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Premature menopause or early menopause: long-term health consequences

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Abstract

Objective—To review and summarize current evidence on the health consequences of premature menopause and early menopause.

Methods—We reviewed existing literature and combined graphically some results from the Mayo Clinic Cohort Study of Oophorectomy and Aging.

Results—Premature menopause or early menopause may be either spontaneous or induced. Women who experience premature menopause (before age 40 years) or early menopause (between ages 40 and 45 years) experience an increased risk of overall mortality, cardiovascular diseases, neurological diseases, psychiatric diseases, osteoporosis, and other sequelae. The risk of adverse outcomes increases with earlier age at the time of menopause. Some of the adverse outcomes may be prevented

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by estrogen treatment initiated after the onset of menopause. However, estrogen alone does not prevent all long-term consequences and other hormonal mechanisms are likely involved.

Conclusions—Regardless of the cause, women who experience hormonal menopause and estrogen deficiency before reaching the median age of natural menopause are at increased risk for morbidity and mortality. Estrogen treatment should be considered for these women, but may not eliminate all of the adverse outcomes.

Keywords

Premature menopause; Early menopause; Estrogen; Bilateral oophorectomy; Mortality; Morbidity

1. Introduction

Premature menopause refers to menopause that occurs before age 40 years, and early menopause refers to menopause that occurs at or before age 45 years, both ranges being well below the median age of natural menopause (age 51 years) [1]. Premature menopause or early menopause can be spontaneous or induced; if induced, it can be due to medical interventions such as chemotherapy or surgical interventions such as bilateral oophorectomy. Regardless of cause, women who experience estrogen deficiency at an age well before the median age of natural menopause are now recognized to be at increased risk for premature morbidity and mortality.

In this review, we present the evidence regarding long-term health outcomes following different types of early menopause. While the hormonal milieu is quite different for women with spontaneous premature ovarian failure compared with women who experienced induced menopause due to bilateral oophorectomy or to cancer treatment, both conditions are associated with long-term health risks. Estrogen replacement appears to mitigate some but not all long-term health consequences of premature menopause or early menopause. Thus, other hormonal mechanisms are likely involved [2].

2. Methods

Using the Medline database, we conducted a comprehensive literature search of publications related to premature or early menopause, using the keywords “premature menopause”, “early menopause”, “surgical menopause”, “induced menopause”, “ovarian failure”, “ovarian insufficiency”, and “bilateral oophorectomy”. We considered observational studies reporting outcomes for women who reached menopause before the age of 45 years and studies comparing health outcomes following induced compared with natural menopause at younger ages. In addition, we combined graphically some results from the Mayo Clinic Cohort Study of Oophorectomy and Aging pertaining to women who were younger than age 45 years at the time of oophorectomy [2].

3. Spontaneous premature ovarian failure (POF) or early menopause

Premature ovarian failure (POF), also now referred to as primary ovarian insufficiency [3] or primary ovarian dysfunction [4], is a syndrome of amenorrhea, low sex steroid levels, and elevated gonadotropin levels among women younger than age 40 years. POF is most frequently idiopathic but may also be due to autoimmune disorders, genetic causes, infections or inflammatory conditions, enzyme deficiencies, or metabolic syndromes [1,3,5]. POF is reported to affect approximately 1% of women under age 40 years [6,7] and spontaneous early menopause is reported to affect approximately 5% of women between ages 40 and 45 years [5].

POF has been found to be associated with intermittent ovarian function in nearly half of the women affected [3]. While spontaneous or induced return of ovarian function is possible, most women with POF experience sustained sex steroid deficiency for longer periods compared with women who experienced spontaneous menopause around the median age. Thus, POF and other causes of premature spontaneous menopause are generally classified together when evaluating long-term health outcomes.

