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REVIEW

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ABSTRACT

Premature ovarian insufficiency (POI) is an increasing public health problem with a prevalence now approaching 4%. POI results in adverse effects on the skeleton and central nervous system as well as disturbances of metabolic and cardiological factors that predispose to a major increased risk of cardiovascular disease (CVD). This article reviews the effects of the premature loss of ovarian function on lipids and lipoproteins, glucose and insulin metabolism, body composition, hemostasis and blood pressure, together with effects on the development of metabolic syndrome and diabetes mellitus. The article examines the effects of POI on vascular endothelial function and inflammation that result in arterial disease, and reviews the effects of hormone replacement therapy (HRT) on these various metabolic processes and on cardiovascular outcomes. It is essential that women with POI receive hormonal treatment to help prevent the development of CVD, and that this treatment is continued at least until the normal age of menopause. It appears that HRT has a more favorable effect than the combined oral contraceptive, but larger clinical trials are needed to establish the optimal treatment. Other therapeutic measures may need to be added to correct existing metabolic abnormalities and, in particular, attention to lifestyle factors such as diet and exercise must be encouraged.

Introduction

Premature ovarian insufficiency (POI), a hypergonadotropic, hypoestrogenic condition of young women aged under 40 years, is a growing public health issue [1]. The often quoted prevalence of 1% now appears to have been an underestimate, with recent global data suggesting a 3.7% pooled prevalence rate, which is likely to be even higher in medium or low Human Development index countries [2]. POI is associated with an increased risk of cardiovascular disease (CVD), osteoporosis and neurological disorders such as dementia and Parkinson's disease. The burden of disease resulting from the premature loss of estrogen due to this condition was demonstrated in a recent large study of Australian women with POI, who were three times more likely to suffer with multimorbidity in their sixties compared to those with menopause at age 50–51 years [3]. Of the 11 conditions studied, cardiometabolic outcomes included diabetes, hypertension, heart disease and stroke. Meta-analyses have already shown that POI is an independent risk factor for coronary heart disease (CHD) [4] and cardiovascular mortality [5]. The Australian study [3] adds to the scientific literature that links POI with an increased burden of cardiometabolic disease.

As iatrogenic interventions for life-threatening conditions become increasingly successful, the rate of iatrogenic POI, due mainly to surgery and chemo/radiotherapy, will also increase, as will the associated morbidity and mortality [6]. A recent large study of women with POI found that the primary composite outcome measure of cardiovascular risk was higher in women with surgical POI (11.3/1000 woman-years), compared to those with spontaneous POI (8.8/1000 woman-years) and to those without POI (5.7/1000 woman-years) [7]. Thus, the potential cardiometabolic sequelae of iatrogenic POI warrant particular scientific scrutiny.

The main aims of this article are to:

- review how the impact of the premature hypoestrogenic state on cardiometabolic risk factors predisposes to CVD in women with POI; and
- propose how cardiometabolic risk can be minimized in women with POI, particularly through hormone replacement therapy (HRT).

Although all women with POI should be advised to replace their hormones at least until the average age of menopause, not all studies have confirmed the benefits. This may be due to study limitations or because the type, duration or route of

administration of HRT was suboptimal. The Premature Ovarian Insufficiency Study of Effectiveness of hormonal therapy (POISE) UK randomized trial should provide useful information regarding the advantages and disadvantages of HRT versus the combined oral contraceptive (COC) pill for cardiovascular health, in addition to bone health and other issues [8]. Future research endeavors will be crucial to identify all determinants of long-term cardiovascular risk and key strategic interventions that will optimize cardiovascular and general health in women with POI [9].

Metabolic factors

Lipids

The menopause transition is associated with alterations in lipid profile, with higher low-density lipoprotein cholesterol and triglyceride levels and lower high-density lipoprotein cholesterol (HDL-C) [10], and women with POI also display unfavorable lipid profiles. In a UK-based cohort study of 144,260 postmenopausal women, 4904 (3.4%) had natural premature menopause and 644 (0.4%) had surgical premature menopause. In models adjusted for age, ethnicity, body mass index (BMI), hypertension and type 2 diabetes mellitus, both spontaneous POI (hazard ratio [HR] 2.36, 95% confidence interval [CI] 1.16–1.61; $p < 0.001$) and surgical premature menopause (HR 2.13, 95% CI 1.50–3.04; $p < 0.001$) were associated with increased risk of hyperlipidemia compared to postmenopausal women with normal-age menopause [7]. In a cross-sectional case–control study of 98 women with an average age of 49 years who had previously been diagnosed with POI, POI was associated with significantly higher total cholesterol and low-density lipoprotein cholesterol and no difference was noted in triglycerides. HDL-C, however, was noted to be raised in women with POI. Higher plasma HDL-C may confer a protective effect on CHD, although it has been postulated that the protective effect of HDL-C is weaker in postmenopausal women [11]. This was consistent with previous data showing an unfavorable lipid profile in women with POI even after correction for age and BMI [12–14].

