and were noted in both women who had unilateral or bilateral oophorectomy. The authors concluded that the age-dependent effect was suggestive of a critical age window for neuroprotection. Women who received estrogen replacement until the age of 50 years did not have an increased risk of cognitive impairment or dementia.[53]

Phung et al.[54] reported a Danish observational cohort study which showed an increased risk of dementia with premenopausal bilateral oophorectomy. An age-dependent effect was noted with women having hysterectomy/oophorectomy at a younger age being at greater risk. The authors concluded that younger women appeared more vulnerable to estrogen deficiency and suggested an age-related effect of premature estrogen deficiency on dementia.

Bove et al.[55] reported an observational study that included 1884 women from two longitudinal studies assessing cognitive decline (The Religious Orders Study and The Rush Memory and Aging Project). Earlier age at the menopause was associated with a faster decline in global cognition as well as memory and was also associated with increased neuropathology and neuritic plaques which have an association with Alzheimer's disease. These findings were not noted in the control group of women who had natural menopause. HRT use for at least 10 years, when administered within a 5-year perimenopausal window, was associated with a protective effect on global cognition.

In older naturally menopausal women, evidence from well-designed studies including randomised controlled studies as the WHI shows no significant improvement or worsening in memory or cognitive function with HRT.[56,57] However, subgroup analysis of the WHI data reported an increase in the risk of dementia in women who initiated combined estrogen and progestogen at 65–79 years of age. These findings, however, should not be extrapolated to younger menopausal women or women with POI. Rocca et al.[58] referred to the concept of a cognitive window of opportunity and timing hypothesis. In a review of the literature on the topic, the same group concluded that initiation of hormone replacement in younger menopausal women is likely to lower the risk of cognitive impairment and dementia and recommended continuing it until the natural age of the menopause.

In summary, women with POI are at increased risk of cognitive impairment. There is limited evidence from prospective controlled studies to guide practice regarding the effects of hormone replacement on cognitive function in women with POI. However, a number of large observational studies have shown a beneficial effect on cognitive function and a lowering of the risk of dementia in younger menopausal women with the use of sex steroid hormone replacement.[59]

Women with POI should be advised that taking hormone replacement until the natural age of the menopause is likely to improve cognitive function and lower their risk of dementia.

Risks associated with HRT

Breast cancer

There is limited evidence assessing the risk of breast cancer in women with POI. In addition, there is lack of evidence from controlled trials on the risk of breast cancer with sex steroid hormone replacement overall or that with various hormone replacement regimens in this group of women. Observational data have suggested that women with POI have a lower risk of breast cancer compared to controls. This is likely to be related to the lower hormone levels associated with the condition. Data on the risk of breast cancer associated with the use of HRT from the WHI and other studies in naturally menopausal women over the age of 50 would not apply to women with POI. Findings from such studies should, therefore, not be extrapolated to this group of women.

Wu et al.[60] reported a population-based cohort from the Shanghai Women's Health Study. The cohort included 36,402 postmenopausal women, of which 1003 cases had POI. After adjusting for variables women with POI were noted to have a decreased incidence of breast cancer (OR 0.59; 95% CI: 0.38–0.91).

Longitudinal data from the Danish Cancer Registry assessed the risk of developing breast cancer in relation to HRT use in a group of 78,380 women aged 40–67 years from 1989 to 2002.[61] The study included 1462 cases of breast cancer. A total of 48,812 women were

50 years old or above at entry, of whom 15,631 were HRT users. An increased risk of breast cancer was noted with current use of HRT in women aged 50 years or above (RR 1.61, 95% CI: 1.38–1.88). However, use of HRT did not increase the risk of breast cancer in women aged 40–49 years (40–44 years old: RR 0.56, 95% CI: 0.07–2.01; 45–49 years old: RR 0.88, 95% CI: 0.62–1.22).

Large longitudinal data from the French E3N study, which included older naturally menopausal women, have shown that micronised progesterone and dydrogesterone may be associated with a lower risk of invasive breast cancer compared to that noted with other progestogens. However, there is lack of evidence on the risk of breast cancer with different progestogen preparations used within sex steroid hormone replacement regimens in women with POI.[62,63]

In summary, observational data have shown that women with POI have a lower risk of breast cancer compared with controls. In addition, sex steroid hormone replacement does not appear to increase the risk of breast cancer in younger menopausal women under the age of 50.