Women with premature spontaneous menopause (including POF) are at increased risk for low bone density, earlier onset osteoporosis and fractures [8], impaired endothelial function [9], earlier onset of coronary heart disease [10], and increased cardiovascular mortality and total mortality [11–16]. Women with POF have been reported to have diminished general and sexual well-being and are less satisfied with their sexual lives [17]. In addition, women with POF have been reported to have more anxiety, depression, somatization, sensitivity, hostility, and psychological distress than women with normal ovaries [17]. POF is frequently associated with autoimmunity, and women with autoimmune POF are at increased risk for adrenal insufficiency, hypothyroidism, diabetes, myasthenia gravis, rheumatoid arthritis, and systemic lupus erythematosus [4,18].

4. Induced premature menopause or early menopause

Induced menopause may result from premenopausal bilateral oophorectomy or from cancer treatments including chemotherapy and radiation. Premature menopause from these causes has increased over time because of the improved success in the treatment of cancer in children, adolescents, and reproductive-age women. Similarly, the practice of prophylactic bilateral oophorectomy at the time of hysterectomy has increased over time [19]. However, evidence for the long-term risks and adverse health outcomes following induced menopause is starting to accumulate.

4.1. Induced menopause following cancer therapy

Ovarian damage from cancer therapy depends on the age at treatment and on the type of treatment. Women younger than age 40 years and children are at lower risk for ovarian failure than older women; however, exposure to higher doses of alkylating agents and higher doses of radiation to the ovary are more likely to induce ovarian failure [20]. Based on the Childhood Cancer Survivor Study (CCSS), a cohort study of survivors of childhood cancer treated at 25 cancer centers throughout North America between 1970 and 1986, approximately 6% of childhood cancer survivors experienced acute ovarian failure (AOF) during cancer treatment or shortly after completing cancer treatment [21]. Another 8% retained ovarian function during treatment but later developed premature menopause [21]. This is believed to be an underestimate of the true population incidence of premature menopause because the median age attained in this group at the time of analysis was only 29 years [22].

Follow-up of childhood cancer survivors has identified an increase in miscarriages, an increase in small for gestational age offspring, and a reduction in live births [21]. Longer term health outcomes, beyond cancer free survival, are not yet available; however, these subjects are expected to be at increased risk for osteoporosis, cardiovascular disease, psychosexual dysfunction, and decreased quality of life [22].

Approximately 25% of breast cancer cases occur in premenopausal women, and breast cancer accounts for one third of cancers in reproductive-age women [23]. Adjuvant chemotherapy and endocrine therapies are now standard, resulting in ovarian insufficiency and sex steroid suppression among many women with a history of breast cancer. Approximately two-thirds of premenopausal women become amenorrheic after starting the chemotherapy regimen most commonly used for breast cancer [24]; however, the overall risk of inducing menopause

depends on the type and dose of chemotherapy and on the age of the woman. Several, but not all, studies have reported improved cancer-free survival in women who developed amenorrhea after chemotherapy [25]. Consequences of induced ovarian failure include premature menopause, infertility, vasomotor symptoms, vaginal dryness, dyspareunia, weight gain, and osteoporosis [26,27].

4.2. Induced menopause following prophylactic bilateral oophorectomy

Approximately 1 in 9 women aged 35–45 years has undergone hysterectomy, with 40 percent undergoing bilateral oophorectomy at the same time, resulting in the abrupt onset of menopause [19]. The practice of prophylactic oophorectomy has increased over time and more than doubled between 1965 and 1990 [19]. Meanwhile, reports now link induced menopause from bilateral oophorectomy with serious health consequences including premature death, cardiovascular and neurologic disease, and osteoporosis, in addition to menopausal symptoms, psychiatric symptoms, and impaired sexual function.

4.2.1. Mortality and cardiovascular disease—The Mayo Clinic Cohort Study of Oophorectomy and Aging involved a population-based sample of 4,780 women and reported increased all-cause mortality in women who underwent prophylactic bilateral oophorectomy before age 45 years [28]. The increased mortality was mainly observed in women who did not take estrogen after the surgery and up until age 45 years (HR 1.93, 95% CI 1.25–2.96). Cardiovascular mortality was also increased in the women who underwent bilateral oophorectomy before age 45 years and did not take estrogen [29].