Body composition

Menopause is associated with changes in body fat distribution, with accumulation of central and visceral adiposity. Several case–control studies have shown that women with POI have increased waist circumference and increased waist-to-hip ratio compared to premenopausal age-matched controls [11,15–17], despite frequently having a lower overall BMI [11]. In women with POI taking HRT, changes in body composition were less marked, with no significant differences in lean and fat mass content or waist-to-hip ratio seen compared to controls [18].

Glucose

Data regarding the effect of POI on glucose and insulin metabolism are conflicting and generally limited to relatively small cohort studies. The two largest studies to date showed that, despite having a lower BMI, women with POI had significantly higher glucose levels [11] and lower insulin sensitivity than controls [19], although other smaller studies did not detect differences in glucose metabolism [14,20].

Hemostasis

Compared with women aged 40–49 years at menopause, women with POI have a significantly increased risk of non-procedurally related venous thromboembolism (HR 1.8, 95% CI 1.2–2.7) even after adjustment for hormone use, age, BMI, past history of venous thromboembolism and smoking status [21]. Early surgical menopause (mean age 43.6 years) has been associated with alterations in hemostatic factors, platelet function and markers of endothelial function [22], and POI patients have been noted to have low-grade systemic coagulation and fibrinolytic activation, as evidenced by elevated D-dimer, white blood cell, mean platelet volume and prothrombin levels [23].

Metabolic effects of HRT in women with POI

There is a lack of prospective data evaluating the metabolic effects of HRT in women with POI, with data frequently extrapolated from other causes of hypogonadism or women with Turner syndrome. Most data point to a benefit from estrogen replacement in terms of lipid and glucose metabolism and body composition. In a group of 25 young hypogonadal women (mean age 31.9 years; range 18.5–42.2 years), increasing doses of HRT (17β-estradiol at 1 mg, 2 mg and 4 mg) resulted in a reduction of carotid intima-media thickness along with increased serum HDL-C and decreased plasma glucose [24]. In a small randomized crossover study of 17 women with Turner syndrome and POI, 6 months of either oral conjugated equine estrogens or ethinylestradiol was associated with normalization of hyperinsulinemia [25]. Meta-analysis of 25 studies, involving 771 patients with Turner syndrome, showed that women on oral estrogen replacement therapy had a higher increase in HDL-C levels when compared to transdermal therapy (weighted mean difference 9.33 mg/dl [95% CI 4.82–13.85]), with no significant effect on other lipid fractions [26]. The body composition of women with POI using HRT is similar to that of women with normal ovarian function with regard to lean and fat mass content and fat distribution [18].

Metabolic syndrome and type 2 diabetes mellitus

Metabolic syndrome is a cluster of cardiometabolic risk factors with a common origin from insulin resistance, including central obesity, hypertension, low HDL-C, high serum triglycerides and impaired glucose tolerance or overt diabetes [27]. The menopausal transition has been associated with an increased prevalence of metabolic syndrome, with an odds ratio ranging between 2 and 4 in postmenopausal women, compared to premenopausal women of the same age (95% CI 2.92–4.30) [27]. This association seems to apply also to

women with POI. Ates et al., comparing women with POI with a mean age of 35 years to age-matched and BMI-matched controls, reported a prevalence of 14.3% of metabolic syndrome in women with POI, as compared to 3.4% in regularly menstruating women [20]. These findings were corroborated by Gunning et al. in a case–control study that included women with POI and age-matched controls (metabolic syndrome prevalence 16% vs. 3%, respectively) [15].

