Best Practice & Research Clinical Obstetrics and Gynaecology 81 (2022) 61–68

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

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Bone and heart health in menopause

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Keywords:
Menopause
Premature ovarian insufficiency
Osteoporosis
Fracture
Cardiovascular disease
Hormone therapy

A B S T R A C T

Age at menopause has been shown to have an impact on bone and heart health, with younger menopause age consistently associated with a higher risk of cardiovascular disease, osteoporosis, and fracture. These risks are particularly high increased among women who encountering menopause at an early age, including women with premature ovarian insufficiency (POI) and early menopause, due to a prolonged period of oestrogen deprivation. Several interventions are suggested to optimise the bone and cardiovascular health of women with menopause including lifestyle modification, dietary supplements, hormonal, and non-hormonal therapies. Hormone therapy (HT) is indicated for women with POI. For women with early menopause, there is a paucity of evidence for the management of bone and cardiovascular health. For women beyond the average age of menopause, HT is not indicated solely for bone protection and cardiovascular health. In this group, screening for bone and heart disease, as well as primary and secondary prevention, should be undertaken in line with national and international guidelines.

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https://doi.org/10.1016/j.bpobgyn.2022.03.002

Menopause spectrum and long-term outcomes

Earlier age of menopause has consistently been associated with increased mortality [1], whilst a later age of menopause is associated with a longer lifespan [2], with a reduction in ischaemic heart disease offsetting slightly increased mortality from uterine and ovarian cancer.

Premature ovarian insufficiency (POI) is defined as menopause before the age of 40 (two standard deviations below the average age of menopause) and affects 1–3% [3–5] of women. Women with untreated POI have higher rates of osteoporosis and fracture at a younger age than controls. Untreated POI is also associated with an increased risk of mortality largely secondary to cardiovascular disease [6,7].

Early menopause, defined as menopause between the age of 40 and 45, affects around 10% of women [5] and is increasingly recognised as being independently associated with an increased risk of fracture [8], cardiovascular disease, and mortality [9,10].

The underlying pathophysiology of these associations is variation in female reproductive sex hormone exposure with oestrogen, specifically, having a direct effect on bone metabolism [11] and endothelial function [12] as well as systemically through the 'metabolic syndrome' [13]. Recent evidence suggests that direct effects are dominant for heart health [14], with menopause type (spontaneous or surgical) and timing having little impact on traditional cardiac risk factors, including lipids, blood pressure, BMI, and HBA1c.

Premature ovarian insufficiency

Bone health

A study of 21,711 post-menopausal women from the Women's Health Initiative Observational Study cohort [15] reported that women who underwent menopause before 40 years of age had a higher fracture risk (hazard ratio (HR) 1.21; 95% CI: 1.02–1.44; $P = 0.03$) compared with women who underwent menopause at age 50 years or older. Bone mineral density (BMD) measurements were also lower in a subset of women who underwent DEXA (Dual-energy X-ray absorptiometry) scans.

A further cross-sectional study [16] in a tertiary centre comparing women with POI ($n = 442$), concurrent controls ($n = 70$), and matched controls ($n = 353$) reported that women with POI had on average 2–3% lower BMD, with African American and Asian women having lower BMD than Caucasians.

Reported modifiable risk factors for low BMD (Z-score <-2, bone density two standard deviations below the age-adjusted mean) reaching statistical significance ($P < 0.05$) included delay in diagnosis of POI (>1 year), low vitamin D levels (<32 ng/ml), non-adherence to HRT, low calcium intake, and lack of weight-bearing exercise [16].

National and international guidelines for the management of POI are available from the British Menopause Society (BMS) [17], European Society of Human Reproduction and Embryology (ESHRE) [18], International Menopause Society (IMS) [19], and the National Institute for Healthcare Excellence (NICE) [20]. A systematic appraisal of clinical guidelines [21] for bone health in women with POI found that most clinical practice guidelines for bone health in POI are of average to poor quality, with limited evidence to support recommendations.

BMS [17], ESHRE [18], and IMS [19] guidelines recommend screening for low BMD with DEXA scan at baseline and again within 5 years of diagnosis, particularly if BMD was low at the initiation of hormone therapy (HT). Guidelines also recommend that the impact of POI on BMD and fracture risk can be ameliorated through the modification of lifestyle risk factors and the provision of exogenous oestrogen-based HT, unless contraindicated.

Recommended lifestyle modifications include a well-balanced diet with the consideration of vitamin D3 supplementation (800–1000 IU/day), encouraging the intake of food rich in calcium and vitamin D-rich foods [19], engaging in adequate weight-bearing exercise, maintaining a healthy weight and smoking cessation, and minimising alcohol consumption [18].

