Premature Ovarian Insufficiency: the need for evidence on the effectiveness of hormonal therapy

Abstract

Premature ovarian insufficiency – the loss of ovarian function before the age of 40, a decade before natural menopause - is a life-changing diagnosis for women. It causes significant short and long-term morbidity related to estrogen deficiency. The condition is managed by providing exogenous estrogen replacement, usually as the oral contraceptive pill or hormone therapy. These preparations have different estrogen formulations and may have differing benefits and risks. At present there are no robust data to inform clinical recommendations and women's decision-making about treatment that they may be taking for many years.

The POISE study has been designed to determine if hormone therapy is superior to combined oral contraceptives on important clinical outcomes and patient-reported symptoms, based on the hypothesis that hormone therapy provides more physiological continuous hormone supplementation with natural estrogens. The study is an open and pragmatic, parallel, randomized controlled trial. The primary outcome is absolute bone mineral density assessed by dual energy X-ray absorptiometry of the lumbar spine after two years of treatment. The study will also investigate cardiovascular markers, symptom relief and acceptability of treatment, and continue to collect long-term data on fractures and cardiovascular events. Results will inform future guidance on management of premature ovarian insufficiency.

Keywords: premature ovarian insufficiency; hormone therapy; reproductive health; bone health; cardiovascular health

Background

Premature ovarian insufficiency (POI) is a clinical syndrome defined by the loss of ovarian activity before the age of 40 years, which affects at least 1 in 100 women [1, 2]. POI is characterized by absent or very irregular periods. Many women experience menopause symptoms, such as hot flashes and night sweats, loss of libido, painful intercourse, cognitive and mood changes and fatigue. The ability to conceive naturally is greatly reduced. The impact

of symptoms and infertility can affect relationships, work and daily activities and cause psychological distress [3].

In the long-term, women with POI have health risks resulting from estrogen deficiency. Bone mineral loss puts them at high risk of osteoporosis and fractures with resulting morbidity [4, 5, 6]. They are more likely to experience early-onset cardiovascular disease (CVD) compared with women who experience menopause at the usual age [7, 8]. An increased risk of degenerative neurological disorders (dementia and Parkinson's disease) has been reported [9, 10]. Life expectancy is slightly reduced, largely due to cardiac disease [11, 12, 13]. Effective treatment of estrogen deficiency has potential benefits in all these domains.

Current management of POI

Women with POI are provided with advice regarding a healthy lifestyle for promotion of bone health and reduction of CVD risk, involving weight-bearing exercise, avoidance of smoking, maintenance of a normal body weight, and the recommended intake of calcium and vitamin D. However, lifestyle measures alone are insufficient, and all professional bodies recommend long-term systemic estrogen treatment at least until the typical age of menopause [14, 15, 16, 17, 18, 19]. No intervention has been shown to improve the chance of spontaneous conception [20, 21], but assisted reproduction using donated eggs has high success rates.

Estrogen replacement is the cornerstone of management. The aim of therapy is to control short-term symptoms and prevent long-term adverse outcomes [22]. The two treatments widely prescribed in the UK as estrogen replacement for women with POI are the combined oral contraceptive pill (COC) and hormone therapy (HT). COC may be seen as socially acceptable for young women and may reduce the stigma associated with menopause. It is also accessible, inexpensive, and provided free of cost to the patient in the UK. The COC, unlike most HT, provides contraceptive cover if this is required. However, HT provides physiological replacement of estrogen and might therefore be a better option for sustaining long-term health. Because women with POI are taking estrogen for many years, even small differences between treatments may have a large impact on long-term health outcomes, so it is important to establish definitively the effectiveness of HT compared with COC.

Outcomes of estrogen replacement

There is remarkably little evidence on the long-term outcomes of estrogen replacement in POI. Extrapolation from studies of menopausal treatments in mid-life [23] may not be applicable to young women; for example, the rate of fracture is influenced by the age-associated risk of falls. Adverse effects of treatment also differ in the younger age group; for example, thrombotic risk is less in younger age-groups, and breast cancer risk has not been shown to be increased by HT in women aged under 40.