Women with POI are at increased risk of developing diabetes late in life. As shown in the InterAct study, a prospective case–cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC), women with POI had 32% higher risk of developing diabetes within a median of 11 years of observation compared to women with age at menopause >50 years [28]. In a recent meta-analysis comprising 191,762 women with 21,664 cases of diabetes, women with POI had 53% higher risk of incident diabetes compared to women with age at menopause >45 years [29]. Furthermore, a prospective cohort analysis of 124,379 postmenopausal women aged 50–79 years from the Women's Health Initiative (WHI) study with over 974,714 person-years of follow-up showed that a shorter reproductive lifespan (<30 years) was associated with 23% higher incidence of diabetes later in life [30]. Finally, the National Health and Nutrition Examination Survey I (NHANES I), evaluating 2597 postmenopausal women without diabetes at baseline, showed that a history of bilateral oophorectomy was associated with a 56% higher risk of developing diabetes compared to women without surgery, during a median of 9.2 years of observation [31]. Beyond the effect of estrogen decline on glucose metabolism and the incidence of type 2 diabetes, POI often co-exists with other endocrine autoimmune disorders, and thus women with POI are also at increased risk of type 1 diabetes [32].

Estrogens exert a beneficial effect on glucose metabolism through a decrease in abdominal fat deposition, an increase of lipid oxidation and energy expenditure, and an improvement in insulin sensitivity and possibly insulin secretion [33]. Most randomized controlled trials and epidemiological studies have shown that HRT reduces the incidence of type 2 diabetes in women without diabetes at baseline (for a review of these studies, see Mauvais-Jarvis et al. [34]). The Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) study [35] and the Nurses' Health Study (NHS) [36] have also included women with early menopause and POI, respectively, and concluded that the beneficial effect of HRT on the incidence of diabetes was evident across the whole age range of the participants. Oral estrogens are superior to transdermal preparations in suppressing hepatic glucose production. On the other hand, transdermal estrogen delivery is associated with lower risk of thrombosis. Concerning progestogens, micronized progesterone, dydrogesterone and transdermal norethisterone are unlikely to mitigate the beneficial effects of estrogens on glucose metabolism. The choice of the HRT regimen must be based on concomitant cardiometabolic risk factors and patient preference [37].

Blood pressure

Normal blood pressure (BP) is defined as 120–129/80–84 mmHg or less. Hypertension is defined as BP over 140/90 mmHg [38]. Hypertension increases with advancing age; younger women have a lower BP than men of a similar age but, as women transition through the menopause, BP tends to increase such that it is greater in women over the age of 55 years than in men [39]. A recent meta-analysis showed a significantly greater prevalence (around 30%) of hypertension in women with early menopause (<45 years) compared with women with normal-age menopause (>45 years) [40]. Hypertension increases the risk of CHD and stroke, and, if uncontrolled, results in end-stage renal disease [38]. Accurate measurement of BP is essential. BP should be measured in all women with POI at the initial consult and, if BP is found to be elevated, referral to a cardiovascular physician for confirmation, investigation and potential treatment is recommended. Unlike some cardiovascular conditions, there is no evidence that the BP threshold for initiating drug treatment, the treatment target, the choice of initial antihypertensive medication or the combination of medications for lowering BP differs for women versus men [41,42]. Management consists of lifestyle advice and drug treatment with a choice of five main classes of drugs, namely angiotensin converting enzyme inhibitors, angiotensin-2 receptor blockers, beta-blockers, calcium channel blockers and diuretics (thiazides and thiazide-like diuretics) [38]. The only caution with some medication in women is pregnancy. Whilst the probability of pregnancy is low in women with POI, this still needs to be considered when prescribing anti-hypertensive treatment [38].

Vascular effects

The close relation between endothelial dysfunction and vascular inflammation in the pathogenesis of atherosclerosis is now widely established [43,44]. Since atherosclerosis, plaque rupture or erosion and myocardial infarction are inflammatory processes, key differences exist in the inflammatory infiltrate between men and women with CHD [45]. Aging and menopause have been associated with an increase in the cytokines interleukin (IL)-1, IL-6 (IL-1β increases IL-6 levels), IL-18 and tumor necrosis factor and in C-reactive protein levels, which are biomarkers of an inflammatory response and are associated with increased risk for heart failure in atherosclerosis patients. However, estrogens have a dual effect on the inflammatory system with both anti-inflammatory and proinflammatory effects, of which the latter increases after menopause [46,47]. Inflammatory aging plays an important part in the pathogenesis of POI, causing an imbalance of the inflammatory cytokine network [48]. It is currently unknown whether anti-inflammatory treatment can halt or even reverse this enhanced risk of atherosclerosis. However, in patients with rheumatoid arthritis, their use might also induce cardiovascular complications by causing elevated BP, higher lipid levels, kidney failure and even congestive heart failure [49]. In addition, in POI women receiving timely and

adequate HRT, signs of accelerated vascular aging have not been demonstrated.

