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Long-term health consequences of premature or early menopause and considerations for management

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Abstract

Aim—To review the current evidence concerning the long-term harmful effects of premature or early menopause, and to discuss some of the clinical implications.

Material and methods—Narrative review of the literature.

Results—Women undergoing premature or early menopause, either following bilateral salpingo-oophorectomy or because of primary ovarian insufficiency, experience the early loss of estrogen and other ovarian hormones. The long-term consequences of premature or early menopause include adverse effects on cognition, mood, cardiovascular, bone, and sexual health, as well as an increased risk of early mortality. The use of hormone therapy has been shown to lessen some, although not all of these risks. Therefore, multiple medical societies recommend providing hormone therapy at least until the natural age of menopause. It is important to individualize hormone therapy for women with early estrogen deficiency, and higher dosages may be needed to approximate physiological concentrations found in premenopausal women. It is also important to address the psychological impact of early menopause and to review the options for fertility and the potential need for contraception, if the ovaries are intact.

Conclusions—Women who undergo premature or early menopause should receive individualized hormone therapy and counseling.

Keywords

premature menopause; early menopause; estrogen; oophorectomy; hormone therapy

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INTRODUCTION

Accumulating evidence suggests that bilateral salpingo-oophorectomy (BSO) performed before the natural age of menopause is associated with adverse long-term health consequences, including increased overall mortality, coronary heart disease (CHD), dementia, parkinsonism, osteoporosis, mood disorders, and sexual dysfunction, among others.^{1–3} Yet, a significant percentage of women still undergo elective BSO at the time of hysterectomy for benign disease (23% of women 40–44 years and 45% of women 45–49 years).^{4–6}

Primary ovarian insufficiency (POI) is another condition causing the loss of ovarian function prior to the natural age of menopause. While the majority of women experience menopause between the ages of 45 and 55 years, approximately 5% of women will enter menopause early, between the ages of 40 and 45 years.^{7, 8} Menopause occurring before the age of 40 years is described as premature and occurs in approximately 1% of women.⁹ This early loss of ovarian function may relate to a number of etiologies, including genetic disorders, autoimmune disorders, infections, or iatrogenic causes related to chemotherapy, radiation, or surgery.¹⁰ The most common cause of premature or early menopause is surgery to remove the ovaries. Natural menopause occurring prematurely or early is often a gradual process; by contrast, the surgical removal of both ovaries results in an abrupt loss of ovarian hormones, including not only estrogen, but also progesterone and testosterone, and disruption of the hypothalamic-pituitary-gonadal axis.^{11–13}

This article reviews the long-term health consequences associated with premature or early menopause and the role of hormone therapy (HT) in mitigating these effects. Because data on long-term health outcomes in women with POI are limited, we will focus on early menopause induced by BSO, but we will include data specific to POI when available.

METHODS

This is a narrative review of the evidence concerning the long term harmful consequences of premature or early menopause either occurring naturally or as a result of surgery. We did not attempt to summarize studies or data from existing clinical or epidemiological studies in a systematic way. In particular, we did not conduct an exhaustive literature search to identify all of the studies of interest. We selected the papers to discuss by judgment and based on our personal experience and our interpretation of the findings. Similarly, we did not use statistical testing or concepts of statistical significance. We also provided some clinical recommendations about the care of women experiencing premature or early menopause based in part on our direct clinical observations and practice.

RESULTS

Neurological effects of early menopause

Oophorectomy prior to menopause was shown to increase the risk of developing cognitive impairment or dementia nearly two-fold in the Mayo Clinic Cohort Study of Oophorectomy and Aging, with a trend of increasing risk with earlier age at oophorectomy.¹⁴ Women who

received estrogen therapy at least through age 50 years did not experience increased risk. A similar finding was noted in a Danish cohort study, revealing an increased risk of dementia in women undergoing oophorectomy prior to age 50 years, with a similar trend of increasing risk with earlier age at oophorectomy.¹⁵ A replication of the Mayo Clinic study by Bove et al. revealed an association between younger age at the time of oophorectomy and more rapid decline in global cognition. In addition, there was an association between younger age at oophorectomy and increased neuropathology (neuritic plaques) associated with Alzheimer's disease.^{16, 17} A mitigating effect of estrogen therapy (ET) on the decline in global cognition associated with early oophorectomy was noted in those who were treated within 5 years of menopause, and for a duration of at least 10 years.^{16, 17}