A 2017 systematic review identified four randomized trials and eight cohort studies of women with idiopathic or iatrogenic POI treated with HT [24]. The review was limited by the quality of studies: all four randomized trials were at high risk of bias, and all studies were generally small and short-term. Meta-analysis was not possible because of the various hormonal preparations used and inconsistency of outcomes. In the systematic review, three studies reported a significant increase in bone mineral density (BMD), whilst two found no change with HT. A review of studies involving women with Turner's syndrome [25], with comparable limitations, reported a significant increase in BMD that differed by type of estrogen but not route of administration, and an increase in high-density lipoprotein plasma levels from oral compared with transdermal estrogen.

Protection against loss of BMD in the first years following diminishing ovarian activity is associated with a reduced risk of osteoporosis and fractures [26]. There is some limited evidence to suggest that HT is superior to COC in maintaining or increasing bone density in women with POI [27, 28]. However, the strength of this evidence is insufficient to change current clinical practice. A two-year open randomized trial of HRT vs COC, with non-randomized observation of women declining treatment, recruited 59 women of whom 36 completed the trial; both COC and HT were better than no treatment and the results favored HT in the outcome of lumbar spine bone density at 2 years (+0.05 g.cm2, 95% CI 0.007-0.092; p=.025) [28] . A cross-over randomized trial comparing physiological HT with COC found that HT lowered systolic and diastolic blood pressure [29] significantly compared with COC. However, only 18 of the 34 participants completed both of the 12-month trial periods.

Rationale for the POISE study

Growing health need

Research is needed now because there is an unmet need which is growing because of increasing awareness and diagnosis of POI. Improved cancer survival, especially childhood cancers, leads to women living with POI due to iatrogenic damage from chemotherapy and radiation. Cytotoxic therapies are also increasingly used for benign diseases (e.g. stem cell transplantation for haemoglobinopathies). With better identification of genetic predisposition to ovarian cancer, more women are choosing risk-reducing bilateral oophorectomy and the majority of these will take estrogen replacement. With increasing longevity, the long-term consequences of POI will be even more visible.

Lack of existing evidence

The National Institute for Health and Care Excellence (NICE) guideline recommendations on HT versus COC for POI were formulated using data from only two small prospective Randomized Controlled Trials (RCTs) [29, 30] and therefore NICE made a research recommendation: *Combined oral contraceptives are often prescribed when this might not be the best treatment in terms of quality of life and preservation of bone density and cardiovascular health. Short- and long-term outcomes of HT versus combined hormonal contraceptives in women with premature ovarian insufficiency therefore need to be investigated [17].* The European Society of Human Reproduction and Embryology (ESHRE) guideline on POI also noted that transdermal estradiol was suggested to be superior to oral estrogens, especially in women with underlying medical conditions, but that there was a lack of evidence on efficacy, patient satisfaction and side effects [15]. Indeed, in the literature to date, there is little to no information on important patient-centered outcomes, such as symptom control, and quality of life.

Clinician feedback

An online survey was conducted in the UK, distributed via the British Menopause Society (BMS) and British Fertility Society (BFS), which was completed by 66 clinicians, of whom 38% were menopause specialists, 14% were general gynecologists and 14% were general practitioners (GPs). Overall, 87% agreed or strongly agreed a RCT was required, with only one dissenter.

The proportion of clinicians currently recommending HT as the first choice was 64%, up from 56% in 2014 [31], although this proportion was higher amongst those whose practice was in infertility or endocrinology. GPs with an interest in women's health were equally likely to prescribe HT or COC, although this may be due to a responder bias as it is believed GPs in the community tend to prescribe COC.

Previous clinician surveys have shown equipoise between the two treatments, but specialist opinion in the UK is moving towards the use of HT whereas COC is more widely used in the community. Professional groups have also highlighted the need for evidence on the relative effectiveness of oral and transdermal HT in treatment of POI [32]. The time to do a trial is now, before opinion hardens and the moment of equipoise is lost.

Patient involvement

Women with POI often report delays in obtaining their diagnosis and difficulties in accessing appropriate medical advice and treatment [33]. Audit of specialist services indicates that women seek information on their treatment options [34].

A survey conducted by two of the largest patient groups in the UK was sent to women with POI and received responses from 242 women. The results showed a strong support for the planned study and that osteoporosis was women's greatest long-term concern. This led to the choice of BMD in the lumbar spine as the primary outcome. Mood changes and lack of energy were highlighted as the most troublesome symptoms and hence were also included as outcomes for the study.