The hallmark of a healthy endothelium is appropriate nitric oxide synthesis and release by vascular endothelial cells in response to a vasodilatory stimulus [47]. Endothelial function is therefore a barometer of vascular health and a predictor of atherosclerosis that may start earlier than usual in women with POI. This elevated risk seems to be higher in women with natural POI than in women after early surgical menopause, caused by a higher genetic susceptibility and more cardiovascular risk factors in women with natural early menopause [50,51]. In non-human primate studies, premature atherosclerosis was found in animal models of POI, but this was not replicated in human studies on subclinical atherosclerosis as assessed by carotid intima-media thickness measurements and coronary artery calcium scoring with computed tomography scans [11,17]. Kalantaridou et al. [52] assessed endothelial function in 18 women with POI before and after 6 months of HRT. The findings were compared with a control group of 20 premenopausal women who were matched for age and BMI. Brachial artery diameter was measured both during hyperemia 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 6 months of HRT in women with POI, flow-mediated dilation increased by more than two-fold and returned to normal values similar to those noted in the control group.

In a recent study in BRCA1/2 mutation carriers after preventive risk-reducing salpingo-oophorectomy, no signs of premature subclinical atherosclerosis were found after 5–24 years, as measured by carotid intima-media thickness and pulse wave velocity [53]. Women with natural or surgically induced menopause before age 40 years have twice the risk of angina and higher severity of angina 1 year post myocardial infarction compared with women experiencing menopause at age 50 years or older [54]. In a meta-analysis, POI was found to be an independent although modest risk factor or marker of CVD (HR 1.61, 95% CI 1.22–2.12, $p = 0.0007$) but not of stroke (HR 1.03, 95% CI 0.88–1.19, $p = 0.74$) [4]. As long-term follow-up data in patients with POI are still limited, individual CVD risk management is recommended, preferably with additional coronary artery calcium measurements, especially when family risk is elevated. The absence of coronary artery calcium has been proven to be a strong predictor of a low 10-year CVD risk and helps with risk stratification and tailored preventive therapy [55].

Cardiovascular outcomes

The protective effect of endogenous estrogens on cardiovascular health is well recognized and age at menopause has been linked to cardiovascular risk since observations that an early surgical menopause increased cardiovascular mortality [56]. It is now well established that women with POI have an increased risk of CVD, with most studies pointing to a 50–60% increased risk [57,58].

Multiple population studies have demonstrated that POI is associated with increased CVD, increased cardiovascular mortality and an earlier age at onset of CVD [4,59–61]. The largest meta-analysis to date was a pooled analysis of 15 observational studies involving 301,438 women [58]. This showed an increased risk of CVD (CHD and stroke) in women with POI (HR 1.55, 95% CI 1.38–1.73) and early menopause (age 40–44 years; HR 1.30, 95% CI 1.22–1.39), after adjustment for age at last follow-up, ethnicity, BMI, smoking status, educational level, hypertension status and use of hormone therapy. The relationship between age at menopause and incident risk of CVD was almost linear; risk of CVD increased by 3% for every year or early menopause.

The UK Biobank cohort study investigated the association of POI with CVD [7]. In the fully adjusted models, overall CVD diagnoses were increased in both surgical POI (HR 1.87, 95% CI 1.36–2.58) and spontaneous POI (HR 1.36, 95% CI 1.19–1.56). Spontaneous POI was associated with increased risk of several CVDs including CHD, ischemic stroke, aortic stenosis, atrial fibrillation and venous thromboembolism, with risk progressively increasing as age of menopause declined.

