Menopause 2

Optimising health after early menopause

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The typical age at menopause is 50–51 years in high-income countries. However, early menopause is common, with around 8% of women in high-income countries and 12% of women globally experiencing menopause between the ages of 40 years and 44 years. Menopause before age 40 years (premature ovarian insufficiency) affects an additional 2–4% of women. Both early menopause and premature ovarian insufficiency can herald an increased risk of chronic disease, including osteoporosis and cardiovascular disease. People who enter menopause at younger ages might also experience distress and feel less supported than those who reach menopause at the average age. Clinical practice guidelines are available for the diagnosis and management of premature ovarian insufficiency, but there is a gap in clinical guidance for early menopause. We argue that instead of distinct age thresholds being applied, early menopause should be seen on a spectrum between premature ovarian insufficiency and menopause at the average age. This Series paper presents evidence for the short-term and long-term consequences of early menopause. We offer a practical framework for clinicians to guide diagnosis and management of early menopause, which considers the nature and severity of symptoms, age and medical history, and the individual's wishes and priorities to optimise their quality of life and short-term and long-term health. We conclude with recommendations for future research to address key gaps in the current evidence.

Introduction

Menopause marks the permanent cessation of menstrual cycles, usually confirmed after 12 consecutive months of amenorrhoea. Natural menopause typically occurs at around age 50–51 years in high-income countries (HICs).[1,2] In clinical practice, the onset of menstrual changes and menopausal symptoms generally indicates the start of perimenopause or menopausal transition. While the menopause is marked by the final menstrual period, symptoms can persist for years into the postmenopause.[3] Early menopause is usually defined as occurring between the ages of 40 years and 44 years, whereas premature ovarian insufficiency indicates menopause before age 40 years. Both can be either spontaneous or iatrogenic, with iatrogenic causes including bilateral oophorectomy and chemotherapy or pelvic radiation treatment for cancer.

In this Series paper, we outline the evidence suggesting that both premature ovarian insufficiency and early menopause are linked with increased risk of chronic conditions in later life, such as cardiovascular disease and osteoporosis, although data are generally scarce around early menopause. Similarly, although consensus guidance exists for diagnosing and managing premature ovarian insufficiency, no guidance is available for early menopause. Given the scarcity of specific evidence regarding the long-term health implications of early menopause, we argue that early menopause should be considered as being on a spectrum between premature ovarian insufficiency and the typical age of menopause. To prevent patients from falling through this gap in care, we offer a practical framework to guide diagnosis and management of early menopause and identify evidence-based approaches for individuals either with or at risk of early menopause to optimise their health and quality of life in the short and long term. This process has identified key evidence gaps for further research and areas where people with early menopause require greater support.

Menopause happens to all people with typically functioning ovaries who reach the relevant age. We recognise that this population includes some transgender men and other gender-diverse people; therefore, in some instances, we have referred to "people" rather than "women" in order to be as accurate and inclusive as possible. However, since much published work refers to people experiencing menopause collectively as women and does not clarify how findings might apply to the specific needs of gender-diverse people, we have also used "women" in some instances, to avoid inappropriate generalisation. More information is needed about the experience of menopause in transgender men and gender-diverse people.[4]

Key messages

- Early menopause, defined as menopause between ages 40 years and 44 years, affects approximately 12% of women globally.
- Diagnosis of early menopause is often delayed and can cause emotional distress, particularly in individuals hoping to become pregnant.
- We propose that early menopause should be considered as being on a spectrum between premature ovarian insufficiency and menopause at the average age.
- We present a framework for the diagnosis and evaluation of early menopause for use in clinical practice.

Search strategy and selection criteria

We conducted a review of published articles up to July, 2023, on the PubMed, Embase, Scopus, and Cochrane

databases. The search was restricted to studies published in English with the following keywords and medical subject heading terms in PubMed (MeSH) and Embase (Emtree): "menopause"; "premature menopause"; "premature ovarian insufficiency"; "early menopause"; "menopausal symptoms"; "vasomotor symptoms"; "menopausal hormone therapy"; "hormone therapy"; "hormone replacement therapy"; and "non-hormonal therapy". For long-term health outcomes, we combined these terms with "chronic disease", "non-communicable disease", "osteoporosis", "fracture", "cardiovascular disease", "heart disease", "stroke", "depression", "dementia", "cancer", and "mortality". We prioritised the most robust evidence from clinical trials, systematic reviews, meta-analyses, and pooled studies. We also reviewed guidelines and position statements from the period 2010–23 on menopause management.