Venous thromboembolism

There is limited evidence available on the risk of venous thromboembolism (VTE) in women with POI or that associated with the use of sex steroid hormone replacement in women with POI.

Canonico et al.[64] reported a study that included pooled data from the Women's Health Initiative study that included 27,035 postmenopausal women ages 50 to 79 years with no history of venous thrombosis. Early menopause (<40 years of age) and late menopause (>55 years of age) were noted to be risk factors for VTE among postmenopausal women. Non-procedure-related venous thrombosis demonstrated a U-shaped relationship between age at the menopause and venous thrombosis risk and this persisted after multivariable analysis ($p < 0.01$). Postmenopausal women with a history of early menopause and late menopause had a higher risk of venous thrombosis compared to women who went into the menopause aged 40–49 years (<40 years old: HR 1.8; 95% CI: 1.2–2.7; >55 years old: HR 1.5; 95% CI: 1.0–2.4).

Large observational studies have shown an increased risk of VTE with the use of the combined oral contraceptive pill. Manzoli et al.[65] reported a meta-analysis that assessed the risk of venous thrombosis in a reproductive population with the use of the combined oral contraceptive pill. The review included 16 cohort and 39 case–control studies. The risk of venous thrombosis was significantly increased in contraceptive pill users compared to non-users (OR 3.41; 95% CI: 2.98–3.92).

In naturally menopausal women, evidence from RCTs including the WHI has shown that oral estrogens increase the risk of VTE, with the highest risk being in the first year of use. However, evidence from large observational studies and meta-analyses has shown that transdermal administration of estradiol in naturally menopausal women is unlikely to increase the risk of venous thromboembolism above that in non-users and is associated with a lower risk compared with oral administration of estradiol.

There is lack of evidence on the risk of venous thrombosis in relation to the route of estradiol administration in women with POI and further research is required to assess this. Findings from studies on older naturally menopausal women should not be directly extrapolated to women with POI. However, taking the plausibility of the findings from these studies, the transdermal route of estradiol administration should be considered in women with POI who are at increased risk of VTE including those with body mass index greater than 30 kg/m^2.

Routes and regimens

Women with POI should be advised to take sex steroid hormone replacement and continue at least until at the natural age of the menopause in the absence of a contra-indication to doing so with an aim of achieving physiological levels of replacement.

There is limited evidence assessing the optimal regimen, dose or route of administration of hormone replacement in women with POI. HRT or the combined contraceptive pill containing ethinyl estradiol would both be suitable options for hormone replacement although HRT may be more beneficial in improving cardiovascular markers and bone health. The details of the latter studies[30,36,37] are discussed in the sections on 'Cardiovascular disease' and 'Bone health', earlier in this document. Ethinyl estradiol (10 μg) is likely to offer an equivalent dose of estrogen replacement to 1–2 mg of estradiol. The active component, however, in standard contraceptive pill regimens is given for 21 days followed by a seven-day pill free/inactive pill period. This will result in women not receiving estrogen replacement for seven days each month and may result in some women experiencing menopausal symptoms during this time. However, ethinyl estradiol has a longer half-life compared to estradiol and most combined contraceptive pill preparations contain 20–35 μg of ethinyl estradiol and thus provide supraphysiological doses of estrogen replacement. A limited number of studies have compared HRT and the combined contraceptive pill in women with POI and within these studies the combined contraceptive pill was administered in the conventional manner in a regimen that provided an

active hormonal component for 21 days followed by a seven-day pill free/inactive pill period.

The contraceptive pills Qlaira (estradiol valerate given in phased doses of 3 mg down to 1 mg with dienogest for 26 days followed by 2 inactive pill days per 28-day cycle) and Zoely (1.5 mg estradiol hemihydrate with nomegestrol acetate for 24 days followed by 4 inactive pill days per 28-day cycle) both contain estradiol instead of ethinyl estradiol and have an extended pill taking phase. These may be considered in women who require contraception.

Further research is required to determine the optimal hormone replacement regimen in this context.