POI and early menopause also appear to be associated with increased risk of cerebrovascular disease [7,58,62,63]. Prospective data from 73,814 participants without CVD in the Nurses' Health Study (NHS) showed that POI was associated with higher risk of CHD (relative risk 1.37, 95% CI 1.14–1.63) as well as stroke (relative risk 1.25, 95% CI 1.04–1.51) [63]. In the recent meta-analysis by Zhu et al. [58] there was an increased risk of stroke in both POI (HR 1.72, 95% CI 1.43–2.07) and early menopause (HR 1.32, 95% CI 1.18–1.48). Not all studies have associated POI with cerebrovascular risk [4,60,61]. However, it may be that follow-up duration of many studies has been insufficient to detect the later onset of stroke events in women compared to coronary disease.

Effect of HRT on cardiovascular outcomes

There are currently no prospective randomized studies establishing the long-term cardiovascular effects from HRT in women with POI. Data are frequently extrapolated from older postmenopausal women or from cohort studies, few of which have been adequately powered or of sufficient duration. In women with early surgical menopause, estrogen replacement appears to have a beneficial effect in terms of a reduction in overall mortality and cardiovascular mortality, as shown in data from the Mayo Clinic [64,65]. Prospective cohort data [66] demonstrated that early and premature menopause were associated with higher risk of ischemic heart disease. Ever use of HRT in women who had surgical menopause was associated with a significantly lower risk of ischemic heart disease compared to never-users. This effect from HRT was not seen in spontaneous menopause. However, the small numbers assessing the latter findings may preclude definite conclusions being drawn [66]. In a cross-sectional study of 385 women with POI [67], lifetime

estrogen exposure was inversely associated with low-density lipoprotein cholesterol, non-HDL-C and risk of CVD, as assessed by Framingham 30-year risk scores. The analyses suggested that – independent of age, ethnicity, smoking status and BMI – for every year a woman with POI is without estrogen exposure, her risk of CVD events increases by 0.18–0.20%, and for every year a woman with POI is exposed to estrogen, her risk of CVD events decreases by 0.15–0.16%.

Cardiovascular outcomes may also vary with the type of estrogen used within HRT in women with POI. In a randomized controlled crossover trial, transdermal estradiol 100–150 μg in combination with vaginal progesterone 400 mg per day for 2 weeks per month was compared to a COC pill containing ethinylestradiol 30 μg and norethisterone [68]. The study included 34 women with POI, of whom 18 completed the study. HRT resulted in significantly lower mean 24-h systolic BP and diastolic BP throughout the 12-month treatment period compared with the COC 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 COC pill. In the recent meta-analysis by Zhu et al. [58], the sub-analysis of seven studies demonstrated that the greatest reduction in CVD incidence was in women with POI or early menopause who used HRT for at least 10 years. Furthermore, women with POI who initiated HRT within 1 year of diagnosis had the lowest risk of CVD, highlighting the importance of prompt treatment and long-term continuation of hormone therapy. Current guidelines recommend continuation of HRT until at least the average age of menopause [1,69,70]. A small randomized trial compared HRT with COC or no treatment and demonstrated a better skeletal effect of HRT compared with COC [71]. Of note, 80% of women taking HRT completed the study compared with only 60% of those taking COC. Outside a clinical trial setting, compliance may well be lower. Unlike HRT, COC does not represent a physiological replacement option for both the type and the dose of steroid hormones. However, some young women with POI may find COC to be a more attractive option (as opposed to HRT – a regimen designed for older postmenopausal women).

Conclusions

POI clearly results in adverse health outcomes, not only CHD but also osteoporosis, osteoarthritis and impaired cognitive function. Because the numbers of women with POI are relatively small, it has been necessary, and not unreasonable, to extrapolate findings from women undergoing menopause at a normal age and apply them to POI. There can be no doubt that POI results in adverse metabolic changes similar to normal age menopause, and these will result in an increased risk for CHD, metabolic syndrome, type 2 diabetes mellitus and premature death. The establishment of large databases of women with POI, such as https://poiregistry.net [72], will lead to a better understanding of the condition and

determine (or confirm) the metabolic abnormalities resulting from the condition. It would appear that HRT will reverse these abnormalities to a large extent, and would be superior to the effects of COC. A large prospective randomized clinical trial is required to establish the clinical outcomes of HRT in the treatment of POI, and such a trial would need to be multi-centered and multi-national in order to achieve the necessary numbers of participants. Until then, it is prudent to regard the treatment of POI in women with HRT as mandatory. Such treatment should be continued at least until the normal age of menopause (51 years), and often beyond. Improvement in lifestyle factors such as diet and physical activity should be encouraged; this is particularly important for those who may not be compliant with therapeutic interventions.

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