

HRT for women with premature ovarian insufficiency: a comprehensive review

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BACKGROUND: Premature ovarian insufficiency (POI), often and misleadingly referred to as 'premature menopause', is defined as a loss of ovarian activity before the age of 40 years and is characterized by irregular or absent periods and reduced fertility. Symptoms include those associated with the natural menopause (night sweats and vaginal dryness), and with the long-term adverse effects of estrogen deficiency (osteoporosis and cardiovascular disease): the latter is believed to explain the shorter life expectancy associated with POI.

OBJECTIVE AND RATIONALE: The objective of the current review was to collect all relevant studies supporting recommendations on the indications, treatment options, and risks of hormone replacement therapy (HRT) (estrogen, progestogens and androgens) for women with POI.

SEARCH METHODS: The current review was written based on the best available evidence on the topic collected for the recently published ESHRE guideline on the management of women with POI. PUBMED/MEDLINE and the Cochrane library were searched in a stepwise approach. Relevant references were summarized in evidence tables, with assessment of the quality.

OUTCOMES: HRT is strongly recommended for women with POI, mainly for vasomotor and genito-urinary symptom relief. In addition, HRT has been shown to have a role in bone protection and probably also in primary prevention of cardiovascular disease. There is little evidence on the optimal type, regimen and dose of HRT; patient preference for route and method of administration of each component of HRT must be considered when prescribing, as should contraceptive needs. In women with POI, physiological replacement of estrogen (and progesterone) is essential for their health, and the controversies that surround the use of HRT in postmenopausal women do not apply.

LIMITATIONS, REASONS FOR CAUTION: N/A.

WIDER IMPLICATIONS: New areas of study on HRT for women with POI should focus on life expectancy, quality of life and neurological function. Furthermore, randomized controlled trials comparing transdermal estradiol with oral estrogens with regard to efficacy, patient satisfaction and side effects are urgently needed.

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Key words: HRT / primary ovarian insufficiency / premature ovarian failure / androgens / estrogen / progesterone

WHAT THIS MEANS FOR THE PATIENT?

This paper summarizes the latest evidence about hormone replacement therapy (HRT) for women with premature ovarian insufficiency (POI), which is sometimes referred to as 'premature menopause'.

Women with POI have low levels of the hormone estrogen, which can lead to hot flushes or symptoms like vaginal dryness and urinary incontinence as well as longer term problems such as osteoporosis. The evidence shows that HRT can improve hot flushes and vaginal and urinary symptoms for women with POI, can help to keep bones healthy, reducing the chance of osteoporosis and may also help to prevent heart disease. Once women reach the time at which they would naturally go through the menopause, at around 50, there should be a discussion about whether, or how long, to continue the treatment.

The summary concludes that although there has been some controversy about links between HRT and breast cancer in older women who have been through the menopause, there is no evidence that HRT increases the chances of getting breast cancer in women with POI who are taking it earlier in their lives. HRT may improve quality of life and life expectancy for women who have POI and is essential for their health.

Introduction

Premature ovarian insufficiency (POI) is a clinical syndrome defined by loss of ovarian activity before the age of 40 years and it affects ~1% of women (Coulam et al., 1986; Luborsky et al., 2003). POI is characterized by infrequent or absent periods with raised gonadotrophins and low estradiol concentrations. Symptoms include infertility, those associated with menopause (hot flushes, night sweats, vaginal dryness and loss of sexuality), and with long-term adverse effects of estrogen deficiency (osteoporosis and cardiovascular disease). The etiology is wide ranging. POI can be iatrogenic (resulting from surgery, chemotherapy and radiotherapy), caused by chromosomal/genetic defects (Turner Syndrome (TS), Fragile-X Syndrome), or it can be associated with autoimmune disorders, infections or environmental factors. In a significant proportion of cases the cause remains elusive (i.e. idiopathic POI) (Maclaran and Panay, 2011).

The widespread prescription of hormone replacement therapy (HRT) for women after a natural menopause fell dramatically following the publication of the Women's Health Initiative (WHI) trial data, but the very different situation in women with POI requires careful consideration of how best to provide long-term hormone replacement for that group. Recently, ESHRE published a guideline for the diagnosis and management of women with POI (European Society of Human Reproduction and Embryology Guideline Group on POI et al., 2016) and this review presents the HRT options for women with POI, based on this guideline. The indications, risks, choice of preparation, regimen, route of administration, dosage and treatment duration for POI, as well as special considerations, are discussed.