Background

Biology

The pool of primordial follicles is established in utero, with a peak of 6–7 million oocytes at 16–20 weeks' gestation.[5] Most follicles undergo atresia and decline to approximately 700 000 normal oocytes at birth, approximately 300 000 oocytes by menarche, and fewer than 1000 oocytes at menopause.[5–7] Both the size of the pool of primordial follicles and the rate of follicular atresia probably determine the timing of menopause, but the underlying mechanisms regulating these factors are poorly understood.[8–10]

Prevalence of early menopause and premature ovarian insufficiency

Estimates for the prevalence of spontaneous early menopause and premature ovarian insufficiency vary substantially according to the population studied. The International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) pooled individual data from over 50 000 women with spontaneous menopause from nine studies in HICs to show that 7·6% of women had early menopause and 2% had premature ovarian insufficiency.[11] Global estimates, from a meta-analysis of 31 studies including over 150 000 women with spontaneous menopause, show a higher prevalence of 12·2% (95% CI 10·5–14) for early menopause, and 3·7% (3·1–4·3) for premature ovarian insufficiency, potentially reflecting a lower mean age at menopause in low-income and middle-income countries (LMICs).[12] A national study from China found a prevalence of 10·9% for spontaneous early menopause and a prevalence of 3·2% for premature ovarian insufficiency.[13] The prevalence in India is even higher at 20·2% for early menopause, with two prevalence estimates for premature ovarian insufficiency of 1·5% and 2·1%,[14,15] and an average age at menopause of 46 years.[16] Another reason for differences in prevalence might be the age limits used for observational studies on menopause (eg, arbitrarily setting a minimum age of 35 years for inclusion in a study will exclude some individuals who had premature ovarian insufficiency at an earlier age).[17] Although secular trends in many countries show an increase in the age at menopause is evident in many countries,[18–20] global evidence is scarce regarding trends in the prevalence of premature ovarian insufficiency and early menopause.[12]

A substantial proportion of cases of premature ovarian insufficiency and early menopause have iatrogenic causes, with wide variations according to gynaecological surgical practices in different countries. A national study in India reported that the prevalence of iatrogenic premature ovarian insufficiency was 1·7%, solely due to bilateral oophorectomy.[14] By contrast, a registry-based study (n=1 036 918) from Sweden reported an overall prevalence of 1·9% for spontaneous and iatrogenic premature ovarian insufficiency and, of these women, 10·7% had iatrogenic premature ovarian insufficiency.[21] As survival rates for young patients with cancer increase, iatrogenic premature ovarian insufficiency and early menopause will probably increase secondary to chemotherapy and radiotherapy.[22]

Risk factors for spontaneous early menopause and premature ovarian insufficiency

Bilateral oophorectomy in premenopausal individuals will induce surgical menopause. Unilateral oophorectomy is also associated with a younger age at menopause, on average 1·8 years younger compared with people with intact ovaries.[23] Hysterectomy alone with ovarian preservation is associated with menopause 1·9 years earlier than in women who do not have this procedure.[24]

The mechanisms underlying spontaneous early menopause and premature ovarian insufficiency are poorly understood. Studies in HICs indicate that genetic factors account for roughly half of the variation in age at natural menopause, estimated at 42% of variation in the UK, 44% in the Netherlands, and 52% in the USA.[25–27] These data are supported by retrospective studies reporting a six-fold to eight-fold increase in the risk of menopause before age 45 years for women with a maternal history of early menopause or premature ovarian insufficiency.[28,29] Recent genome-wide association studies have also identified specific genetic factors linked with the timing of menopause that provide insights on potential causal pathways for ovarian ageing.[30]

Nulliparity is associated with early menopause and premature ovarian insufficiency, although the direction of this relationship is uncertain since there could be shared factors that affect both nulliparity and age at menopause. The InterLACE consortium found (in a pooled analysis of 51 450 women in nine studies) that nulliparous women were twice as likely to have premature ovarian insufficiency and 30% more likely to have early menopause than women with two or more children.[11] Nulliparous women who also had early

menarche (before age 12 years) had a five-fold increased risk of premature ovarian insufficiency and double the risk of early menopause, compared with women who had menarche at 12 years or older with two or more children.[11] In studies from LMICs, women in India[31] and China[13] with premature ovarian insufficiency were more likely to have had an earlier age when first giving birth and a shorter duration of breastfeeding, although again the causal pathways at work remain unclear.