Transdermal administration of estradiol avoids the first pass effect through the liver and as a result does not alter the coagulation cascade in the same way noted with oral estrogens. Laboratory data in naturally menopausal women have shown a neutral impact on thrombin generation, the coagulation cascade and pro-inflammatory markers with transdermal administration of estradiol. In addition, data from large observational studies have shown that transdermal administration of estradiol in naturally menopausal women is associated with a lower risk of venous thromboembolism and stroke compared with oral estradiol administration and no increased risk when compared with age-matched controls not receiving HRT.[66–68] However, there is limited evidence comparing transdermal administration of estradiol with oral administration in women with POI and further research is required to assess this. From a plausibility point of view, it is likely that transdermal administration would confer the same advantages and the transdermal route of estradiol administration should therefore be considered in women at risk of VTE including those with raised body mass index.

The aim of hormone replacement in women with POI should be to achieve physiological levels of estradiol.[69] Suggested replacement doses would be 75–100 µg a day of transdermal estradiol patches, 2 mg equivalent of estradiol gel (the latter may vary with different products e.g. with preparations containing 0.6 mg per measure, the dose would be two to four measures a day), 2 mg a day of oral estradiol or 10 µg a day of ethinyl estradiol.

Non-hysterectomised women require progestogen replacement for 12–14 days a month within a cyclic regimen to avoid endometrial hyperplasia and minimise the risk of endometrial cancer with unopposed estrogen. Alternatively, a continuous combined regimen would be an option in women who have not had a menstrual period for over two years. A cyclic regimen may be preferred in women wishing to achieve a pregnancy as this stimulates regular proliferation of the endometrium.

There is limited evidence comparing different progestogen regimens in women with POI. An RCT in naturally postmenopausal women (The Postmenopausal Estrogen/Progestin Interventions, PEPI) showed that cyclic micronised progesterone in a dose 200 mg/day for 12 days/month was as effective as cyclic medroxyprogesterone acetate in a dose 10 mg/day for 12 days/month and continuous medroxyprogesterone acetate in a dose 2.5 mg/day with no significant difference in the risk of endometrial hyperplasia between these three regimens.[70]

Micronised progesterone and dydrogesterone have a more selective effect on progesterone receptors and have less interaction with androgenic and mineralcorticoid receptors compared with other progestogens. As a result, they are generally associated with less progestogenic side-effects compared with other progestogens.

In addition, evidence from observational studies in naturally menopausal women has shown that micronised progesterone and pregnane derivatives as dydrogesterone may be associated with a lower risk of venous thromboembolism compared with other progestogens in particular norpregnane derivatives. This evidence should not be directly extrapolated to women with POI but should be taken into consideration when prescribing hormone replacement to women at risk of venous thromboembolism including those with raised body mass index.

A recent systematic review assessed the impact of micronised progesterone on the endometrium in naturally menopausal women. Forty studies were included in the systematic review, and the authors concluded that oral micronised progesterone provides endometrial protection if applied sequentially for 12–14 days/month in a dose of 200 mg/day for up to five years. In addition, vaginal micronised progesterone may provide endometrial protection if applied sequentially for 10 days/month in a dose of 45 mg/day at 4% or every other day in a dose of 100 mg/day for up to three to five years. In addition, the review concluded that transdermal micronised progesterone does not provide sufficient endometrial protection.[71]

The levonorgestrel intrauterine system (LNG IUS) provides adequate endometrial protection in women receiving estrogen hormone replacement therapy. It results in a direct release of progestogen into the endometrial cavity and is thus likely to be associated with less systemic progestogenic side effects compared with other oral preparations. The LNG IUS has a four-year license for use in this context. However, it is now common practice in many countries including the UK to use it for five years for endometrial protection in this context.

Sexual function

Women with POI may experience changes in sexual function related to the decline in their hormone levels.

These effects may be of sudden onset in women who undergo oophorectomy or of a more gradual onset in women with idiopathic POI.

Estrogen replacement, systemic or topical, may improve sexual function. Systemic estrogen replacement can improve sexual desire and libido and would be beneficial in women with 'sexual interest-arousal disorder' (previously referred to as 'hypoactive sexual desire disorder'). In addition, topical vaginal estrogen replacement can improve dyspareunia secondary to vaginal atrophy, through its proliferative effect on the vulval and vaginal epithelium.