A systematic review of oestrogen-based HT in POI [22] reported that HT prevents loss of or increases BMD compared to BMD in women receiving placebo. However, limitations in the evidence base include

high risk of bias, use of surrogate end points, and heterogeneity in the formulation, dose, administration route, and regimen of HT.

In a randomised, double-blind, single-centre, placebo-controlled clinical trial [23], women with POI were allocated to oestradiol and progestin replacement (n = 72) or oestradiol, progestin, and testosterone replacement (n = 73). Results were compared with a control group of healthy women (n = 70). At screening, women with POI had significantly lower BMD compared with controls (0.77 vs 0.81 g/cm [2], P = 0.001). Control participants lost femoral neck BMD over the study period, whereas women with POI on oestradiol and progestin therapy gained BMD. After 12 months of BMD of treated women with POI did not differ from controls.

Further evidence in support of HT is that poor compliance with HT is associated with decreased BMD [24]. In a cohort study of 162 women with POI, 69 women had ceased HT for at least one year, which was associated with lower BMD and higher rates of osteopenia and osteoporosis.

Significant differences in BMD have also been reported between treatment with hormone replacement therapy (HRT) and the combined oral contraceptive pill (COCP), with HRT appearing to have a favourable impact on BMD.

A small randomised control trial (RCT) [25] of 34 women with POI comparing 'physiological' HT (transdermal oestradiol, 100 μg daily for week 1, 150 μg for weeks 2–4; vaginal progesterone, 200 mg twice daily for weeks 3–4) and 'standard' HRT (oral ethinyloestradiol 30 μg and 1.5 mg norethisterone daily for weeks 1–3, week 4 'pill-free') showed that BMD z-score was −0·89 (95% CI: −1·27 to −0·51) and increased by +0·17 (CI + 0·07 to +0·27) with 'physiological' HT (P = 0·003), compared with +0·07 (CI -0·03 to +0·18) during 'standard' HT (P = 0·2). A larger RCT of 59 women with POI compared COCP with HRT and supported the finding that HRT was more effective in increasing BMD, with BMD at the lumbar spine +0.050 g/cm [2]; (95% CI: 0.007–0.092; P = 0.025) vs COCP at 2 years [26].

In the previously described RCT by Popat et al., the addition of testosterone to adequate oestrogen/progestogen HT [23] did not significantly increase BMD. Given the potential risks of testosterone exposure, its routine use for bone health is not supported.

Heart health

A systematic review and meta-analysis [27] of 10 observational studies including 190,588 women reported that POI was associated with an increased risk of ischaemic heart disease or dying from heart disease (HR 1.69, 95% CI: 1.29–2.21, p = 0.0001) and total cardiovascular disease (HR 1.61, 95% CI: 1.22–2.12, p = 0.0007).

A subsequent individual patient meta-analysis [9] of 15 observational studies, including 301,438 participants, compared women with POI with women who underwent menopause at the age of 50–51; women with POI had an increased risk of cardiovascular disease (HR 1·55, 95% CI: 1·38–1·73; p < 0·0001).

Although no longitudinal outcome data are available to recommend HT to improve heart health in POI, guidelines including BMS [17], ESHRE [18], IMS [19], and NICE [20] strongly recommend that HT is commenced, and that HT should be continued at least until the average age of natural menopause in women with POI. Evidence to support this recommendation is from several small studies using surrogate endpoints.

HT appears to improve vascular endothelial biomarkers in women with POI. A small study [28] assessing vascular endothelial dysfunction using flow-mediated dilation in 18 women before and 6 months after initiating HT compared with 20 healthy controls showed that endothelial dysfunction present prior to treatment normalised with HT treatment. A further study [29] of 20 women with hypogonadism, including POI, showed a reduction in carotid intima-media thickness, a validated biomarker of cardiovascular disease risk, as well as an increase in high-density lipoprotein and decrease in plasma glucose.

HT with HRT appears to have a favourable effect on blood pressure compared with the COCP. A small RCT [30] of 34 women with POI compared COCP and HRT (transdermal estradiol 100 μg + vaginal progesterone) assessing cardiovascular endpoints: systolic and diastolic blood pressure were 7.3 mmHg (95% CI: 2.5–12.0 mm Hg) and 7.4 mm Hg (95% CI: 3.9–11.0 mm Hg) lower at 12 months, respectively.

Early menopause

Bone and heart health

In a cohort of 4725 post-menopausal women, early menopause was associated with an increased risk of fracture (OR = 1.5; CI: 1.2–1.8) [8]. A further prospective observational study included 390 women with early menopause [31] (defined in this study as menopause before age 47). After a long-term follow-up of 30 years, women with early menopause had increased rates of osteoporosis (RR:1.83, 95% CI: 1.22–2.74), fragility fracture (RR:1.68, 95% CI: 1.05–2.57), and mortality (RR:1.59, 95% CI: 1.04–2.36) compared with those with menopause over the age of 47.