Globally, cigarette smoking is a well established risk factor for early menopause.[13,14,32,33] InterLACE reported that participants who currently smoked were twice as likely to have premature ovarian insufficiency as those who had never smoked, and 80% more likely to have early menopause.[34] There was a consistent dose–response relationship for participants who currently smoked and those who formerly smoked (duration and cumulative dose), but those who stopped smoking at least 10 years before menopause had a similar risk of early menopause to individuals who had never smoked. The prevalence of smoking has declined markedly in many HICs over recent decades, but the effect of this decline on rates of early menopause and premature ovarian insufficiency has yet to be documented.

Implications of early menopause and premature ovarian insufficiency

Menopausal symptoms

The effect of menopause and its symptoms on individuals will be highly contextual.[35] Common symptoms directly attributable to menopause include vasomotor symptoms (including hot flushes and night sweats), sleep disturbance, and vaginal dryness.[36–38] In addition, some studies have identified depressed mood and aches and joint pain,[39] with south Asian and Chinese women (living in HICs) more likely to report joint pain.[40,41] The prevalence of moderate-to-severe vasomotor symptoms in natural menopause also varies considerably across populations, with prevalence findings from an international survey ranging from 40% in Europe and 34% in the USA to 16% in Japan.[42] Whether menopausal symptoms following early menopause and premature ovarian insufficiency differ in nature, severity, or duration compared with symptoms following menopause at the average age is unknown. For iatrogenic early menopause and premature ovarian insufficiency, the abrupt cessation of oestrogen is thought to lead to more severe symptoms.[43] However, in the only prospective controlled study of surgical menopause, vasomotor symptoms at 12 months affected 82% of individuals who did not take menopausal hormone therapy (MHT), including 68% who reported mild symptoms, suggesting that severe vasomotor symptoms are not inevitable after surgical menopause.[44]

The diagnosis of menopause from 5 years to a decade or more earlier than expected can carry stigma and might affect self-esteem.[45] Symptoms in the years leading up to menopause can affect intimate relationships and, for some people, the loss of fertility can be especially distressing. The experience of menopausal symptoms can affect not only an individual's quality of life but also their effectiveness in the workplace, with economic consequences due to lower workforce participation rates.[46–48] For example, a 2022 study from the UK found that women with early menopause had lower labour market participation at age 50 years than other women.[47]

For individuals with iatrogenic early menopause or premature ovarian insufficiency, the change in circulating sex steroid concentrations occurs suddenly, and often in the context of treatment burden (eg, from chemotherapy) for a recent disease diagnosis, such as breast cancer. Some studies of women with iatrogenic premature ovarian insufficiency report low social support,[49] moderate-to-severe emotional distress,[50] and high rates of depression.[51] Although studies are scarce, some of these adverse outcomes could plausibly apply to people with menopause in their early 40s.

Longer-term health implications

Bone health

Oestrogens contribute to the regulation of bone resorption and formation.[10] Women with premature ovarian insufficiency and early menopause are at increased risk of fragility fractures. A cross-sectional study of 4725 women from the Netherlands found that those with spontaneous early menopause or premature ovarian insufficiency had a 50% higher overall fracture rate up to age 80 years compared with those with menopause at the average age.[52] Similar findings are reported in prospective studies from Sweden (osteoporosis and fragility fracture by age 77 years)[53] and the Netherlands (vertebral fractures at age 62 years).[54]

Cardiovascular disease

Since the late 1980s, cardiovascular risk has been thought to be influenced by oestrogen exposure, contributing to gender differences in the incidence of cardiovascular disease. People with early menopause or premature ovarian insufficiency are at increased risk of coronary heart disease, stroke, and cardiovascular disease-related mortality.[55–57] Pooled data from 15 studies (from Australia, Japan, Scandinavia, the UK, and the USA) show that women with spontaneous early menopause had a 30% increased risk (and women with premature ovarian insufficiency had a 55% increased risk) of a cardiovascular disease event compared with individuals with menopause at age 50–54 years, although these risks attenuated over time, with no difference found by age 70 years.[58] Women with surgical early menopause or premature ovarian insufficiency were at an even higher relative risk (60% and 90%, respectively) for cardiovascular disease events.[59] Findings from the UK Biobank study show both spontaneous and iatrogenic premature ovarian insufficiency are associated with increased risk of

hyperlipidaemia, hypertension, and type 2 diabetes, compared with menopause at the average age.[60]

Mental health and neurological conditions

Unfortunately, little is known about early menopause and mental health. Premature ovarian insufficiency might negatively affect mental health in the short and long term. A meta-analysis of four studies with 3033 women with spontaneous premature ovarian insufficiency found that they were twice as likely to develop depression compared with women with menopause at age 40 years or older.[61] In a retrospective UK study of 136 women with premature ovarian insufficiency, 78% reported a negative effect on their self-image and confidence and lower general health, mental wellbeing, and sexual satisfaction compared with before their diagnosis.[62] No evidence for the mental health effects of early menopause was identified in our review of the literature.