The Danish Nurse Cohort Study, a prospective cohort study of nearly 20 000 women, reported an increased risk of ischemic heart disease among women who underwent bilateral oophorectomy before age 40 years compared to after age 45 years. There was a smaller increased risk for ischemic heart disease among women who experienced natural menopause before age 40 years. Among the women who experienced menopause as a result of bilateral oophorectomy, estrogen therapy was associated with significant protection against ischemic heart disease. The benefit from estrogen was most pronounced for current users and for women who started treatment within 1 year after surgery [30].

In 2009, Parker and colleagues reported results from the Nurses' Health Study cohort of 30 000 women who underwent hysterectomy for benign disease, comparing outcomes following ovarian conservation versus bilateral oophorectomy [31]. Hysterectomy with bilateral oophorectomy before age 45 years was associated with an increased risk for coronary heart disease, even when analyses were adjusted for known cardiovascular risk factors and for use of estrogen therapy. Oophorectomy at any age was associated with an increased risk of death, including coronary heart disease and lung cancer deaths.

In summary, data consistently show an increased risk for cardiovascular disease in women who undergo bilateral oophorectomy inducing premature menopause or early menopause. Estrogen replacement proximate to bilateral oophorectomy appears to be particularly important for reducing premature coronary heart disease and death in this group of women.

4.2.2. Neurologic outcomes—Women in the Mayo Clinic Cohort Study of Oophorectomy and Aging who underwent bilateral oophorectomy before the onset of natural menopause had an increased risk of cognitive impairment or dementia when compared with referent women, and the risk increased with younger age at oophorectomy [2]. The increased risk among these women was restricted to those who did not take estrogen after surgery and until at least age 50 years. Thus, it is suggested that estrogen treatment following oophorectomy protected against the increased risk. The Mayo Clinic Cohort Study of Oophorectomy and Aging also showed

that women who underwent bilateral oophorectomy before menopause were at increased risk of parkinsonism, and the risk increased with younger age at time of oophorectomy [2].

Other studies have evaluated cognitive function and memory function in surgically menopausal women, but age-specific data are limited. Nappi and colleagues reported that women who underwent surgical menopause following bilateral oophorectomy underperformed on certain memory tasks [32]. Scores among the surgically menopausal women tended to be lower when the oophorectomy occurred at younger ages. In a longitudinal study in Egypt, women who underwent surgical menopause had significantly decreased global cognitive functioning scores and memory scale scores 3 to 6 months after oophorectomy compared with premenopausal controls [33]. Lower performance correlated with lower estradiol levels.

Sherwin evaluated 50 women before and after hysterectomy with bilateral oophorectomy or ovarian conservation and found a reduction in cognitive function in the women who underwent bilateral oophorectomy (mean age 45.4 years) if no hormone therapy was given [34]. Women who underwent hysterectomy with ovarian conservation and women with bilateral oophorectomy who were given estrogen, androgens, or both, experienced no declines in cognitive function [34]. These short-term clinical trials suggested that cognitive and memory functions correlate with sex steroid hormone levels, and that estrogen maintained at physiologic levels improves cognitive functions [35].

In summary, some cohort studies reported an increased risk for neurologic impairment following bilateral oophorectomy, with a suggestion of increased risk when surgical menopause occurs at a younger age, and reduced risk when estrogen replacement was given. By contrast, two other studies reported limited or no memory and cognitive differences among women with bilateral oophorectomy versus hysterectomy or natural menopause [36,37]. However, there was no delineation in these studies of the subgroup of women who might be at greatest risk – i.e., women undergoing bilateral oophorectomy before age 45 years.