In contrast to studies of oophorectomy before the natural age of menopause, studies on ET after menopause and risk of dementia have yielded conflicting results which may be explained by the timing hypothesis. The timing hypothesis suggests that ET may have neuroprotective effects when provided close to the menopausal transition, whereas ET may have detrimental effects and may increase the risk of cognitive impairment or dementia if given to older women. This adverse effect in older women may relate to the presence of existing vascular or neurologic disease, or to an increased risk of thrombosis.^{12, 18–20} In the Women's Health Initiative Memory Study (WHIMS), an increased risk of cognitive impairment or dementia was observed with conjugated equine estrogens alone (ET) or with conjugated equine estrogens combined with a progestin (HT) when used in women aged 65–79 years. Three observational studies have provided additional support for the timing hypothesis, with evidence for reduced risk of dementia when HT is started early after menopause, but either no advantage or increased risk when started later in life.^{12, 19, 21–23}

Establishing causality in the association between estrogen deprivation due to early BSO and cognitive impairment or dementia is difficult, and effects may be modified by genetic factors (variants in the estrogen receptor 1 gene, apolipoprotein E gene, or other genes) as well as by non-genetic factors such as alcohol or tobacco use, education, and the presence of obesity or diabetes.¹⁹ Indeed, a causal relationship is suggested by the studies of Rocca et al. and Bove et al. in which women who received ET after early BSO did not experience the same deleterious cognitive effects experienced by the women who did not.^{14, 16, 17}

An increased risk of parkinsonism has been linked to both unilateral and bilateral oophorectomy before the natural age of menopause, and ET does not attenuate this association.^{13, 24}

The risk of glaucoma is increased in women undergoing BSO prior to the age of 43 years, and the risk does not appear to be reduced by the use of ET.²⁵ It has been suggested that early estrogen loss accelerates aging of the optic nerve and increases susceptibility to glaucomatous changes.²⁶ In addition, the risk of macular degeneration has been found to be increased in women undergoing early menopause caused by unilateral or bilateral oophorectomy under the age of 45 years. However, the risk was not increased in women experiencing natural menopause under the age of 45 years.²⁷ These ophthalmologic risks of early oophorectomy may be another manifestation of early aging of the central nervous system in the setting of premature estrogen deficiency.

Mood and early menopause

BSO before natural menopause has been linked with an increased risk of depression and anxiety, but age-specific data are limited. Studies on the effects of surgically induced early menopause have compared women undergoing BSO at the time of hysterectomy to women undergoing hysterectomy alone. A retrospective study evaluating outcomes after hysterectomy at a single hospital in Sweden compared women whose ovaries were preserved or removed and took ET or no therapy. Anxiety and depression were significantly greater after BSO and less with ET use.²⁸ A prospective evaluation of women aged 45 years and younger undergoing hysterectomy in New Zealand found higher rates of depression after BSO than with ovarian conservation. However, higher rates of depression were present in these women before surgery and persisted over the three years of follow-up.²⁹ The Maryland Women's Health Study, which included women undergoing hysterectomy mostly between the ages of 31–49 years, found that women who underwent BSO had significantly poorer emotional health outcomes at 24 months than women whose ovaries were preserved.³⁰ The Mayo Clinic Cohort Study of Oophorectomy and Aging evaluated long-term outcomes (median 24 years of follow-up) after BSO compared with no oophorectomy in the general population (Olmsted County, MN) and found an increased risk of *de novo* depression and *de novo* anxiety symptoms in woman who underwent BSO. The increased risk was greater for woman younger at the time of surgery, and was not ameliorated by ET use.³¹