The administration of systemic testosterone has been shown in a number of randomised trials to improve sexual function, including sexual desire and orgasm. Testosterone replacement can be considered, particularly in women where hormone replacement in the form of estrogen with or without progesterone has not been effective, although long-term safety data on testosterone replacement are limited.[72]

Androgenic side effects are minimal and assessment of serum androgen levels is unlikely to be beneficial as there is poor correlation between circulating androgen levels and clinical symptoms.

There is limited availability of licensed female androgenic preparations and most products currently used in this context in the UK are prescribed outside their licensed indication.

Support

A diagnosis of POI can have a detrimental effect on emotional and psychological wellbeing. Patients may benefit from discussions to identify the need for appropriate support and counselling or other types of therapy provided either on an individual or group basis.

Women with POI should therefore be provided with adequate information and advice on the availability of support, counselling or other suitable therapy. Information on support groups including national self-support groups as the Daisy Network in the UK (www.daisynetwork.org.uk) may also be beneficial and should also be offered to women diagnosed with the condition.

Summary of recommendations

- Diagnosis of POI should be based on a combination of oligomenorrhoea/amenorrhoea of more than four months' duration associated with elevated gonadotropins (FSH >40 IU/l) on at least two occasions measured four to six weeks apart in women under the age of 40. AMH should not be routinely used to diagnose POI but may have a role when the diagnosis of POI is inconclusive.
- Advice should be given to women with POI regarding lifestyle modification and bone health. This should include information on a balanced diet, adequate calcium and vitamin D intake, exercise, smoking cessation as well as avoidance of excessive alcohol intake.
- Systemic sex steroid hormone replacement is effective for the management of menopausal symptoms in women with POI and topical estrogen preparations are effective for the management of symptoms related to urogenital atrophy.
- Women with POI are at increased risk of cardiovascular disease, osteoporosis and cognitive impairment. Sex steroid hormone replacement is likely to lower the long-term risk of cardiovascular disease in women with POI, prevent osteoporosis and have a beneficial effect on cognitive function.
- Women with POI should be advised to take hormone replacement and continue to do so at least until the natural age of the menopause in the absence of a contra-indication to minimise this risk. The aim of hormone replacement in women with POI should be to achieve physiological levels of estradiol.
- There is limited evidence assessing the optimal regimen, dose or route of administration of hormone replacement in women with POI. HRT and the combined oral contraceptive pill containing ethinyl estradiol would both be suitable options for hormone replacement, although HRT may be more beneficial in improving bone health and cardiovascular markers compared to the combined oral contraceptive pill.
- Sex steroid hormone replacement should be considered the preferred choice of treatment for the prevention and management of osteoporosis in women with POI. Bisphosphonates should not be first line treatment for the management of osteoporosis in women with POI and should only be considered after discussion with an osteoporosis specialist.
- Assessment of bone mineral density should be considered at the time of diagnosis of POI. The frequency of repeat bone density assessment should be guided by the woman's risk for developing osteoporosis and consideration should be given to repeat bone mineral density assessment in women with osteoporosis within two to three years of the diagnosis.
- Women with POI can have intermittent ovarian activity and have a chance of natural conception estimated to be in the region of 5%–10%. Assisted reproduction techniques using the woman's own eggs are unlikely to be successful and oocyte donation remains the most effective intervention in this context.
- Fertility preservation techniques including oocyte/embryo cryopreservation or ovarian tissue cryopreservation are unlikely to be successful in women

with established POI. However, fertility preservation and in particular oocyte/embryo cryopreservation would be suitable options for women at risk of POI including those due to undergo chemotherapy or radiotherapy that may diminish their ovarian function or women with a strong family history of POI.

- Observational data have shown that women with POI have a lower risk of breast cancer compared with controls. HRT does not appear to increase the risk of breast cancer in younger menopausal women under the age of 50.
- There is limited evidence on the risk of VTE in women with POI or that associated with the use of sex steroid hormone replacement in this group of women. Data from large observational studies and meta-analyses has shown that transdermal administration of estradiol is unlikely to increase the risk of venous thromboembolism in naturally menopausal women. The transdermal route of estradiol administration should therefore be considered in women with POI who are at increased risk of venous thrombosis including those with body mass index greater than 30 kg/m^2.
- Further research is required to assess the optimal regimen, dose or route of administration of hormone replacement in women with POI. In addition, National and International databases as the POI Registry (https://poiregistry.net) are required to allow collection of data that may allow better understanding and management of the condition.

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