Surgical menopause at or before age 45 years has been associated with higher risk of dementia and faster overall cognitive decline,[63] but the specific relationship between early menopause and premature ovarian insufficiency and neurological conditions is less clear. A cohort study based on the Korean National Health Insurance System database (with prospective data on 4·7 million post-menopausal women) reported that early menopause or premature ovarian insufficiency was associated with all-cause dementia, with the risk declining as age at menopause increased.[64] In a French population cohort study (n=4868), however, no association was found between early menopause and a decline in cognitive function in later life (tested across multiple domains), whereas both surgical and spontaneous premature ovarian insufficiency were linked with a decline in verbal fluency and visual memory.[65]

Oestrogen-sensitive cancers

Breast cancer is the most common cancer in HICs, and most breast cancers are oestrogen-sensitive. Women with menopause before age 45 years are at lower relative risk of breast cancer (by 27% for early menopause and 33% for premature ovarian insufficiency),[66,67] and at lower risk for endometrial and ovarian cancers compared with women with menopause at age 50–54 years.[10,66]

Life expectancy

Overall the evidence indicates that earlier natural menopause is associated with higher all-cause mortality,[68] and this risk is greater with premature ovarian insufficiency than with early menopause. A meta-analysis of seven studies found that premature ovarian insufficiency was linked with a 40% increased relative risk (RR; 95% CI 1·10–1·77) of all-cause mortality, whereas for women with early menopause the association was limited to a small increased risk of ischaemic heart disease (RR 1·09, 1·00–1·18).[69] A large US study of women with natural menopause who did not smoke and had not had MHT[70] found that early menopause was linked with a 9% increased relative risk of death due to coronary heart disease and a 19% increased risk for respiratory disease, which were the two main contributors to a small but identifiable increased risk of all-cause mortality (RR 1·04, 95% CI 1·00–1·08). Similarly, a large Canadian study of prophylactic bilateral oophorectomy[71] found that women with iatrogenic early menopause had a higher likelihood of all-cause mortality (hazard ratio 1·16, 95% CI 1·04–1·30) and this association increased further for those with iatrogenic premature ovarian insufficiency (1·31, 1·18–1·45) compared with women who had this surgery at age 50–55 years. This study included women both with and without hormone therapy, and for both the early menopause and premature ovarian insufficiency groups the association with all-cause mortality was largely driven by deaths from causes other than cancer.[71]

Diagnosis and management of early menopause

The initial challenge for health professionals is to make the diagnosis of early menopause and to explain the condition and potential consequences. Most international guidelines advise offering MHT to individuals without contraindications following early menopause.[72–74] MHT is highly effective for short-term symptoms, but it has not been shown to improve long-term health outcomes. Early menopause has implications for fertility, contraception, and potentially for sexual function. Addressing the psychological needs of people with early menopause and offering long-term follow-up and support is crucial.[45,50,75]

Diagnosis

The diagnosis of early menopause might not be straightforward unless a clear iatrogenic cause is identified. In individuals with spontaneous early menopause presenting with secondary amenorrhoea, vasomotor symptoms, or both, investigations are indicated to establish the diagnosis.[76] Some people will be amenorrhoeic after hysterectomy with ovarian conservation, or while taking long-acting progestogen contraception, so the diagnosis is made on the basis of symptoms and biochemistry. There are no consensus criteria for diagnosing early menopause after cancer treatment, which can cause transient or fluctuating symptoms.

Although evidence on early menopause diagnoses is scarce, some studies report that people with premature ovarian insufficiency might experience delayed diagnosis. In a US study,[77] more than half of women with spontaneous premature ovarian insufficiency reported seeing three different clinicians, and for 25% of the women, establishing a diagnosis took over 5 years. Similarly, for 25% of Australian women with premature ovarian insufficiency, diagnosis was delayed for more than 2 years and most saw at least two clinicians.[51] As a result, some individuals might be categorised as having early menopause rather than premature ovarian insufficiency. Most women receiving a diagnosis of spontaneous premature ovarian insufficiency

are dissatisfied with the clinical interaction,[50] but we do not know the views of people diagnosed with early menopause. For both groups, navigating treatment entails further complexity as patients grapple with the risks and efficacy of hormonal and non-hormonal therapies.[78]