Not all studies reported psychological distress after BSO performed before natural menopause. Investigators from the Study of Women's Health Across the Nation, which followed perimenopausal women between the ages of 42–52, found no increase in depressive or anxiety symptoms after BSO compared to hysterectomy alone or natural menopause.³² In a small, observational study, women at increased risk for ovarian cancer who underwent risk-reducing BSO reported greater psychological climacteric symptoms compared with naturally menopausal referent women, but also reported less anxiety and cancer fear after the surgery.³³ Another observational study evaluating women with a history of breast cancer reported greater depression and anxiety in women who underwent BSO compared to cancer-affected women whose ovaries were intact.³⁴

Systematic investigation and long-term studies of women with POI are limited, but the link to psychological distress seems clear. The diagnosis of POI and unexpected infertility can be life-altering and grief-inducing.^{35–37} Women with POI experience lower perceived social support, isolation, depression, and an increased lifetime risk of depression,^{38, 39} and have lower self-esteem, increased shyness, and social anxiety.⁴⁰ Although women affected by POI may or may not report experiencing severe emotional distress, they often ask for guidance and support.⁴¹ Providing emotional support is considered an essential part of the management of women with POI.³⁵

Bone density and early menopause

Bone loss with natural menopause is reported over a 5–7 year period starting approximately 2–3 years before menopause, peaking in the first three years after menopause at approximately 2.4% annually, then declining to around 1.2% annually.^{42, 43} The bone loss in

premenopausal women with BSO, however, was found to be more than two-fold higher than in women with natural menopause in a study by Yoshida, et al. Women with early BSO demonstrated a significant increase in urinary N-telopeptide (NTx) and a decrease in bone mineral density (BMD) within 12 months of BSO compared to age-matched women with intact ovaries.⁴⁴

The early and late effects of age at menopause and type of menopause (natural menopause, early menopause, and early BSO) on BMD were compared in a cross-sectional study by Hadjidakis, et al.⁴⁵ Menopausal women who had never received HT were categorized in five-year age groups between the ages of 45 and 70 years, and lumbar spine and femoral neck BMD were determined. Women with early menopause had lower vertebral and femoral neck T-scores than those with natural menopause in the 45–55 year age group. However, by age 65–70 years, there was no statistical difference between the early and natural menopause groups. Women with early BSO had lower vertebral BMD compared to those with natural menopause between ages 45–50 years, but remained stable through ages 65–70 years. While there was a significant decrease in both vertebral and femoral neck BMD between the 45–50 year and 65–70 year segments in women with natural menopause, there was no significant difference in vertebral or femoral neck BMD between successive age groups in either the early menopause or early BSO groups.⁴⁵ Francucci et al. found women with menopause between ages 40–44 years to have lower vertebral BMD compared to those with natural menopause. While BMD fell in both groups over time, the difference in vertebral BMD did not differ between those with early or natural menopause after age 55 years.⁴⁶

Studies on fracture risk in early menopause compared to natural menopause have demonstrated an increase in fracture rates compatible with the associated bone loss, with ET being protective against fracture.^{47, 48} However, studies have been inconsistent in women over age 70 years. Gardsell et al. found 50% more fractures with early menopause until age 70 years, while van Der Voort et al. reported an increase in fracture after age 70 years.^{49, 50} A cohort study of women in Olmsted County, MN with premenopausal BSO followed over 20 years found a modest increase in distal wrist fracture and vertebral fracture, but not hip fracture. However, most women utilized ET to an average age of 47 years.⁵¹ A cohort from the Study of Osteoporotic Fractures found that women with premenopausal BSO, with and without subsequent ET, did not have a greater risk for non-vertebral fracture after two decades of follow-up compared with women who experienced natural menopause.⁵²

Although studies have demonstrated greater bone loss in the initial years following estrogen deficiency in women with early menopause compared to women with menopause at average age, the results of studies assessing fracture risk in women with early versus average age menopause have been inconsistent.^{44–52}

Cardiovascular effects of early menopause

There is a significant body of literature associating early menopause with increased risk of cardiovascular disease (CVD) and death. In the Framingham Study, women in their forties who were postmenopausal were found to have an increased incidence of CVD compared to age-matched women who were premenopausal. This initial observation prompted the hypothesis that estrogen is protective against CVD.⁵³ Similarly, an increased CVD risk in

women with early menopause compared to women with menopause at age 50 years or older was noted in a meta-analysis, with the greatest risk in women with early BSO.⁵⁴ Parashar et al. noted that the age at menopause impacts the risk of angina following myocardial infarction. Women with natural or surgically induced menopause before age 40 years were found to have twice the risk of angina and higher severity of angina one year post-myocardial infarction compared with women experiencing menopause at age 50 years or older.⁵⁵ In addition, young women with POI had significantly impaired vascular endothelial function, with restoration of function noted within six months of initiating HT.⁵⁶