4.2.3. Mood and sexual function—Bilateral prophylactic oophorectomy seems to be associated with an increased long-term risk of de novo anxiety symptoms, as evidenced by the Mayo Clinic Cohort Study of Oophorectomy and Aging [2]. Women in this study who underwent bilateral oophorectomy at younger ages (before age 49 years) were at greater risk for anxiety, and treatment with estrogen did not modify the risk. An increase in depressive symptoms diagnosed by a physician was also found in this study, but the association was weaker [2].

The link between oophorectomy and depression has been recognized for many years, but age-specific data are limited. In one study, women who underwent oophorectomy along with hysterectomy had significantly greater anxiety and depression, and less positive well-being than the women whose ovaries had been conserved [38]. Oophorectomized women taking estrogen reported less anxiety and depression, and their psychological well-being was similar to women whose ovaries had been conserved. Oophorectomized women also reported more impaired sexual function compared to women with intact ovaries; however, these sexual symptoms were not ameliorated by taking estrogen [38].

In contrast, a more recent prospective study of 323 women evaluated psychological well-being and sexual function at baseline and one year after simple hysterectomy versus hysterectomy with oophorectomy. The changes between baseline and follow-up in psychological well-being and in reported sexual function did not vary between the two groups [39].

Several studies reported negative psychosocial and sexual consequences of prophylactic oophorectomy performed in women at increased risk for breast cancer or ovarian cancer, such

as women with a family history of breast cancer or ovarian cancer or with a *BRCA* mutation. Madalinska and colleagues compared the quality of life in women with prophylactic oophorectomy versus women with periodic gynecologic screening (846 women aged 30–59 years). The most common adverse effects of bilateral oophorectomy were increased hot flashes, night sweats, vaginal dryness, dyspareunia, weight gain, and a loss of interest in sex [40]. Estrogen therapy reduced but did not eliminate vasomotor symptoms, and was associated with an increase in vaginal dryness and dyspareunia.

Fang and colleagues prospectively compared the quality of life in 75 women at increased risk for ovarian cancer who received prophylactic oophorectomy versus gynecologic screening [41]. The women who underwent oophorectomy (mean age 46 years) experienced poorer physical functioning, greater pain, less vitality, poorer social functioning, greater discomfort and less satisfaction with sexual activities at one month; however, many of the symptoms improved by 6 months except hot flashes and sexual impairment. Overall, women who underwent prophylactic oophorectomy were more likely to experience hot flashes, dyspareunia, and less satisfaction with sexual intercourse.

In a study of 503 Norwegian women at increased risk of breast cancer or ovarian cancer, women who underwent prophylactic bilateral oophorectomy at a mean age of 48.5 years experienced more palpitations, constipation, pain, stiffness, osteoporosis, and musculoskeletal disease following surgery compared with population controls, even after adjustment for use of hormone therapy [42]. However, prophylactic bilateral oophorectomy was associated with lower levels of depression and mental distress after surgery, probably because of reduced concerns about cancer risk.

Dennerstein and colleagues compared findings among surgically or naturally menopausal women, using validated measures of female sexual function in the Women's International Study of Health and Sexuality (WISHeS) [43]. Women who underwent hysterectomy with bilateral oophorectomy were more likely to have low sexual desire, less likely to be sexually active, and more likely to be dissatisfied with their sex life and partner relationships. Women younger than age 50 years (mean age 44 years) who had undergone bilateral oophorectomy were twice as likely to have low sexual desire compared with premenopausal women; however, the likelihood of low desire was significantly reduced with hormone therapy.

4.2.4. Osteoporosis—Numerous studies have shown that bone loss accelerates following menopause. The earlier in life that menopause occurs, the lower bone density will be later in life [8]. Therefore, oophorectomy before age 45 years is a well-established risk-factor for osteoporosis. Even in women who undergo bilateral oophorectomy after natural menopause, the risk of osteoporotic fracture may be increased compared with women with intact ovaries [44]. Estrogen therapy prevents bone loss and reduces fracture risk following oophorectomy [45]; however, the long-term use of estrogen therapy – which would be needed for bone protection in these women at increased risk – has declined after the publication of results from the Women's Health Initiative clinical trials [2].