Treatment options

Lifestyle interventions

Advice on healthy lifestyles should be a routine part of clinical interactions with health professionals and is particularly relevant for people experiencing early menopause or premature ovarian insufficiency. In these patients, the aims should be reducing cardiovascular risk (eg, through smoking cessation) and promoting bone health (eg, through weight-bearing exercise and a calcium-rich diet).[2]

Non-hormonal treatments

Complementary and alternative remedies are widely marketed and used for vasomotor symptoms.[79] There is a lack of evidence for the efficacy of herbal treatments and dietary supplements to relieve vasomotor symptoms, with the possible exception of isoflavones and black cohosh, and findings of studies might not translate into clinical practice, as preparations vary considerably.[76,80] Psychological interventions, particularly cognitive behavioural therapy, reduce the effects of vasomotor symptoms and improve sleep and mood disturbance generally associated with menopause.[76,81] A randomised control trial (RCT) has shown the efficacy of mindfulness for reducing hot flashes and improving quality of life for women with premature ovarian insufficiency.[82]

Non-hormonal pharmacological treatments[83] are offered to people who have contraindications to oestrogen treatment (eg, individuals with oestrogen-sensitive breast cancer).[84] For vasomotor symptoms, the most widely used treatments are selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors.[83] Gabapentinoids and oxybutynin are less widely used, but neurokinin-3 receptor antagonists, such as fezolinetant, show promise in reducing moderate-to-severe vasomotor symptoms associated with menopause.[85,86]

Pharmacological treatments for women with low bone mineral density include vitamin D and calcium supplements,[87,88] but the value of these interventions has not been explored in young women and is likely to vary in different populations according to ethnicity and dietary habits. Bisphosphonates are not generally used in spontaneous early menopause but can be given in oncology practice, particularly when oestrogen is contraindicated.[89]

Hormonal treatments

In the general population, MHT is highly effective in relieving some symptoms of menopause with a dose-dependent response, and it is generally prescribed as physiological oestradiol-based preparations.[80] Oestrogen is given in combination with progestogen to avoid unscheduled bleeding and the risk of endometrial hyperplasia, unless individuals have undergone hysterectomy. A combined oral contraceptive might be a convenient and acceptable preparation for young people with premature ovarian insufficiency, although the relative efficacy of this treatment compared with MHT, for both short-term and long-term outcomes, is unclear. Serious adverse effects from a combined oral contraceptive are rare but increase with age,[75,90] so MHT is preferred for early menopause. Systemic treatment can be given orally or transdermally, the latter having metabolic advantages. Topical (intravaginal) treatment is effective in relieving urogenital symptoms and might be required in addition to MHT;[75] endometrial protection is not required with topical oestrogen.

Oestrogen replacement is recommended following both premature ovarian insufficiency and early menopause until the typical age of menopause,[74,91] but the optimum duration of use is uncertain. Although oestrogen treatment is often initiated for symptom control, longer-term use is advised in the expectation of improved health outcomes. The adverse health effects of early menopause are less severe than those of premature ovarian insufficiency, as would be expected given the relative duration and degree of oestrogen loss.[58,68,92] There might, therefore, be fewer potential health benefits from MHT for early menopause than for premature ovarian insufficiency. Moreover, these treatment benefits need to be set against the risks of adverse effects, which are related to age.

Prevention of osteoporosis and the maintenance of bone health is a major rationale for the use of MHT following premature ovarian insufficiency.[2] Clinical guidance is extrapolated from the Women's Health Initiative (WHI) data, which showed that MHT in older postmenopausal women improves bone mineral density and reduces vertebral and hip fracture risk.[93,94] However, fractures are uncommon in women younger than 45 years (the association between low bone mineral density and fracture is age-dependent, mediated by falls).[95] There are a few small prospective studies showing the benefit of MHT on bone health in premature ovarian insufficiency.[2] However, bone health in early menopause specifically has not been sufficiently studied.

Early cohort studies suggested that MHT might have a role in the prevention of cardiovascular disease in postmenopausal women but this role was not confirmed by large randomised trials.[96,97] The largest trial (the WHI) showed an increase in the risk of ischaemic heart disease and stroke in people taking oestrogen.[97,98] However, a subgroup analysis of women aged 50–59 years showed some risk reduction in coronary heart disease and mortality with MHT.[99,100] Although a Cochrane review found reduced risk for coronary heart disease for women who started MHT less than 10 years after the menopause (RR 0·52, 95% CI 0·29–0·96), it confirmed an increased risk of venous thromboembolism (1·74, 1·11–2·73), and

was unable to support the use of MHT for primary or secondary prevention of coronary heart disease.[99] Findings from the analysis of pooled data from InterLACE[59] only detected a reduction in risk in cardiovascular disease for women with MHT after surgical early menopause or premature ovarian insufficiency, but not for those with spontaneous early menopause and premature ovarian insufficiency. A study of women in the USA with bilateral oophorectomy before age 45 years[101] found that those receiving MHT had no evidence of increased mortality from cardiovascular disease compared with women from the same age group who did not have bilateral oophorectomy, whereas those who had not taken MHT were at increased risk (hazard ratio [HR] 1·84, 95% CI 1·27–2·68), compared with women from the same age group who did not have bilateral oophorectomy.[101] There are no RCTs of MHT, however, in women with early menopause or premature ovarian insufficiency.