Two recent studies suggest an association between early menopause and heart failure risk. In the Multi-ethnic study of Atherosclerosis, the risk of heart failure was increased by 66% in those undergoing menopause earlier than age 45 years compared with women experiencing later menopause, with a 4% decrease in risk with every one-year increase in age at menopause.⁵⁷ Similarly, Rahman et al. reported a 36% increase in the incidence of heart failure in women with natural menopause at ages 40–45 years compared to those with menopause at ages 50–54 years, with a 2% decrease in heart failure risk with every one-year increase in age at menopause.⁵⁸ It remains unclear whether estrogen deficiency plays a role in the etiology of heart failure in women or whether other cardiovascular risk factors contribute to earlier age at menopause as well as to cardiovascular disease risk (confounding by other risk factors).^{59, 60}

BSO prior to the natural age of menopause is associated with early mortality which is thought to relate primarily to an increased risk of CHD. The Mayo Clinic Cohort Study of Oophorectomy and Aging found an increased risk of mortality in women who underwent BSO prior to the age of 45 years and were not treated with ET compared with referent women.^{61–63} In the Nurse's Health Study, women who underwent BSO before the age of 50 years had a significant increase in all-cause, total cancer, and cardiovascular mortality over 28 years of follow-up.³ Similarly, Gierach et al. found younger age at BSO to be associated with increased risk of all-cause mortality, and specifically with mortality related to CHD. This risk decreased progressively with increasing age at BSO, disappearing by the age of 50 years. HT was found to attenuate the mortality risk related to BSO.⁶⁴

Not all investigators have been able to confirm findings of increased risk of stroke in women with premature menopause,^{65, 66} but multiple observational studies have demonstrated that early onset menopause, or reduced lifespan of ovarian activity, is associated with an increased risk of stroke, in particular ischemic stroke.^{67–72} The Multi-Ethnic Study of Atherosclerosis noted that women of varying ethnic backgrounds with early natural or surgically induced menopause had increased risk of CHD and stroke.⁷³ Although ET poses an increased risk of stroke for older women, it appears to be protective in women before the age of 50 years.^{2, 72}

Early menopause is associated with increased risk of CVD events and mortality, with early BSO being a greater risk than early natural menopause. HT appears to reduce the cardiovascular risk in early natural and surgically induced menopause.

Sexual function after early menopause

BSO results in a sudden and immediate decline in estrogen, progesterone, and testosterone. In contrast, the loss of ovarian function may be more gradual in the setting of spontaneous premature or early menopause or in the setting of cancer treatment with chemotherapy or radiation, and may be associated with symptoms that are not necessarily identified as relating to hormone loss, including insomnia, mood swings, arthralgias, and changes in sexual function. The sexual function of women undergoing menopause prior to the natural age is impacted not only by the loss of hormonal function, but also by the etiology of the loss (surgery for a benign condition, treatment of a malignancy with surgery, chemotherapy or radiation, genetic causes, autoimmune disease, or other cause). Other potential contributors to sexual function include the woman's life cycle stage, personal factors including coping mechanisms, as well as family, relationship, and societal influences.⁷⁴ Discussions regarding fertility, options for parenthood, and the potential need for contraception (due to spontaneous return of ovulation) are just a few of the issues to be considered when caring for women with early menopause.