Materials and Methods

The ESHRE guideline for management of women with POI, and the evidence presented here, was developed based on the manual for ESHRE guideline development (Vermeulen et al., 2014) by a multidisciplinary group of clinicians and a patient representative. In short, PICO (Patients, Intervention, Comparator, Outcome) questions were drafted and corresponding key words were used for the literature searches in PUBMED, Cochrane and PsycInfo where appropriate. For the literature search on HRT, we used the following search terms: ('Primary Ovarian Insufficiency'[Mesh] OR 'Primary Ovarian Insufficiency' OR 'gonadal dysgenesis' OR 'Premature Ovarian Failure' OR 'early menopause' OR 'premature menopause' OR 'hypergonadotropic hypogonadism' OR 'Ovarian dysgenesis' OR 'Primary ovarian failure' OR 'Hypergonadotropic amenorrhea' OR 'surgical menopause' OR 'Bilateral

Salpingo-Oophorectomy' OR 'Bilateral Oophorectomy' OR 'iatrogenic menopause' OR 'radiation menopause') AND (((oral OR transdermal OR uterine OR 'dose titration' OR continuous OR sequential OR vaginal OR Implants OR subcutaneous OR patch) AND (estrogen OR estradiol) OR ('contraceptive ring')) OR (progesterone OR progestagen OR progestogen OR 'Cyclic medroxyprogesterone acetate' OR 'Oral micronized progesterone' OR 'Norethisterone' OR 'dydrogesterone' OR 'natural progestogens' OR 'vaginal progestogens' OR 'synthetic progestogens' OR 'oral contraceptives' OR 'oral contraceptive pill' OR OCP OR COCP OR 'Levonogestrel intrauterine device' OR 'Vaginal estrogen and testosterone supplements' OR Androgen OR 'androgenic hormone' OR testosterone OR DHEA OR 'dihydroepiandrosterone' OR Dehydroepiandrosterone OR HRT OR 'hormone replacement therapy'). Relevant references were preselected by the research specialist and confirmed by a guideline development group member. Evidence tables were prepared and the quality of all papers was assessed according to standardized checklists. Recommendations were formulated based on the collected evidence, taking into account expertise of clinicians and patients, and benefits and harms. A grade was assigned to each recommendation indicating the strength of the supporting evidence. Before finalization, ESHRE members and national societies were invited to submit comments to the paper: comments and replies were summarized in a review report (European Society of Human Reproduction and Embryology Guideline Group on POI, 2015).

Results

Indications

Vasomotor symptoms are a major reason for women with POI to use HRT. Hot flushes were reported less in women with iatrogenic POI using estrogen replacement as compared to non-users (Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT–ES) score 48.4 versus 54.9) (Absolom et al., 2008). After prophylactic bilateral salpingo-oophorectomy (BSO), hot flushes were reported in 20% of women using HRT as compared to 41% of non-users (20% versus 41%) (Madalinska et al., 2006). Of women with chemotherapy-induced POI using HRT, 66% reported a significant reduction in hot flushes, insomnia, and psychological and emotional changes (Piccioni et al., 2004). Whilst there is little evidence on the efficacy of HRT for vasomotor symptoms in women with spontaneous idiopathic POI, clinical experience is that symptoms respond rapidly to systemic HRT.

Genito-urinary symptoms (vaginal dryness, irritation, urinary frequency and incontinence) were also less prevalent in women with POI using HRT as compared to non-users (Nachtigall, 1994; Bygdeman

and Swahn, 1996; Piccioni *et al.*, 2004; Madalinska *et al.*, 2006), and studies comparing before and after treatment showed improvements in vaginal moisture (Nachtigall, 1994; Bygdeman and Swahn, 1996). Other options for vaginal symptoms include vaginal lubricants and moisturizers although these are best used in combination with estrogen therapy, unless contraindicated.

There is evidence that HRT reduces the impact of POI on bone health (Prior *et al.*, 1997; Crofton *et al.*, 2010; Kodama *et al.*, 2012; Popat *et al.*, 2014; Cartwright *et al.*, 2016). With regard to cardiovascular health, small studies have shown that combined HRT treatment (i.e. estrogen and progesterone) restored endothelial dysfunction in POI women (Kalantaridou *et al.*, 2004), decreased the risk for ischemic heart disease (Lokkegaard *et al.*, 2006), and eliminated the increased cardiovascular disease mortality associated with BSO (hazard ratio (HR), 0.65; 95% CI, 0.30–1.41) (Bain *et al.*, 1981; Kalantaridou *et al.*, 2004; Lokkegaard *et al.*, 2006; Rivera *et al.*, 2009). Data on a potential effect of HRT on neurological health and quality of life are inconclusive. We found no studies investigating whether HRT has a beneficial effect on life expectancy and quality of life in POI, although an indirect benefit from the effect on cardiovascular morbidity and vasomotor symptoms, respectively, can be expected.

