Commentary

Does the Type of Hormone Replacement Matter in Premature Ovarian Insufficiency?

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Abstract

The syndrome of Premature Ovarian Insufficiency (POI) was first described in 1942 by Albright et al., (1942) [1]. The condition is characterised by infrequent ovulation that manifests as oligomenorrhoea or amenorrhoea (which may be primary or secondary) or, hypoestrogenism and a reactive elevation in gonadotrophin levels occurring in women under the age of 40 years [2-6]. It is estimated to affect 1% of women under 40 years, 0.1% of women under 30 years [2,3,5,7] and 0.01% of women under 20 years of age [7].

The syndrome can have devastating short and long-term effects secondary to the deficiency of sex steroids. Short-term symptoms include climacteric symptoms such as vasomotor symptoms, reduced libido, irritability, disruption of well-being and sexuality [8], insomnia, mood disturbances and urogenital symptoms (vaginal dryness, dyspareunia, urinary symptoms) [9] while approximately 12-14% of women with POI are asymptomatic [9]. Long-term sequelae include loss of bone mineral density (BMD), increased risk of cardiovascular disease and cognitive impairment (including dementia) as well as subfertility [4,5].

Bone density is thought to diminish at a rate of approximately 2-3% per year after the onset of the menopause, slowing by 10 years. The degree of BMD loss in POI patients is proportional to the degree and duration of oestrogen deficiency, and greater in cases of primary amenorrhoea. Approximately 8-14% of POI sufferers have been estimated to develop osteoporosis [6].

The incidence of ischaemic heart disease (IHD), mortality secondary to IHD and overall mortality is higher in women with POI [10,11]. This negative impact is persistent irrespective of the cause of POI. A large systematic review and meta-analysis undertaken by Roeters van Lennep et al., [12] including 190,588 women with POI under the age of 40 years, from 10 prospective observational studies with a follow up period of more than 3 years, demonstrated a 69% in-

creased risk of IHD (hazard ratio [HR] 1.69, 95% confidence interval [CI] 1.29-2.21, p=0.0001) and 61% risk of cardiovascular disease (HR 1.61, 95% CI 1.22-2.12, p=0.0007) in women who underwent an early menopause [12].

Evidence on the adverse health risks associated with POI is mainly derived from observational cohort studies. The authors of a large population-based study conducted in the USA, comparing the survival of women whom had undergone an oophorectomy for a non-cancerous indication, with age-matched controls who had not undergone an oophorectomy, concluded that bilateral oophorectomy prior to 45 years of age is associated with a 67% increased mortality rate (HR 1.67, 95% CI 1.16-2.40, p=0.006) [13]. This finding was further supported by the Nurse's Health Study which found a 12% increased risk of all-cause mortality (HR 1.12, 95% CI 1.03-1.21), fatal and 17% increased risk in non-fatal coronary heart disease (HR 1.17, 95% CI 1.02-1.35) when a bilateral oophorectomy is performed in conjunction with a hysterectomy for benign disease prior to 50 years of age [14].

Observational studies to date have since shown that the hypoestrogenic state, counteracted with oestrogen replacement, can have a positive effect. Several observational studies have found a lowering in the risk of cardiovascular disease and its related morbidity and mortality in women with POI who have received oestrogen replacement therapy [10,11,15].

Oestrogen is commonly available in three different chemical forms: 17β-estradiol (main ovarian active component); ethinylestradiol (synthetic estrogen); and, conjugated equine estrogens (CEE) (derived from the urine of pregnant mares). Estradiol or CEE is commonly given as hormone replacement therapy (HRT), whereas the oral contraceptive pill contains ethinylestradiol. Whilst there is a good body of evidence to support oestrogen replacement in these women, there is limited evidence comparing these regimens which has subsequently led to considerable variation in practices amongst clinicians.

Whist a significant amount has been discussed about the value of oestrogen in women with POI, Progestogens are equally important in non-hysterectomised women receiving oestrogen replacement therapy. The current body of evidence recommends progestogens for at least 10-14 days per month, to reduce the risk of endometrial cancer [15,16] (relative risk [RR] 2.1-5.7) [15] by opposing the proliferative effects of oestrogens [17,18]. The biological actions of natural progesterone are multi-fold, including anti-gonadotropic, anti-oestrogenic, anti-androgenic and anti-mineralocorticoid properties [19,20]. There are many different classes of progestogens, each with different pharmacological properties dependent upon the parent molecule from which they are derived, testosterone or progesterone, and thus, they have different side effect profiles [17,20]. These differences may help to explain why progestogens can partially oppose the beneficial effects of oestrogen [17].