Sexual function in women is modulated by estrogens and androgens, with estrogen mediating vaginal congestion and lubrication, and testosterone promoting desire and arousal centrally through effects on dopamine and contributing to the peripheral response through an effect on nitric oxide.⁷⁵ Signs and symptoms of estrogen deficiency include vaginal thinning, dryness, loss of elasticity, as well as difficulty with sexual arousal, interest, and sexual pain.⁷⁶ In a study of women undergoing risk reducing BSO, oophorectomized women reported significantly more vaginal dryness and dyspareunia than did the control group, despite the use of HT after surgery, suggesting that changes in sexual functioning are sustained and not entirely reversed by HT following BSO.⁷⁷ Sexual dysfunction in women with early BSO is often multifactorial, related not just to the physiologic consequences of hormonal deprivation, but also to psychological aspects.^{74, 75}

DISCUSSION

Management of the woman with early menopause

Table 1 summarizes our recommendations for women who experienced premature or early menopause. It is important not to apply the results of the Women's Health Initiative (WHI) trials to the clinical care of all women, especially to women experiencing early menopause as the result of BSO or POI. The decline in the use of HT in hysterectomized women since publication of the WHI has been dramatic, even in woman younger than age 50 years, and continues to decline.^{78–80} Educating women and their healthcare providers that the results of the WHI trials should not be extrapolated to women younger than the natural age of menopause is a priority.

Treatment with HT has been shown to mitigate the adverse effects of early menopause on multiple outcomes.^{1, 61} In contrast to women experiencing natural menopause at the average age and in whom the primary reason to consider initiation of HT is moderately severe vasomotor symptoms, women who experience menopause prior to age 45 years may benefit from HT not only to manage symptoms, but also to maintain bone density and reduce the

cardiovascular and neuro-cognitive effects of estrogen deficiency.^{10, 12, 14, 19} Treatment considerations include the use of oral contraceptives (particularly for women with POI, in whom ovarian function may still occur) or menopausal HT (ET with a progestogen in women with a uterus, or ET alone in women without a uterus).⁸¹ Although rare, women with POI have a 5–10% chance of spontaneous conception and need to be counseled accordingly.⁸

The current recommendation for women experiencing early or premature menopause to consider HT at least until the natural age of menopause is supported by the American Society for Reproductive Medicine, the Asia Pacific Menopause Federation, the Endocrine Society, the European Menopause and Andropause Society, the International Menopause Society, the International Osteoporosis Foundation, the North American Menopause Society, and the British Medical Society.^{82–84} If symptoms dictate, longer duration therapy may be considered.⁸²

Optimal estrogen dose

Although there are no studies that investigated the optimal estrogen dose for women with POI and BSO, higher doses are often needed for symptom control. A dose equivalent to at least 100 µg of transdermal estradiol is often suggested because this dose may achieve a blood estradiol concentration approximating that of menstruating women.^{35, 81}

Individualization of therapy is particularly important for women with POI. Recent studies on route, dose, and formulation of ET in hypogonadal girls with Turner syndrome suggested that high dose transdermal estradiol (approximating blood estradiol and estrone concentrations found in normal menstruating adolescent girls) results in an estrogen milieu that is most physiologic.^{85, 86}

Other hormones

ET use has been shown to not fully protect against the increased risk of parkinsonism, depression and anxiety, and glaucoma associated with early BSO, raising the question of whether the loss of testosterone or progesterone, or perhaps elevated levels of gonadotrophins in women undergoing BSO at a young age might pose neurological risk.^{13,24,31} In addition, women with early menopause, particularly those with BSO, may experience persistent problems with sexual dysfunction despite presumed adequate estrogen replacement. Although treatment with testosterone has been associated with improved sexual function in oophorectomized women,^{87, 88} it is not routinely recommended by the Endocrine Society as treatment following oophorectomy or in the setting of POI because there are no adequate data regarding efficacy and long-term safety. The Endocrine Society does support the use of testosterone in postmenopausal women with hypoactive sexual desire disorder (now termed sexual interest and arousal disorder) in whom no contraindication exists.⁸⁹ However, there are no FDA-approved testosterone preparations available for women in the US, and utilizing a product formulated for men is discouraged.⁹⁰

Other potential benefits of replacing testosterone in women with early menopause have been investigated. In a recent study by Guerrieri et al., treatment with testosterone was not associated with improvement in quality of life or self-esteem in women with POI and had

minimal effect on mood, suggesting that these symptoms were not reflective of androgen deficiency in this population.⁹¹ Although additional studies are needed, current recommendations do not support the use of androgen therapy in women for these indications.⁸⁹