In conclusion, HRT is indicated for the treatment of vasomotor and genito-urinary symptoms in women with POI. It is also recommended to maintain bone health and prevent osteoporosis, and may have a role in the primary prevention of cardiovascular disease (Table I).

HRT treatment options

Research on the optimal HRT for women with POI is limited.

Type of preparations

There are three types of estrogen for hormone replacement: 17 β -estradiol (where the main physiological estrogen is the active component),

ethinylestradiol and conjugated equine estrogens. Oral contraceptives contain the potent synthetic estrogen ethinylestradiol, which by definition provides a pharmacological rather than a physiological replacement dose, with unfavorable effects on lipid profile and hemostatic factors plus an increased risk of venous thromboembolism (VTE). 17 β -Estradiol may be preferable to the combined oral contraceptive pill (COCP) in women with POI with regard to bone health (increased bone formation and decreased resorption) and cardiovascular health (lower blood pressure, reduced plasma angiotensin II and s-creatinine) (Langrish *et al.*, 2009; Crofton *et al.*, 2010). There are new COCPs containing estradiol: as yet there are no comparative studies on their risks of VTE, so the indication for their use remains contraception. There is a consensus that equine estrogens should not be used for HRT in women with POI given that a more physiological alternative (estradiol) is available.

There is little evidence on the effects of various progestogens in HRT for women with POI. Evidence from older postmenopausal women favors micronized natural progesterone, as it is associated with a more favorable cardiovascular profile (Mueck, 2012) and possibly reduced breast cancer risk (Davey, 2013), with similar efficacy for protecting the endometrium (The Writing Group for the PEPI, 1996).

Regimens

Continuous estrogen replacement is required to avoid symptoms of estrogen deficiency. Some women using the COCP for POI will be symptomatic during the pill-free week, and the conventional 3+1 week regimen results in no hormone replacement for 25% of the time. Cyclical regimens stimulating active functioning of the endometrium are necessary for women desiring pregnancy (by oocyte donation) (O'Donnell *et al.*, 2012), even though the risk of endometrial hyperplasia/carcinoma may be slightly higher (Furness *et al.*, 2012; Morch *et al.*, 2012). Cycle length can be individualized, but probably should not be longer than 12 weeks to protect the endometrium. The COCP and

Table I Indications for HRT use by women with POI.

Sequelae of POI	Indication for HRT?	Supporting recommendation/conclusion	Grade ¹
Vasomotor symptoms	YES	HRT is recommended	C
Genito-urinary symptoms	YES	Systemic and local estrogens are effective treatments	A
Life expectancy	?	Life expectancy appears to be reduced due to cardiovascular mortality: HRT may be of indirect benefit	n/a ²
Bone health	YES	HRT is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture	C
Cardiovascular health	YES	Despite lack of longitudinal outcome data, early initiation of HRT is strongly recommended to control future risk of cardiovascular disease; it should be continued until the average age of natural menopause	C
Quality of life	?	Quality of life appears to be reduced: HRT may be of indirect benefit	n/a ²
Sexual function	YES	Adequate estrogen replacement is the starting point for normalizing sexual function. Local estrogen may also be required to treat dyspareunia	C
Neurological function	?	HRT to reduce the possible risk of cognitive impairment should be considered at least until the average age of natural menopause	C

POI, premature ovarian insufficiency; HRT, hormone replacement therapy.

¹The grade of a recommendation reflects the strength of the evidence supporting it. Grade A indicates that the recommendation is based on a high quality systematic review or multiple randomized controlled trials (RCTs), Grade B recommendations are based on a single RCT or a large trial or study of high quality, Grade C on moderate quality trials or studies and Grade D on at least moderate quality non-analytical studies.

²Not applicable.

continuous combined HRT both decrease risk of endometrial cancer in healthy women and so are probably safe for POI women (Furness et al., 2012).

Women with POI but an absent uterus will not need progestogen supplementation and can receive unopposed estrogen.