The patient group formed during the design stage will continue to provide support and input throughout the duration of the study.

Objectives of the POISE study

The primary objective is to determine the relative effectiveness, in terms of BMD, of HT compared to COC. Additional objectives are to determine the relative effectiveness for

treatment of symptoms and quality of life, which are important outcomes for women. In addition, the study will examine the relative effectiveness of oral and transdermal route of administration of HT. Finally, the study aims to document the long-term outcomes of treatment.

Study design

POISE (Premature Ovarian Insufficiency Study of Effectiveness of hormonal therapy) is a multi-centre prospective, open, two-group parallel randomized controlled, superiority study performed in gynaecology clinics throughout the UK. Eligible women will be individually randomized on a 1:1 ratio to HT or COC treatment groups and requested to remain on their allocated treatment for a minimum duration of 2 years and if possible for 5 years.

The primary outcome is absolute BMD assessed by dual energy X-ray absorptiometry (DEXA) of the lumbar spine after two years of treatment. Recruitment of 480 women is required to achieve ≥ 90% power to detect a difference in mean of 0.05 g/cm^2 in lumbar spine BMD between HT and the COC. The trial should also have sufficient power to detect a mean difference of 0.075g/cm^2 between oral and transdermal HT preparations. Secondary outcomes include cardiovascular markers, symptom control, adverse effects and acceptability of treatment.

Eligibility for the study

The target population will be women with a diagnosis of POI, whether idiopathic, autoimmune, chromosomal or iatrogenic. Diagnosis will be based on menopausal symptoms, including no or infrequent periods, and elevated follicle stimulating hormone on two blood samples, taken 4-6 weeks apart[17]. Women aged between 18 and 40 years old at the time of randomization will be included in the study. The lower age limit of 18 years is to ensure that where applicable puberty induction has completed, achieving menarche and final height and the upper age of 40 years is based on the accepted definition of POI [17, 35]

Women intending to conceive within the next year will be excluded from entering the study. Women with POI have impaired fertility and are likely to require assisted conception using in vitro fertilization (IVF) with donor eggs. These procedures have to be planned and are

dependent on clinic timescales, donor availability, and funding, meaning that even women who may be starting to consider their options with regards to pregnancy at the point of entering the study are unlikely to become pregnant within a year. It is hoped by excluding women intending pregnancy within the first year the number of participants likely to remain on treatment for POI and for whom primary outcome data can be obtained at 2 years will be maximized. Any extension of the exclusion period beyond this is expected to further reduce loss of primary outcome and have a negative effect on recruitment with women being less certain of their future fertility plans rendering themselves ineligible.

Women already taking HT or COC treatment are eligible to take part in the study if they are willing to stop treatment for a washout period and potentially receive the same class of therapy again. The washout period will be for a minimum of 4 weeks, to allow time for their hormone levels to return to a pre-treatment level thus allowing a realistic assessment of symptoms and quality of life at baseline. BMD will be measured within 6 months prior to study entry.

Women with any contraindications to HT or COC, women taking other drugs affecting BMD and women receiving sex steroid hormones for puberty induction will be excluded.

Study treatments

The study is two-group design, with participants randomized to receive either HT or the COC. For HT the study mandates that HT is a continuous preparation with a daily dose of 17β-estradiol of 2mg orally or a 50μg patch or 1.5mg of gel transdermally (these are considered clinically equivalent). The formulation is not specified but the daily starting dose of estradiol is mandated. If a woman requires progestogen this may be given cyclically or continuously and the formulation will not be specified.

For COC the study mandates that the COC contains 30μg ethinylestradiol in a monophasic formulation. To reflect the fact that HT is taken continuously, an extended COC regimen (tricycling for 63 days followed by a 7-day hormone-free interval) will be used as the comparator.

The HT and COC doses are those widely used in treatment of POI in current practice and derived from professional guidance[36]. The dose and formulation of these study treatments can be modified at the discretion of the clinician, following discussion with the participant, with all changes recorded. Participants will remain in the study and will complete all remaining assessments and questionnaires as planned.

Choice of primary outcome

Absolute BMD in the lumbar spine has been chosen as the primary outcome, reflecting patient survey feedback and because the association between POI, bone loss and fracture risk is well-recognised [37]. Bone mineral loss consequent on estrogen deficiency in POI is detectable after one year [38] and women with POI are more likely to experience fracture[6]. Additionally, BMD measurement using DEXA scanning is accurate and reproducible, less likely to be affected by confounders than other measurements such as cardiovascular markers, easily available in clinical practice, and acceptable to patients. It is relevant to long-term definitive outcomes and associated with a hard endpoint (fracture).