Concern was raised by the Women's Health Initiative study's findings of an increased risk of dementia in older users of MHT, which might reflect the thrombotic risk of MHT.[102] There is very little information, however, on the effect of oestrogen treatment on cognitive function in younger people with early menopause or premature ovarian insufficiency. A population-based cohort study of women aged at least 65 years found that both spontaneous and surgical premature ovarian insufficiency were associated with poorer cognitive function in later life,[65] but found no evidence of a cognitive benefit from MHT.

Risk of breast cancer is slightly increased in healthy premenopausal women with long-term use of a combined oral contraceptive[103,104] and is increased in older postmenopausal women taking combined MHT.[105,106] However, the type of MHT is important: long-term follow-up from participants in the Women's Health Initiative study showed a reduction in breast cancer risk with previous use of oestrogen alone, but an increased risk with previous use of combined MHT.[107] Whether the type of progestogen affects breast cancer risk is uncertain.[108] Breast cancer risk increases with both age and the duration of MHT use. For women with early menopause starting MHT aged 40–44 years, observational data suggest that the increase in breast cancer risk is similar to that in women with menopause at the average age.[106] Few women in long-term observational studies started MHT before the age of 40 years, although these women are at increased risk after more than 15 years of MHT use.[106] There are no randomised data relating to breast cancer risk in early menopause or premature ovarian insufficiency.

Optimising health outcomes for women with early menopause

Clinical guidelines

Existing clinical practice guidelines for menopause management rarely address early menopause. A systematic review of 22 current guidelines[109] found that some include premature ovarian insufficiency but have little advice in relation to early menopause. For example, the UK National Institute for Health and Care Excellence guidelines on the diagnosis and management of menopause include some recommendations on premature ovarian insufficiency and address the diagnosis of early menopause but not its management.[76] The European Society of Human Reproduction and Embryology published specific premature ovarian insufficiency guidelines in 2015, but has no clinical guidelines for early menopause.[2]

In 2014, Jane and Davis[110] produced a practitioner toolkit for managing menopause in women aged 40 years and older on the basis of recommendations in position statements and practice guidelines. Building on this model, we have, in turn, developed a practical clinical framework to assist with diagnosis and management of early menopause (figure).

Management recommendations are limited by the scarcity of evidence relating specifically to early menopause. However, the boundaries between typical menopause, early menopause, and premature ovarian insufficiency are arbitrary, and age cutoffs are often crossed in clinical practice during the lengthy process of menopause transition. Early menopause occupies a zone between premature ovarian insufficiency and menopause at the typical age, so extrapolating from existing studies in these groups while awaiting further targeted studies seems reasonable.

People with early menopause should be aware of the potential long-term risks, including osteoporosis, fractures, and cardiovascular disease. Ensuring this awareness provides an opportunity for a broader discussion on the key role of health behaviours (eg, smoking cessation, healthy diet, healthy bodyweight, and exercise) for cardiometabolic health and maintenance of bone density. Clinicians might also see opportunities to address specific risk factors.

Individualised care

Considerable scope exists to provide a more holistic and individualised approach to the management of early menopause. This approach could be part of a broader attitude to reproductive health that ideally engages with individuals, especially those at risk of early menopause, well before the menopausal transition.[111] For example, discussion of early menopause should be part of consultations with individuals with *BRCA1/2* mutations, which place them at high risk of breast and ovarian cancer, who might be planning the timing of risk-reducing bilateral salpingo-oophorectomy.

Improving community information on early menopause and premature ovarian insufficiency and natural menopause could aid prompt diagnoses. Social media is often a primary source of health information for women[112] and there is a need for objective and evidence-based online resources. For example, a co-designed digital health resource for women with early menopause or premature ovarian insufficiency and health practitioners targets these unmet needs for information

and support management.[113] Clinical guidelines should now routinely be translated into lay terms, allowing patients direct access to high-quality information.