Route of administration

Systemic estrogen can be administered orally or transdermally. Transdermal options include patches, which can be associated with skin irritation and gels. Subcutaneous implants, nasal sprays and injectable estrogen preparations are also available, although not in all countries. Local treatment (administered vaginally as creams/pessaries or an estrogen-releasing ring), in addition to systemic estrogen replacement, may be required in some women for adequate treatment of genito-urinary symptoms (Suckling et al., 2006). Local estrogen treatment is not believed to carry a risk of endometrial hyperplasia in the licensed dosage, based on data from older menopausal women (Suckling, 2006 #25).

Transdermal estrogen avoids first-pass metabolism by the liver (Chetkowski et al., 1986), and achieves higher plasma levels of circulating estradiol with a lower treatment dose, resulting in fewer circulating estrogen metabolites (Goodman, 2012). In older postmenopausal women, transdermal estrogen has a lower risk of myocardial infarction, VTE, stroke and breast cancer (Lokkegaard et al., 2008; Nelson, 2009; Canonico et al., 2010; Divasta and Gordon, 2010; Renoux et al., 2010a, b; Goodman, 2012). It is unclear whether these apparent advantages apply to women with POI, who are replacing a deficiency as opposed to prolonging estrogen exposure beyond their reproductive lifetime.

Progestogens can be administered via the oral, transdermal, vaginal or intra-uterine routes. No studies were identified comparing route of administration for progestogens in POI. However, there is no reason to believe that their effectiveness for endometrial protection would differ between young and older postmenopausal women. If the woman prefers a bleed-free regimen, a progestogen-releasing intra-uterine system will provide sufficient protection from endometrial hyperplasia (Ewies and Alfahily, 2012), with fewer side effects compared to systemic progestogen treatment (Pirimoglu et al., 2011). This regimen also provides contraception. Vaginal micronized progesterone (tablet) may have the benefit of achieving higher levels within the uterus with lower doses compared to oral (Fatemi et al., 2007). The safety of transdermal natural progesterone has not been established for endometrial protection and one study concluded that in a continuous regimen it was insufficient to fully attenuate the mitogenic effect of estrogen (Vashisht et al., 2005). Women should be informed that while there may be advantages to micronized natural progesterone, the strongest evidence of for endometrial protection is with oral cyclical administration.

In conclusion, estradiol is preferred to ethinylestradiol or conjugated equine estrogens, and a progestogen is required unless the uterus is absent. Some young women with POI may find using the COCP more acceptable than branded HRT preparations, and may, therefore, be more compliant with treatment. The other important consideration is contraceptive need, particularly since spontaneous ovarian activity can occur in POI, and HRT is not contraceptive. Given the paucity of evidence regarding the optimum route(s) of administration, patient preference is an important consideration, as this increases compliance

with treatment. Oral cyclical micronized natural progesterone may have the lowest risk of cardiovascular effects and breast cancer with the benefit of evidence for endometrial protection compared to synthetic progestogens.

Dose

Dose-response trials for HRT are sparse in women with POI. It was shown that increasing doses of estrogen (4 mg of 17 β -estradiol versus 1 and 2 mg) resulted in a reduction in intima media thickness in women with POI, with no effect on other cardiovascular parameters (Ostberg et al., 2007). Cyclical transdermal estradiol (100 μ g/day week 1 then 150 μ g/day weeks 2–4) for 12 months improved bone mineral density (BMD), reduced markers of bone breakdown and increased markers of bone formation in a small group of young women with POI with a variety of causes (average age 27 years) (Crofton et al., 2010). Recent evidence suggests that 2 mg of 17 β -estradiol orally is sufficient to maintain BMD (study in TS patients), and the effects are equal to 4 mg (Cleemann et al., 2017). Titrating the dose against vasomotor symptoms may be helpful, although some women with POI have minimal symptoms. The dose required to treat vasomotor symptoms may not be the same as that required for cardiovascular or bone protection, or to achieve peak bone mass. It would appear reasonable to aim for physiological estradiol levels, as found in the serum of women with normal menstrual cycles, with an average 50–100 pg/ml (180–370 pmol/l) (Mishell et al., 1971; MacNaughton et al., 1992). These levels can be achieved in women with POI with 100 μ g estradiol transdermally (Steingold et al., 1991; Popat et al., 2008). Similar levels can be provided by 2–4 mg estradiol orally, but serum levels of estrone become supra-physiological, which is of uncertain clinical significance (Steingold et al., 1991). No data were identified for any particular dose for symptom relief in women with POI, although transdermal 100 μ g/day may be sufficient in most (Nelson, 2009).