Two years has been chosen as the primary end-point. In previous studies of estrogen replacement, response has been detectable at one year, with further improvement over time [39, 40]. Treatment-switching, other types of non-adherence (e.g. taking a break from therapy for fertility treatment), and loss to follow-up are likely to increase after 2 years. Whilst effectiveness over a longer follow-up period is certainly of interest, treatment effect at 2 years while the majority of participants are expected to still be taking allocated treatment will most usefully inform clinical practice.

Short and longer-term outcomes

Currently there is not a core outcome set for POI; the Core Outcome Set for Menopausal Symptoms (COMMA) is awaited [41]. A number of additional short- and longer-term outcomes will be assessed throughout the POISE study including the re-assessment of BMD at 5 years.

To determine the early impact on bone metabolism and cardiovascular health, blood samples will be collected from women at selected sites. This will be used to provide insight into the immediate response of bone turnover and measurement of fasting lipids, glucose, insulin, renal function, liver function and thrombotic markers will contribute to the assessment of cardiovascular effects of hormone treatment. Cardiovascular health will be assessed in all women by measurement of blood pressure and weight throughout the study. After 5 years, the study will continue to collect long term data on diagnoses of cancer, cardiovascular disease, cognitive impairment, bone fracture and mortality from centralized routine data.

Mood changes and lack of energy were highlighted as the most troublesome symptoms in the patient survey. The MENQOL-Intervention questionnaire [42] will be used throughout the study to measure the impact of treatment on vasomotor, physical, sexual and psychosocial domains.

Sexual activity is an important dimension of quality of life, particularly in this young population who may also have anxieties around fertility. The Sexual Activity Questionnaire (SAQ) [43] has been selected to report this outcome. POI symptoms can also impact women's work and social productivity, with economic implications. The Work Productivity and Activity Impairment (WPAI) questionnaire [44] will be tailored to POI and given to participants alongside the MENQOL and SAQ.

Data collection and analysis

Follow up timepoints have been timed to try and coincide with routine clinic visits to assist in the collection of outcome data (Figure 1). Participants will be given the option to complete study questionnaires electronically which will include questions relating to treatment adherence and adverse effects.

Analysis of the primary outcome measure (absolute lumbar spine BMD at 2 years) will be performed using a mixed effects model using all available follow-up data (1 year, 2 year), adjusted for the baseline BMD score and the minimisation variables, with recruiting site entered as a random effect. The model will include a treatment-by-time interaction to estimate the between group difference at each follow-up time-point with 2 years being the primary treatment

comparison. Participants will be analysed according to randomised group regardless of treatment actually received. Analysis will not be adjusted for dosage changes within HT/COC, nor for the type of progestogen. It is acknowledged that route of estrogen administration and progestogen type may also influence some secondary outcomes.

Long-term follow-up

The study will convert to an efficient, cohort study after 5 years follow-up, utilizing some patient reported outcomes but also routine data sources to collect outcomes for up to 10 years. This design acknowledges that adherence with the randomized allocation will decrease over time, due to patient preference and life circumstances, rendering the intention to treat comparison unlikely to sustain any differences between treatments, if such exist. However, continued follow-up of this cohort of young women will add valuable information on the long-term health outcomes of POI.

Summary

Better quality evidence is needed to optimize the management of young women with POI and improve their short-term quality of life and long-term morbidity and mortality. Estrogen treatment is given for many years: for some women, the choice between the COC or HRT may depend upon contraceptive needs, but if both are acceptable alternatives, we need to enable women to make an informed decision. The POISE study aims to identify the most effective treatment option for women with POI for relief of symptoms, quality of life and sexual function, and protection against long-term adverse consequences of estrogen deficiency. By informing and improving guidance for primary and secondary care clinicians, both in the UK and internationally, and through liaison with professional organizations and patient groups, POISE aims to have a major impact on the management of this chronic condition.

Potential conflict of interest

The authors report no conflict of interest.

Source of funding

This project is funded by the National Institute for Health Research (NIHR) HTA Programme (project reference NIHR128757). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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