Micronised progesterone and dydrogesterone in contrast, have a more selective effect on progesterone receptors with less interaction with androgenic and mineralocorticoid receptors compared with other progestogens.

Another hormone that plays an important role in hair growth, libido and behaviour (energy and mood) is testosterone. Testosterone belongs to a group of hormones referred to as androgens. Twenty-five percent of the premenopausal androgen production is derived from the ovaries [6]. Furthermore, testosterone has been implicated in improving cardiovascular function both directly through coronary artery dilatation secondary to improvements in endothelial cell function and indirectly, by impacting secondary markers of coronary artery disease such as improved exercise tolerance, muscle strength, glucose metabolism and increasing the conversion of testosterone to oestrogen [21].

Testosterone replacement in the United Kingdom (UK) is highly restricted. Tibolone is a synthetic HRT that contains a combination of oestrogen, progestogen and testosterone. It is also available as an implant in certain clinics. The patch however, was withdrawn from

the UK market in 2012, stating commercial reasons. Testosterone is also available as a gel, but this is off-license for women. Testosterone is currently available only as an additional therapy to women using oestrogen. Reported adverse effects include voice deepening, hirsutism and male pattern alopecia or liver dysfunction.

The evidence regarding the use of hormone therapy in women with POI is currently limited to single randomised controlled trials (RCT), large non-randomised trials, case-control or cohort studies of moderate quality (The ESHRE Guideline Group on POI et al., 2016). Women with POI represent a unique population and therefore, the results of studies largely including older women using hormone therapy should not be extrapolated to this group [9]. These older studies also failed to address the benefits of hormone therapy given at the 'window of opportunity' in younger women.

The cardioprotective role of oestrogens is thought to work through their favourable impact on surrogate markers of cardiovascular disease such as lipids and lipoprotein profiles [22,23] (reduce low-density lipoprotein [LDL] and increase high-density lipoprotein [HDL]) [15,17], endothelial function and their anti-inflammatory and anti-oxidant properties [22,24,25]. Oestrogen replacement therapy has also been shown to improve insulin sensitivity, lower diastolic blood pressure (BP) and stimulate the production of vasodilating factors such as nitric oxide [17,19,26] and prostaglandins by the vessels [17].

Kalantaridou et al., [27] assessed endothelial function in women with POI before and after 6 months of hormone replacement therapy (HRT) (oral 0.625mg CEE with cyclical 5mg medroxyprogesterone acetate) (n=18) versus controls. Women receiving HRT demonstrated a more than 2-fold increase in the flow-mediated dilation, comparable to the control group, but this did not reach statistical significance [27].

Cardiovascular health could also be reflected in blood pressure (BP) changes. A study conducted by Langrish et al., [28] comparing

HRT (transdermal estradiol with cyclical vaginal progesterone) with the combined oral contraceptive pill (COCP) (ethinylestradiol 30μg with 1•5mg norethisterone) in a randomized controlled crossover pilot trial (n=18 [completed the study]) found that HRT resulted in significantly lower mean 24-hour BP and also had a more beneficial effect on renal function [28].

As highlighted previously, estrogen is vital in regulating and maintaining bone structure in women and should be considered first-line treatment for the prevention and management of osteoporosis in women with POI. However, the data regarding the impact of HRT on BMD in women with POI has largely come from observational studies [6].

A retrospective observational study of POI women with Turner's Syndrome (n=54), conducted by Kodama et al., [29] found that oral CEE with cyclical dydrogesterone significantly increased the BMD in comparison with low dose CEE and the control group who did not receive HRT [29].

Crofton et al., [30] reported on the same randomised controlled crossover pilot trial as Langrish et al., [28] and found that HRT increased the lumbar spine BMD with a positive effect on bone formation markers compared to the COCP [30].

An open-labelled RCT comparing changes in BMD with HRT (Nuvelle – estradiol 2mg and levonorgestrel 75μg) and the COCP (Microgynon 30 – ethinylestradiol 30μg and levonorgestrel 150 μg) with a non-randomised observational group that declined treatment concluded that HRT significantly increased the lumbar spine BMD at two years and that the COCP had more significant benefit than receiving no treatment [31].