Prevention of osteoporosis and bone fractures

Although short-term HT may not have a long-term effect on fracture rate, adequate calcium and vitamin D intake are important for bone health. The recommendations for calcium and vitamin D intake for women experiencing early menopause do not differ from those for women who enter menopause at the natural age. The Institute of Medicine recommends a daily intake of 1,200 mg of calcium and 600 IU of vitamin D for women between the ages of 51 and 70 years.⁹² The National Osteoporosis Foundation recommends counseling women to reduce the risk of osteoporosis and fracture through the following interventions: smoking cessation and avoidance of excess alcohol intake, assessment of the risk of falling, regular weight-bearing exercise and muscle strengthening, and a daily intake of 1,200 mg of calcium for women 51 years of age and older and 800–1000 IU of vitamin D, including supplements if needed.⁹³

Recommendations for the timing of BMD testing in women who have experienced early-onset menopause vary. In women with breast cancer, BMD measurement is suggested within 3 months of treatment-induced menopause.⁹⁴ A two year window for measurement of BMD has been recommended in women with risk-reducing BSO who have not initiated ET.⁹⁵ BMD measurement has also been suggested for women undergoing menopause under the age of 45 years because of the increased risk of spine and hip fracture before the age of 70 years.⁹⁶

Mental health

Psychological functioning has been found to be relatively poor in women with early menopause compared to women with menopause at the average age.⁹⁷ Women with early menopause often have difficulty adapting to an altered self-image, to sexual dysfunction, and to the loss of fertility associated with estrogen deprivation, and may benefit from referral to a psychologist or sex therapist.^{10, 98} Fertility preservation may be considered in women prior to initiation of chemotherapy or radiation treatment and in women with POI, and counseling with a fertility specialist is recommended.¹⁰ International groups such as the Daisy Network are useful resources for patients with POI.^{81, 99}

CONCLUSION

Premature or early menopause is associated with numerous adverse health outcomes including cognitive impairment, dementia, parkinsonism, glaucoma, CHD, osteoporosis, mood disorders, sexual dysfunction, and increased overall mortality. The results of trials pertaining to HT in older menopausal women cannot be extrapolated to women experiencing early menopause or POI. Unless a strong contraindication exists, HT is recommended at least until the natural age of menopause to protect against these negative effects, and may be considered for a longer duration if needed based on symptoms. A higher dose of HT may be

needed to approximate physiologic blood estradiol concentrations in premenopausal menstruating women. Counseling regarding cardiovascular disease prevention, osteoporosis, and fracture risk reduction is suggested. Attention to the psychological impact of early menopause is essential, and referral to a mental health professional may be of benefit.

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Table 1

Recommendations for women who experience premature or early menopause

The results of the Women’s Health Initiative trials do not apply to women who have experienced early or premature menopause
Women experiencing menopause prior to age 45 (as a result of primary ovarian insufficiency or bilateral salpingo-oophorectomy) benefit from hormone therapy not only for vasomotor symptom management, but also for prevention of adverse cardiovascular, bone and neuro-cognitive effects related to premature estrogen deficiency
Several medical societies recommend that hormone therapy should be considered at least until the natural age of menopause for women experiencing early or premature menopause
Higher doses of estrogen (at least the equivalent of 100 µg of transdermal estradiol) may be needed to approximate blood estradiol concentrations similar to those of menstruating women
Women with primary ovarian insufficiency have a 5–10% chance of spontaneous conception and require appropriate counseling about contraception if pregnancy is not desired
Although testosterone has been shown to improve sexual function in women, it is not currently routinely recommended in women with primary ovarian insufficiency or bilateral salpingo-oophorectomy
Counseling regarding bone health includes recommendations for weight-bearing exercise, muscle strengthening, fall risk assessment, smoking cessation and avoidance of excess alcohol intake, along with a daily dietary intake of 1200 mg of calcium and 600–1000 IU of vitamin D, including supplements if needed
Women with primary ovarian insufficiency or bilateral salpingo-oophorectomy may benefit from psychological support to help address issues associated with early menopause including loss of fertility, changes in self-image, and sexual dysfunction