5. Discussion

Premature menopause and early menopause, whether spontaneous or induced, are associated with long-term health risks which may include premature death, cardiovascular disease, neurologic disease, osteoporosis, psychosexual dysfunction, and mood disorders. Estrogen mitigates some but not all of these consequences.

The most common interpretation of these findings is that premature or early menopause is the first step in a chain of causality leading to tissue or organ dysfunctions and lesions via hormonal

mechanisms [2]. However, before discussing this interpretation more extensively, we also mention the alternative hypothesis that premature or early menopause is the result of an accelerated aging process determined by genetic or non-genetic causes and involving all tissues and organs throughout the body, including the ovaries [46]. Under this hypothesis, the hormonal changes following premature or early menopause have no causal role in the development of premature death, cardiovascular disease, neurologic disease, osteoporosis, psychosexual dysfunction, and mood disorders. The evidence in support of this hypothesis is limited.

Whether different types of premature menopause or early menopause result in different long-term health consequences remains unknown. Their hormonal milieus differ because the postmenopausal ovary is hormonally active, producing small amounts of estradiol and estrone, as well as androgens including testosterone, androstenedione, and dehydroepiandrosterone [47]. Following bilateral oophorectomy in premenopausal women, estradiol levels drop, testosterone levels drop by 40–50%, and follicle-stimulating hormone levels rise abruptly. Women undergoing bilateral oophorectomy continue to have lower levels of androgens than naturally menopausal women even beyond 65 years of age [48].

With POF, follicle-stimulating hormone levels are elevated and estradiol levels are low, but sporadic increases in estradiol may occur [49]. Ovarian androgens remain age-appropriate in these women [50]. Ovarian failure caused by cancer therapy, when permanent, is associated with elevated follicle-stimulating hormone levels and reduced estradiol levels similar to natural menopause; androgen function has not been well-characterized. Overall, different consequences from the different types of menopause may relate to the extent of disruption of the hypothalamic-pituitary-ovarian axis as much as to the reduced levels of circulating sex steroid hormones [2].

Concern about the risks of hormone therapy following publication of results from the Women's Health Initiative clinical trials may be inappropriate if applied to women with premature menopause or early menopause who typically need estrogen in adequate replacement doses for a duration of time long enough to reduce the consequences of prolonged estrogen deficiency. It is important that clinicians not withhold health-promoting estrogen replacement for these women.

Professional organizations including the North American Menopause Society, the British Menopause Society, and the International Menopause Society recommend estrogen replacement therapy for women with premature menopause or premature ovarian failure [51–53]. There is some evidence, although not from randomized controlled clinical trials, that restoring pathologically low estrogen levels will reduce the later development of cardiovascular disease, osteoporosis, and possibly dementia. This leads to the general recommendation that estrogen be continued in women who experience premature menopause or early menopause until at least around the median age of natural menopause (approximately age 51 years).

The health benefits of prophylactic bilateral oophorectomy for reducing the risk of breast, ovarian, and fallopian tube cancers in women known to be at increased risk, such as *BRCA1* or *BRCA2* mutation carriers, is well-established [54]. However, for those women not known to be at increased risk of cancer, early spontaneous menopause or early induced menopause may result in more risks than benefits, and should be accompanied by estrogen replacement. Even in women with *BRCA1* or *BRCA2* mutations who undergo risk-reducing prophylactic bilateral oophorectomy before age 45 years, short-term estrogen replacement is an option [54]. The age of onset of estrogen deficiency appears to be an important determinant of long-term health [2].