Progestogen dose depends on that the concurrent dose of estrogen, and the regimen. Continuous regimens require a minimum of 1 mg of oral norethisterone daily or 2.5 mg medroxyprogesterone acetate (MPA) at the moderate to high doses of estrogen that should be provided for women with POI. Sequential regimens require 10 mg MPA for a minimum of 10–12 days per month, or 200 mg oral micronized progesterone, although this is based on data from postmenopausal women (Furness et al., 2012).

Duration

No evidence was identified regarding the duration of HRT for women with POI. The consensus is that HRT should be continued at least until the age of natural menopause, i.e. around 50 years (Pitkin et al., 2007; Vujovic et al., 2010). Continuation thereafter should be based on discussion with the patient in the light of current evidence regarding risks and benefits in women taking HRT after the age of natural menopause, with additional consideration of patient-specific issues such as pre-existing bone density.

Risks of HRT

Breast cancer

An increased risk of breast cancer, estimated to be 2.3% for each year of use, has been a concern for older postmenopausal women using HRT (Collaborative Group on Hormonal Factors in Breast Cancer,

1997; Beral, 2003; Ewertz *et al.*, 2005). The incidence of breast cancer in women with POI has been sparsely investigated and probably over-estimated. The risk may be reduced in women with untreated POI, due to reduced estrogen exposure (Rebbeck *et al.*, 2009; Wu *et al.*, 2014). HRT does not affect breast density in women with spontaneous POI (Benetti-Pinto *et al.*, 2008; Soares *et al.*, 2010). Other studies confirm the absence of an increased risk for breast cancer in women with POI taking HRT (Ewertz *et al.*, 2005; Bosze *et al.*, 2006).

Endometrial cancer and hyperplasia

Estrogen-only HRT is associated with increased risk for endometrial hyperplasia and cancer in natural menopausal women, but this is not the case for regimens combining estrogens with continuous progestogens (Furness *et al.*, 2012). Only combined regimens should be used in women with POI and an intact uterus although as this is so well established in women with natural menopause there are no studies specifically addressing this in women with POI.

Stroke

Studies have shown an increased risk of thrombotic stroke in older postmenopausal women (Marjoribanks *et al.*, 2012; Gu *et al.*, 2014). In young women with POI, the absolute risk for stroke is extremely low, with no studies on the effect of HRT treatment.

Venous thromboembolism

Only one study assessed the risks of VTE in women with POI, finding no significant association between first VTE and HRT use, compared with placebo. However, analyses restricted to non-procedure-related VTE showed a U-shaped relationship with age at last period: after adjustment for potential confounders, women with POI or who experienced menopause at 56 years or older had increased thrombotic risk compared to women with menopause between 40 and 49 years (adjusted HR 1.8, 95% CI 1.2–2.8) while using HRT (Canonic *et al.*, 2014). Known risk factors for VTE in non-POI users of the COCP, such as smoking and obesity, may also apply to women with POI using the COCP.

In conclusion, women with POI should be informed that HRT before the age of natural menopause has not been found to increase the risk of breast cancer. Progestogen should be given in combination with estrogen to protect the endometrium. Women with POI and lifestyle risk factors for VTE should be advised how to reduce these.

Monitoring HRT

No routine tests are required to monitor HRT in women with POI. Specific tests may be prompted by particular symptoms or concerns, although there is no evidence to guide the optimum monitoring strategy. Serum estradiol is not helpful (except for monitoring HRT implants) and assays do not measure ethinylestradiol or estrone. There is no value in monitoring FSH since it will often not normalize (Davies and Cartwright, 2012). Regular follow-up, for example yearly, is recommended to review compliance, satisfaction, side-effects and possible need for change of regimen or route of administration. Compliance may be improved by engaging the patient in discussion of treatment choices (Cartwright *et al.*, 2012).

Mammography for breast cancer screening should be provided as for the normal population, as should other screening e.g. for cervical and bowel cancer.

Measurement of BMD with dual-energy X-ray absorptiometry (DEXA) should be considered at diagnosis of POI, especially in the presence of additional risk factors for poor bone health (e.g. long duration of estrogen deficiency and history of low impact fractures). If osteoporosis is diagnosed and estrogen replacement or other therapy initiated, BMD measurement should be repeated within 5 years. Referral to an osteoporosis specialist may be appropriate if BMD remains refractory to HRT. A decrease in BMD should prompt a review of HRT and of other potential factors. If the BMD is normal and adequate systemic estrogen replacement is commenced, the value of a repeat DEXA scan is low.