Future recommendations

Reducing the risk of early menopause

The incidence of iatrogenic early menopause can be reduced by changes in the management of benign gynaecological conditions (eg, hysterectomy rates have reduced since the introduction of intrauterine progestogen devices), and by modifications in oncology practice (eg, the use of less gonadotoxic chemotherapy regimens).

Research priorities

There are substantial gaps in our knowledge of the cause, natural history, and optimal management of early

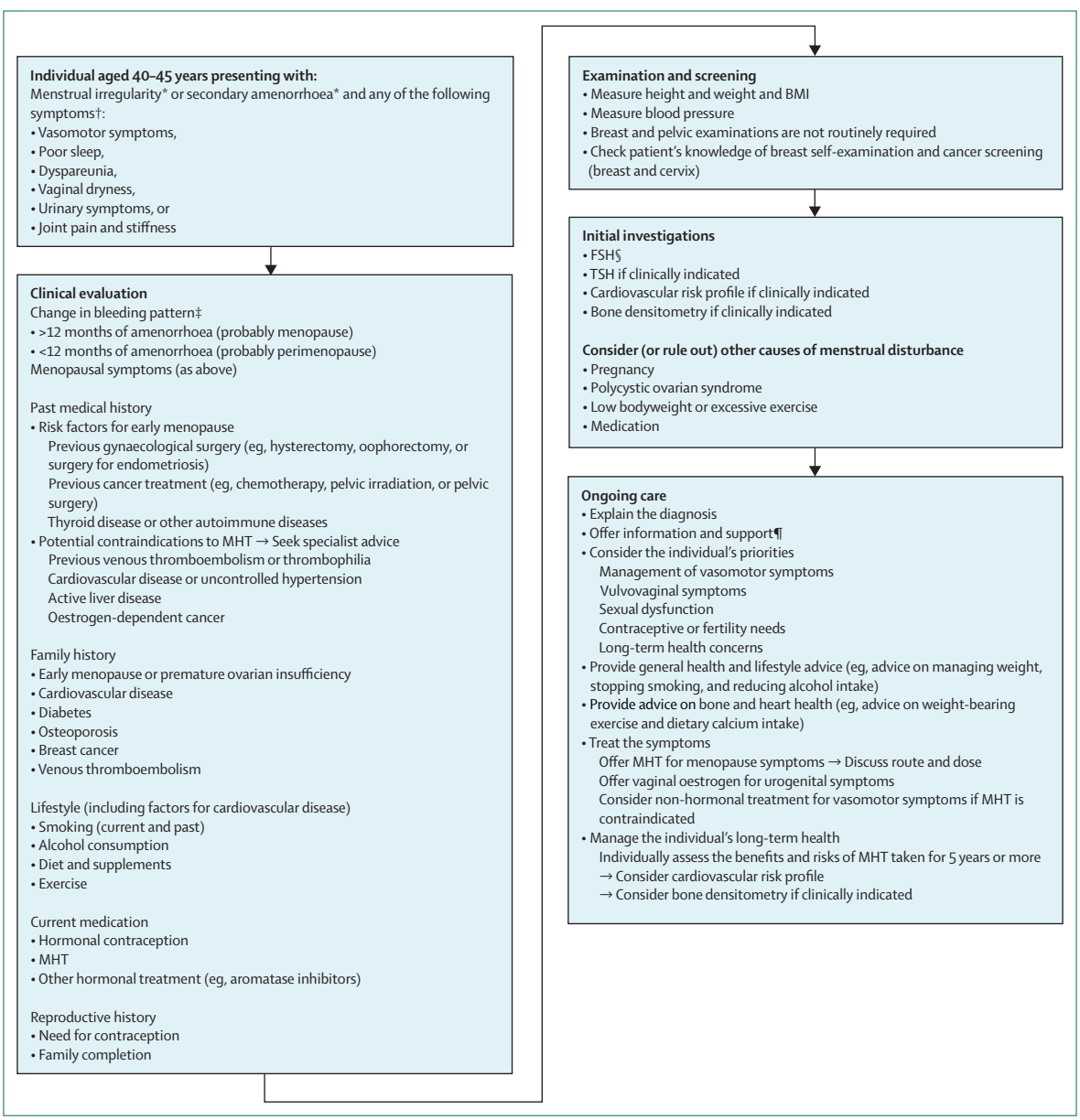

Figure: **Practical framework for diagnosis, evaluation, and management of early menopause**
FSH=follicle-stimulating hormone. MHT=menopausal hormone therapy. TSH=thyroid-stimulating hormone. *Might not be apparent if the individual is taking hormonal contraception or has had a previous hysterectomy. †Symptoms of menopause can vary between individuals and in the same individual over time. Some people have no symptoms apart from cessation of menstruation. Symptoms such as mood disturbances, anxiety, brain fog, palpitations, and low libido are common but might not be attributable to menopause. ‡Intermenstrual or post-coital bleeding needs further investigation; also consider further investigation for heavier bleeding. §A raised FSH concentration is confirmation of a diagnosis, but a typical FSH concentration does not rule out perimenopause. If uncertain, repeat testing might be needed. This test can guide contraceptive needs. FSH is of no value while the individual is taking combined oral contraception, and of limited value if they are taking any hormonal treatment. ¶For example, Healthtalk Australia's digital resource on early menopause and the Daisy Network

For more on **Healthtalk Australia's digital resource on early menopause** see https://www.healthtalkaustralia.org/early-menopause-experiences-and-perspectives-of-women-and-health-professionals/

For more on the **Daisy Network** see https://www.daisynetwork.org/

menopause (panel). There are also important evidence gaps for both premature ovarian insufficiency and early menopause in LMICs, particular around under-reporting.[114,115] Governments should be encouraged to look beyond reproductive and child health programmes and consider the health consequences of ageing and management of associated conditions, such as menopause.

With the shift to routine digital health management, there might be new opportunities to collect detailed data on the diagnosis and management of early menopause. Similarly, the rise of digital health hubs on early menopause and premature ovarian insufficiency provides considerable research opportunities to engage with people on their menopausal experiences and evaluate the effect of information strategies on subsequent treatment choices.

In summary, approximately 8–10% of women globally experience early menopause, but the causes, natural history, and potential long-term health outcomes are poorly understood. In particular, whether MHT confers long-term health benefits for people with early menopause is unclear. Information on early menopause is largely extrapolated from existing evidence on premature ovarian insufficiency or from studies of menopause at the average age. Interpretation of this evidence assumes a spectrum of age at menopause, with consequences reflecting the timing and duration of oestrogen withdrawal. Unfortunately, there is insufficient evidence for current guidance advising MHT until the average age at menopause (ie, 50 years) and so treatment should be considered on an individualised basis. Clinicians and researchers should work with people experiencing early menopause to establish their personal priorities for research and wishes for treatment.