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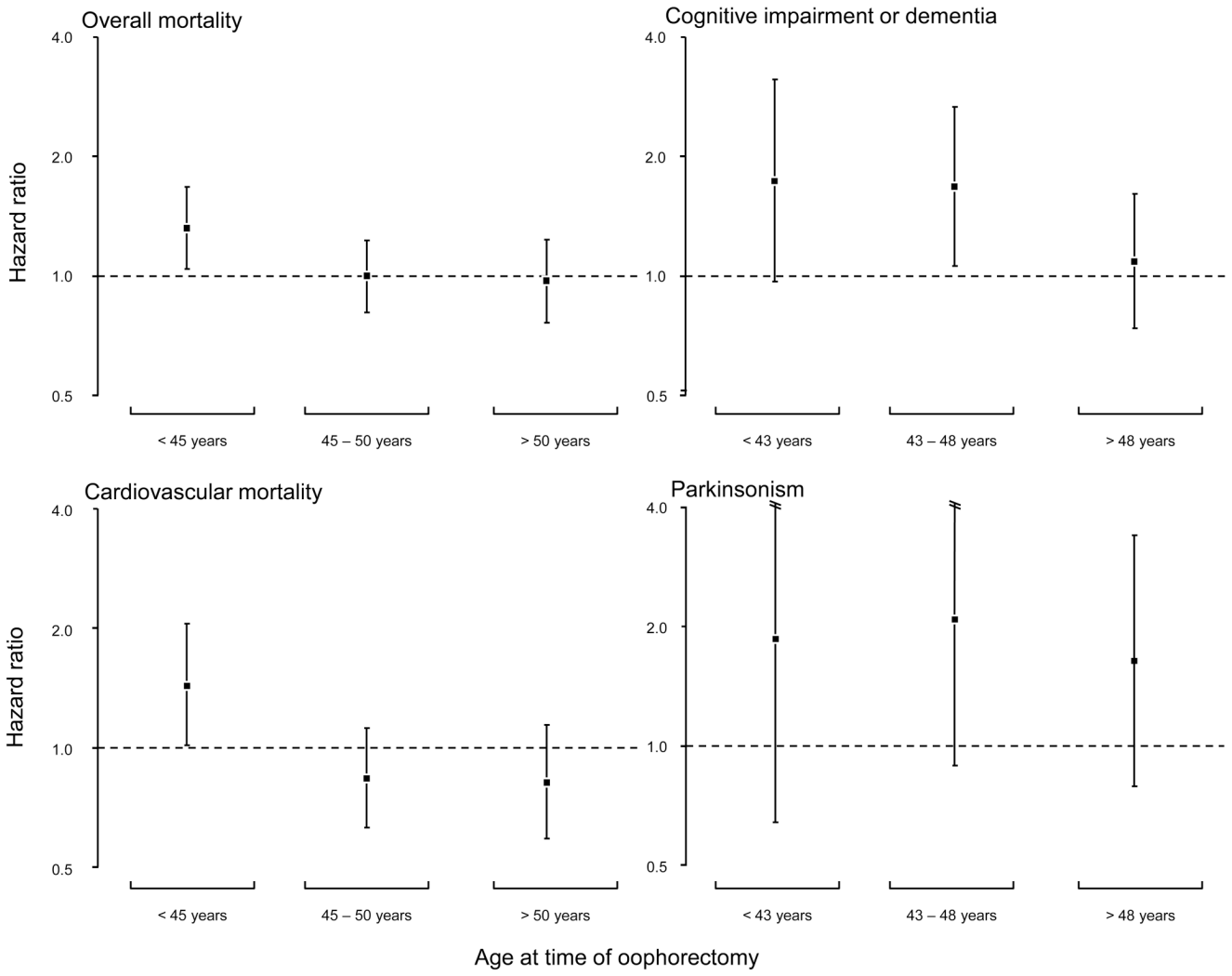

Figure 1.

The effects of bilateral oophorectomy increased with younger age at the time of oophorectomy for several outcomes investigated by the Mayo Clinic Cohort Study of Oophorectomy and Aging [2,28,29]. Risk was expressed using hazard ratios and 95% confidence intervals. The age strata on the x-axis are slightly different for overall mortality and cardiovascular mortality versus cognitive impairment or dementia and parkinsonism.