Women with POI plus special issues

Turner syndrome

POI may have more severe implications in TS with respect to bone, cardiovascular and neurological health. In adult TS women, the focus of treatment changes from growth and puberty induction to maintenance of health, including bone health (Davies, 2010; Freriks *et al.*, 2011). Although TS women may have features other than estrogen deficiency that impact on bone health and fracture risk, adequate estrogen replacement therapy is indicated (Khastgir *et al.*, 2003; Crofton *et al.*, 2010; Kodama *et al.*, 2012). In addition to estrogen, TS women may benefit from vitamin D and calcium supplements, plus regular exercise. If osteoporosis or a high fracture risk is present, medical treatment for osteoporosis may be indicated (Bondy and Turner Syndrome Study Group, 2007).

TS women are twice as likely to develop coronary artery disease and/or cerebrovascular disease as the general population (Gravholt *et al.*, 1998). They have an excess of several cardiovascular risk factors including hypertension, obesity, impaired glucose tolerance and hyperlipidaemia (Turtle *et al.*, 2013). In addition, cardiovascular mortality is four times higher (Swerdlow *et al.*, 2001). Short-term studies of HRT in TS women have failed to show a favorable effect on lipid profile (Gravholt *et al.*, 1998; Elsheikh *et al.*, 2000), or on ambulatory arterial stiffness index (Mortensen *et al.*, 2009). Intima media thickness decreased significantly in 25 POI women using increasing doses of HRT, with no change in other cardiovascular parameters (Ostberg *et al.*, 2007). Whether HRT is cardio-protective in TS women and whether it should be recommended for this indication is still unclear.

Abnormal neuro-cognitive profiles (worse emotional recognition and lower visuo-spatial, attentional, working memory and executive function) are well described in females with TS, which may partly be due to estrogen deprivation (Ross *et al.*, 2006). Estrogen would appear to improve executive ability, memory and motor function, while other features such as visuo-spatial processing, visual memory and arithmetic skills, might not change (Downey *et al.*, 1991; Swillen *et al.*, 1993; Romans *et al.*, 1998; Ross *et al.*, 1998).

Maintaining uterine health with estrogen and progestogen replacement is likely to be as important for TS women as for women with karyotypically normal POI. Similarly, HRT is likely to benefit the genitourinary system and psychosexual health of women with TS. In conclusion, girls and women with POI caused by TS should be offered HRT throughout the normal reproductive lifespan. Estrogen replacement

treatment should aim to mimic the normal reproductive lifetime exposure: higher estrogen dose (100 µg patch) during young adulthood, decreasing to 50 µg patches (which is sufficient for protection against osteoporosis) by age 30–35 years, and continuing treatment at least up to 50 years (Bondy, 2005; Bondy and Turner Syndrome Study Group, 2007). Progesterone replacement, rather than any progestin derivative, is also recommended, with cycling on a monthly to tri-monthly basis.

After breast cancer and for BRCA gene mutation carriers

Vasomotor symptoms in particular may be worsened by adjuvant endocrine treatments after chemotherapy for breast cancer (Day et al., 1999). HRT (combined estrogen and progestogen) has been shown to increase the risk of developing breast cancer in postmenopausal women (Rossouw et al., 2002; Holmberg and Anderson, 2004; Beral et al., 2007), although not in all trials (von Schoultz and Rutqvist, 2005; Fahlen et al., 2013). Even though the data are inconsistent, HRT is widely accepted to be contraindicated in breast cancer survivors (Antoine et al., 2007). It is not clear if estrogen receptor status of the original tumor influences the risk of recurrence with HRT use. Following a healthy lifestyle (e.g. no smoking, regular weight-bearing exercise, achieving/maintaining a healthy weight) are important recommendations for breast cancer survivors (Duijts et al., 2009; Kwan et al., 2010; McTieman et al., 2010). Non-hormonal treatments may reduce vasomotor symptoms, but evidence is scarce (Rada et al., 2010) and the safety of phytoestrogens in women with a history of estrogen-dependent cancer is unknown (Dennehy, 2006). Gabapentin, venlafaxine and fluoxetine may help relieve vasomotor symptoms in breast cancer survivors (Rada et al., 2010; Murthy and Chamberlain, 2012). If the benefits of reducing debilitating vasomotor symptoms and increasing quality of life outweigh the risks, HRT may still be considered.