Panel: Research priorities to improve our knowledge of early menopause

More information is needed on:

- People's experiences of early menopause diagnoses, particularly how to reduce diagnostic delay to inform effective interventions
- The priorities of people who experience the menopause transition for research gaps in early menopause to guide the future research agenda; in collaboration with the James Lind Alliance, a Menopause Priority Setting Partnership is underway, including people with premature ovarian insufficiency and early menopause
- The views of patients on the optimal management of early menopause, including unmet needs around diagnosis and treatment
- The causes and natural history of early menopause to establish who is at risk
- Long-term health outcomes following early menopause, which need to be assessed in prospective studies to inform prevention and early diagnosis of adverse outcomes
- Early menopause across diverse populations, including in low-income and middle-income countries
- The safety and effectiveness of treatment options (including but not limited to menopausal hormone therapy) following early menopause, in particular in managing menopausal symptoms, improving quality of life, and reducing chronic disease risks in both the short and long term
- The effectiveness of interventions for people with early menopause in improving health behaviours that reduce the potential risk of cardiovascular disease and poor bone health

Contributors

MH and GDM conceived and designed this Series paper. GDM wrote the initial draft and was responsible for revising this draft on the basis of comments from all other authors. MCD, SH, H-FC, SR, KM, and MH made substantial contributions to the conception or design of this Series paper; or to the acquisition, analysis, or interpretation of data. MCD, SH, H-FC, SR, KM, and MH made substantial contributions to drafting this Series paper or revising it critically for important intellectual content; and gave their final approval of the submitted version. MCD, SH, H-FC, SR, KM, and MH agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MH is responsible for the final approval of this manuscript.

Declaration of interests

MH declares salary funding from the Australian National Health and Medical Research Council, support for meeting attendance from the UK National Institute for Health and Care Excellence, and the following roles: principal investigator for a clinical trial of salpingectomy vs salpingo-oophorectomy for prevention of ovarian cancer (TUBA-WISP II); board member for Breastscreen Victoria; editor for the Cochrane Collaboration; recipient of a fellowship from the Lundbeck Foundation (2022-23); site investigator for a clinical trial of a non-hormonal agent (Q-122) for vasomotor symptoms in patients with breast cancer (QUE Oncology, 2020-22); and site investigator for a clinical trial of a medical device for treating vaginal dryness (Madorra). All other authors declare no competing interests.

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