Similar associations have been found between early menopause and heart disease. An individual patient data meta-analysis of 301,438 women [9] found that women with early menopause (40–44 years) had an increased risk of cardiovascular disease relative to women at undergoing menopause at the average age (HR:1·30, Cl: 1·22–1·39; $p < 0·0001$).

Whilst there is clear and growing evidence that early menopause is associated with an increased risk of poor bone and cardiovascular health, there is a lack of studies considering interventions in this population and no guidelines are available. A pragmatic approach to treatment is to assess and manage bone and heart health risk factors with consideration of HT for the prevention of disease on an individual basis.

Menopause

Bone health

Post-menopausal women are at increased risk of low BMD, osteoporosis, and fracture [32] The most common post-menopausal fractures are hip, vertebral, and wrist [33]. Fractures are associated with reduced quality of life [34] and increased mortality, with mortality rates of around 36% in the year following a hip fracture [35].

Suggested lifestyle interventions, for all post-menopausal women, to maintain BMD include weight-bearing exercise, smoking cessation, maintaining a healthy weight, and eating a balanced diet, whilst minimising alcohol intake [36].

Recommendations for screening for low BMD are guided by national and international guidelines. The UK National Osteoporosis Guideline [36] identifies risk factors for low BMD, including low BMI, history of fracture, parental hip fracture, smoking, glucocorticoid use, alcohol excess, and rheumatoid arthritis. Risk factors for low BMD can be combined into a Fracture Risk Assessment Tool (FRAX) score to guide further investigation including bone densitometry assessment with a DEXA scan [36]. Suggested pharmacological treatments for women diagnosed with low BMD include vitamin D, calcium, and bisphosphonates [36].

The Women's Health Initiative (WHI) calcium and vitamin D trial assigned 36,282 post-menopausal women to receive 1000 mg elemental calcium carbonate and 400 IU of vitamin D3 or placebo daily. After an average intervention period of 7.0 years, a non-significant trend towards a lower rate of hip fracture was seen in the calcium and vitamin D group (HR 0.62, 95% CI: 0.38–1.00). When these results were combined with additional WHI observational data, the finding reached statistical significance (HR 0.65, 95% CI: 0.44–0.98) [37]. However, unless women are calcium deficient, the increased cardiovascular risk associated with calcium supplementation likely outweighs the benefits at a population average risk level [38].

In several large RCTs, HRT has been shown to reduce the risk of fracture in women at the population average risk of fracture. In the WHI trial [39], women who were assigned to conjugated equine oestrogen, 0.625 mg/day, and medroxyprogesterone acetate, 2.5 mg/day, had fewer fractures than women assigned to placebo (HR 0.76; 95% CI: 0.69–0.83). A further WHI RCT in women without a uterus [40], receiving oestrogen-only HT, showed a similar effect, with a significantly reduced incidence of hip fracture (HR 0.61; 95% CI: 0.41–0.91).

However, whilst these results are strong evidence for the beneficial effect of HRT on bone health, they must be considered alongside consideration of the overall risks and benefits of HRT for women beyond the average age of menopause.

Heart health

There has been a longstanding recognition of gender-based difference in cardiovascular risk, mediated by oestrogen exposure, with premenopausal women experiencing lower rates of cardiovascular disease than men or post-menopausal women [41].

Early cohort studies reported associations between HT and a reduction in cardiovascular disease [42,43]. A further cohort showed a trend towards increased risk of cardiovascular disease in women with cardiovascular risk factors at the time of commencing treatment, with greater risk the greater number of cardiovascular risk factors [44].

Whilst these findings encouraged widespread HRT use for primary prevention of cardiac disease, including for women asymptomatic of menopausal symptoms, two significant RCTs were subsequently reported which reversed the initial enthusiasm for HT for heart health.

The Heart and Estrogen/progestin Replacement Study (HERS) study [45] was a large blinded randomised trial of HRT for secondary prevention of cardiovascular disease. A total of 2763 women, with coronary disease, younger than 80 (mean age 66.7) were randomised to receive 0.625 mg of conjugated equine oestrogens and 2.5 mg of medroxyprogesterone acetate or placebo on a daily basis. After an average of 4.1 years of follow-up, there was no significant difference in a composite outcome of myocardial infarct or coronary heart disease death (relative hazard (RH) 0.99; 95% CI: 0.80–1.22) or overall mortality (RH 1.08; 95% CI: 0.84–1.38).

The WHI RCT [46] sought to assess the risks and benefits of HT in 16,608 healthy post-menopausal women aged 50–79 years (average age 63). Participants received conjugated equine oestrogens, 0.625 mg, plus medroxyprogesterone acetate or placebo, 2.5 mg, on daily basis. A statistically significant increase in ischaemic heart disease (HR 1.29; 95% CI: 1.02–1.63) and total cardiovascular disease (arterial and venous) (HR 1.22; 95% CI: 1.09–1.36) was reported.