Carriers of mutations in the BRCA1/2 genes may be recommended prophylactic premenopausal BSO to reduce their risks of breast and ovarian cancer (Rebbeck et al., 2009). Surgery can result in severe hot flashes, vaginal dryness, sexual dysfunction, sleep disturbances, cognitive changes and increased risk of cardiovascular disease (Finch and Narod, 2011; Finch et al., 2012). HRT significantly reduces vasomotor symptoms after prophylactic BSO (Madalinska et al., 2006) but does not significantly alter the reduction in breast cancer risk associated with BSO for BRCA1/2 mutation carriers, as compared to carriers without BSO or HRT (Armstrong et al., 2004; Rebbeck et al., 2005).

In conclusion, and in contrast to breast cancer survivors, HRT is a treatment option for BRCA1/2 carriers without personal history of breast cancer, after prophylactic BSO.

Endometriosis

Oophorectomy is an option for improving pain related to endometriosis (Dunselman et al., 2014). As it is an estrogen-dependent disease, the use of estrogen replacement therapy in women with endometriosis and POI (for instance after hysterectomy and BSO) could theoretically reactivate residual disease, produce new lesions, or even lead to malignant transformation of endometriosis. However, there are no studies assessing the effect of HRT on endometriosis in POI patients.

Continuous combined estrogen/progestogen therapy can be effective for the treatment of vasomotor symptoms and may reduce the risk of endometriosis reactivation after oophorectomy.

Other medical issues

Co-existing medical issues can affect HRT options, and transdermal administration of estrogen may be the preferred route in many of these cases (Davies and Cartwright, 2012).

Migraine. Migraine with aura is a risk factor for ischemic stroke, which may be greatest in younger women (under 50 years old) (Kurth et al., 2006). No studies were identified for the risk of stroke in women with POI and migraine, although POI itself is a risk factor for stroke. HRT use in healthy postmenopausal women may be a risk factor for stroke (Magliano et al., 2006; Sare et al., 2008) but there is insufficient evidence to support any link between stroke and HRT use by migraine-sufferers (Boussier et al., 2000; MacGregor, 2007). Migraine is not a contraindication to HRT use by women with POI. Changing dose, route of administration or regimen may help if migraine worsens during HRT. Transdermal delivery may be the lowest-risk route of administration of estrogen for migraine-sufferers with aura.

Hypertension. Women with POI show increased cardiovascular morbidity and mortality. As hypertension is a leading risk for cardiovascular disease, heart attack and stroke, hypertensive women with POI could be at increased risk for cardiovascular morbidity. Furthermore, hypertension is a well-accepted contraindication for COCP. No evidence was found regarding the effect of HRT in hypertensive POI patients. One study showed that physiological HRT was associated with a lower blood pressure compared to a standard HRT regimen in non-hypertensive POI patients (Langrish et al., 2009). From evidence in older postmenopausal women a recent review reported significant inconsistencies between studies (Cannoletta and Cagnacci, 2014). Studies evaluating transdermal estradiol were more consistent, showing either a neutral or hypotensive effect. Progestins do not seem to prevent the effect of estrogen on blood pressure, but the interaction is not well studied. Hypertension is not a contraindication to HRT use in POI and should be treated normally; transdermal estradiol is the preferred method of delivery.

History of prior VTE. No studies were found on the risk of VTE recurrence in women with POI and prior VTE. VTE is the most prevalent serious adverse effect of HRT in older postmenopausal women (Canonico et al., 2008). In the WHI study, an increase in the risk of pulmonary embolism (HR 2.13, 95% CI 1.39–3.25) was confirmed in women using oral HRT compared to placebo (Rossouw et al., 2002). HRT is contraindicated in postmenopausal women with VTE risk factors. Transdermal estrogen has been suggested as treatments for severe vasomotor symptoms in postmenopausal women with prior VTE (Canonico et al., 2008; Renoux et al., 2010b; Formoso et al., 2012). The impact of progestogen on VTE recurrence is not well studied, but may be relevant, as the WHI trials showed that the risk of VTE was higher with estrogen and MPA, as compared to estrogen alone (Manson et al., 2013). In conclusion, transdermal is the preferred route for delivery of estradiol in women with POI at increased risk of VTE. Those with prior VTE or a thrombophilic disorder should be referred to a hematologist prior to commencing HRT.