Observational studies have shown an increased risk of cognitive impairment and dementia in women with early onset menopause. The Mayo Clinic Cohort Study of Oophorectomy and Aging evaluated the impact of a unilateral or bilateral oophorectomy before the start of the menopause on the development of cognitive impairment and demen-

tia (n=1489) [32]. They found a 46% increased risk compared to controls (HR.1.46, 95% CI 1.13-1.90); higher in younger women. They postulated a cognitive window of opportunity and timing hypothesis, whereby commencement of HRT in younger menopausal women is likely to lower the risk of cognitive impairment and dementia. They went further to recommended estrogen replacement until the age of 50 years in this subgroup of women [32].

Bove et al., [33] reported on The Religious Orders Study and The Rush Memory and Aging Project (n=1884), concluding that HRT, when administered within a 5-year perimenopausal window, for at least 10 years, has a protective effect on global cognition [33].

The benefit and adverse effects all proposed treatments should be individualised. As such, one should pay careful consideration to the data surrounding risks and benefits from the earlier studies conducted on HRT. These were conducted in a different age category compared to women suffering from POI.

Observational data have shown that women with POI have a lower risk of breast cancer compared with controls. There is a small increased risk after five years (linked to the progesterone component). Wu et al., [34] reported a 41% decreased incidence of breast cancer (odds ratio [OR] 0.59, 95% CI 0.38-0.91) from the Shanghai Women's Health Study (n=1003 POI patients) [34]. The Danish Cancer Registry assessed the risk of developing breast cancer with HRT use (n=78,380 women aged 40-67 years) and found no increased risk 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) [35]. The French E3N study found that the risk of breast cancer is lower with micronised progesterone and dydrogesterone versus other progestogens [36,37].

Canonico et al., [38] pooled data from the Women's Health Initiative study and found that extremes of ages were risk factors for venous thromboembolic disease (VTE): early menopause (<40: HR 1.8, 95% CI 1.2-2.7); and, late menopause (>55: HR 1.5, 95% CI 1.0-2.4)

[38]. Whilst Manzoli et al., [39] reported a 3-fold increased risk of VTE with the COCP versus non-users (OR 3.41, 95% CI 2.98-3.92) [39].

The progesterone component is said to influence the VTE risk; evidence from observational studies in naturally menopausal women has shown that micronised progesterone and pregnane derivatives such as dydrogesterone may be associated with lower risk compared with other progestogens, in particular, norpregnane derivatives.

The ESTHER (EStrogen and THromboEmbolism Risk) study group, a French case-controlled study, reported that oral but not transdermal oestrogen is associated with an increased risk of VTE disease in postmenopausal women [40,41]. Transdermal oestrogen has not been found to alter the coagulation cascade secondary to its first pass effect. Oestrogen patches also lead to more steady plasma concentrations [42] resembling physiological levels and higher peak levels at lower dosages [6]. Furthermore, they have a slower rate of absorption and avoidance of gastrointestinal conversion to oestrogen metabolites [43] secondary to lower hepatic exposure [25,28]. Transdermal oestrogen is also thought to have less of a negative impact on insulin-like growth factor 1; a beneficial impact on the serum lipid profile and inflammatory markers [6].

The aim in women with POI is to achieve physiological levels of estradiol until the natural age of the menopause. Non-hysterectomised women also require progesterone replacement for 10-14 days a month within a cyclic regimen to minimise the risk of endometrial cancer with unopposed estrogen.

The difficulty with the COCP is that they can have a seven-day pill-free period resulting in women not receiving estrogen replacement for those seven days each month, potentially resulting in some women experiencing menopausal symptoms during this time. Furthermore, older preparations also provide two-three times the dose of required estradiol, giving supraphysiological levels. Newer pills such

as Qlaira (phased dosing) and Zoely both include estradiol instead of ethinylestradiol and have an extended tablet taking phase. These may be considered in women who also require concomitant contraception [9].

In conclusion, women with POI represent a different cohort to naturally menopausal women >50 years of age. HRT positively impacts bone, cardiovascular health, cognitive function and climacteric symptoms. HRT and the COCP containing ethinylestradiol are both suitable options, although HRT may be associated with less side effects and a lower risk profile. Transdermal oestrogen over oral preparations is preferential in high-risk groups and hormone replacement should aim to achieve physiological hormonal levels until at least the natural age of the menopause.

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