A criticism of the WHI trial is that it is not reflective of current practice limiting the applicability of its conclusions. The trial enrolled woman who were, on average, 10 years older than the average age of menopause and HT was given orally with a synthetic progestogen.

A 2020 Cochrane review [47] of 26 RCTs and 47 observational studies of menopausal HT found that, overall, menopausal HT was not associated with a change in all-cause mortality, cardiovascular disease, or myocardial infarct. However, analysis remained limited by the heterogeneity of formulation and route of HRT. Overall, the review concluded that HT should not be recommended for the prevention of cardiovascular or other chronic diseases.

Recent research has focused on the timing of HT initiation, with the hypothesis that HT may have beneficial cardiovascular effects if commenced in younger menopausal women, closer to the average age of menopause, before CVD becomes established [48]. In a randomised trial [49] of 643 women stratified into <6 years post-menopause and >10 years post-menopause, oral oestradiol was associated with less progression of atherosclerosis, as measured by the change in carotid intima-media thickness, than placebo when HT was initiated within 6 years of menopause but not when it was initiated 10 or more years after menopause.

Current practice and guidelines advocate a risk factor-based approach to primary prevention of cardiovascular disease, including smoking cessation, weight loss, regular exercise, blood pressure control, lipid management, and screening and management of diabetes [21].

Contraindications and risks of hormone therapy in women beyond the average age of menopause

For a significant number of women, HRT is contraindicated. Contraindications include a personal history of venous thromboembolism (VTE), active cardiovascular disease, and a personal history of breast cancer [21]. Women with a personal history of breast cancer, including early breast cancer, taking HRT, have a significantly increased risk of recurrence (RH 3.3; 95% CI: 1.5–7.4) [50].

There are also risks associated with HRT use. At standard doses, current oral HRT use increases the risk of VTE, although there is no increased risk associated with transdermal HRT [21,47].

HRT use has also been associated with an increased risk of ovarian cancer [51], and combined HRT with synthetic progestogens has been associated with an increased risk of breast cancer [52]. Micronised progesterone is, however, also available, which has not been associated with an increased

risk of breast cancer up to 5 years of use [53]. Progestogen can now also be administered through an intrauterine system which, theoretically, lessens the risk of breast cancer by avoiding systemic progestogen exposure.

Summary

The earlier the age at which menopause occurs the greater the risk of long-term impact on bone and heart health. Women with POI are at the greatest risk of cardiovascular disease, osteoporosis, and fracture and should receive HT, unless contraindicated, until they reach the average age of menopause. A healthy lifestyle should be encouraged, and Vitamin D supplementation should be considered. Early menopause has more recently been recognised as a risk factor for bone and cardiovascular disease; however, evidence for intervention in this population is lacking.

For women beyond the average age of menopause, although HT likely has a benefit for bone and possibly cardiovascular health, depending on the timing of initiation, the overall risk-benefit profile is such that HRT is not indicated for the promotion of bone and heart health alone. Current guidance and consensus are to limit HT to the treatment of menopausal symptoms at the lowest effective dose for the shortest possible time [21].

Women beyond the average age of menopause should, therefore, receive general lifestyle advice, screening, and primary prevention of bone and heart disease in line with national and international guidelines. Further studies are needed to better understand the risks and benefits of menopausal HT in this population using contemporary HRT formulations and routes of delivery.

Practice Points

- Earlier age of menopause is a risk factor for cardiovascular disease, osteoporosis, and fracture, women with POI and early menopause should be managed through modification of lifestyle, dietary supplements, and consideration of hormone therapy and non-hormonal therapies.
- Premature ovarian insufficiency is a sex steroid deficiency and an indication for hormone therapy with HRT or COCP.
- In women beyond the age of natural menopause, HRT should be used at the lowest effective dose for the shortest duration of time for symptoms and not initiated for bone or cardiovascular health.

Research Agenda

- The optimum formulation of hormone therapy (HRT vs COCP) and HRT route (oral vs transdermal) for treating POI is unknown. The POISE trial commencing in 24 UK sites from March 2022 seeks to answer this question.
- Studies should consider what role HRT plays in the management of early menopause by assessing the impact on bone and cardiovascular health and the overall risks and benefits of HRT in this population.
- Studies should consider what the optimum timing, formulation, and route of HRT are to maximise the benefits and limit the risks of HRT in women beyond the natural age of menopause.

Declaration of competing interest

ZN is a co-applicant on the NIHR funded POISE and BLUSH trials.
BAW none.
MCD is chief investigator for the NIHR funded POISE and BLUSH trials.

Acknowledgements

None.

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