Obesity. No studies were found evaluating HRT in overweight or obese women with POI. The risk of VTE is increased in postmenopausal women with a raised BMI (>25 kg/m²) using oral estrogen therapy

(pooled odds ratio 2.6; 95% CI 2.1–3.3) (Canonico *et al.*, 2006, 2008). Transdermal estradiol is the preferred method of delivery for women with POI requiring HRT who are obese or overweight.

Fibroids. Estrogens and progestogens could potentially promote fibroid growth. No evidence was found for the effects of HRT on fibroids in women with POI. Two systematic reviews of postmenopausal women showed no significant increase in clinical symptoms or adverse effects associated with fibroid growth after HRT use (Ang *et al.*, 2001; Ciarmela *et al.*, 2014). Fibroids are not a contraindication to HRT use by women with POI.

Treatment with androgens

There is debate whether androgen concentrations are different in women with spontaneous POI compared to those in age-matched cycling women (Janse *et al.*, 2012). In contrast, women who underwent oophorectomy at a young age are probably hypoandrogenic owing to the lack of ovarian androgen production, which makes up 25% of the total production in premenopausal women (Longcope, 1986; Sluijmer *et al.*, 1995; Burger, 2002; Fogle *et al.*, 2007; Janse *et al.*, 2012). Androgen replacement therapy has been suggested as treatment for diminished sexual function, neurological complaints and decreased bone density caused by POI.

Indications

Several studies have shown improved sexual function after oophorectomy, with testosterone patches (Shifren *et al.*, 2000; Braunstein *et al.*, 2005; Buster *et al.*, 2005; Simon *et al.*, 2005; Davis *et al.*, 2006). All involved short-term treatment and follow-up, and reported mild or minimal adverse effects. The benefits seem to be similar in surgically and naturally postmenopausal women with and without estrogen therapy (Davis *et al.*, 2006; Panay *et al.*, 2010).

Studies of neurological function are limited to TS girls and older postmenopausal women. Oxandrolone-treated TS girls showed improved working memory performance only after 2 years of treatment, compared to girls receiving placebo (Ross *et al.*, 2003). Studies in the elderly showed conflicting results (Wisniewski *et al.*, 2002; Davison *et al.*, 2011; Kocoska-Maras *et al.*, 2011).

Testosterone may increase BMD when used with estrogen replacement, above that achieved with estrogen alone. However the evidence is limited to two studies in surgically menopausal women. One found that spine (but not hip or radius) BMD increased non-significantly in the group that received adjuvant testosterone compared to estrogen alone (Watts *et al.*, 1995). In the other, spine and hip BMD increased significantly with androgen plus estrogen compared to estrogen alone (Barrett-Connor *et al.*, 1999).

Risks

The risks of androgen treatment in women are unclear. Androgenic side effects (acne, hirsutism, deepening of the voice and androgenic alopecia) are rare with doses below 300 µg of testosterone per day (Buster *et al.*, 2005; Simon *et al.*, 2005).

Conclusive data on long-term safety with regard to endometrial hypertrophy and breast cancer are not yet available (Davis *et al.*, 2008, 2009; Davis and Davison, 2012).

Routes of administration, duration and monitoring

Testosterone may be administered transdermally (gel/patch/cream), orally or through an implant although commercial preparations for women are very limited. No research was identified for any of these routes of administration in women with POI. The major complaint is of application site effects, and 4% of patch users discontinue treatment for this reason (Simon *et al.*, 2005). Women's preferences need to be taken into account when deciding on the route of administration.

In conclusion, women should be informed that androgen treatment is only supported by limited data, and that long-term health effects are not clear yet. If androgen therapy is commenced, treatment effect should be evaluated after 3–6 months and should possibly be limited to 24 months.

Conclusion

HRT is strongly recommended for women with POI, mainly for vasomotor and genito-urinary symptom relief and the primary prevention of bone loss but probably also for cardiovascular disease. Quality of life and life expectancy may be reduced by POI, and HRT may help improve both. A registry of women with POI would help our understanding of the long-term consequences of the condition and to refine treatment options. What is clear is that the controversies that surround the use of HRT in postmenopausal women do not apply to women with POI and that the physiological replacement of estrogen (and progesterone) is essential for their health.

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Authors' roles

The concept and evidence are based on the ESHRE guideline on management of women with POI, which was chaired by LW. This review was written by L.W. and N.V., based on the guideline chapter on HRT written by N.V., L.W., F.J., R.A.A. and M.D.

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Conflict of interest

None declared.

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