Prophylactic oophorectomy in pre-menopausal women and long term health – a review

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Abstract

Objective—To review the data on long-term outcomes in women who underwent prophylactic bilateral oophorectomy, a common surgical procedure that has more than doubled in frequency since the 1960s.

Study design—Literature review of published data on consequences of prophylactic bilateral oophorectomy. Special emphasis was given to the Mayo Clinic Cohort Study of Oophorectomy and Aging.

Main outcome measures—Overall mortality, cardiovascular disease, cognitive impairment and dementia, parkinsonism, osteoporosis, psychological well-being, and sexual function.

Results—There is a growing body of evidence suggesting that the premature loss of ovarian function caused by bilateral oophorectomy performed before natural menopause is associated with several negative outcomes. In particular, studies have revealed an increased risk of premature death, cardiovascular disease, cognitive impairment or dementia, parkinsonism, osteoporosis and bone fractures, decline in psychological well-being, and decline in sexual function. The effects involve different organs (e.g., heart, bone, or brain), and different functions within organs (e.g., cognitive, motor, or emotional brain functions). Estrogen treatment may prevent some of these negative outcomes, but not all.

Conclusion—The potential adverse effects of prophylactic bilateral oophorectomy on heart health, neurologic health, bone health, and quality of life should be carefully weighed against its potential benefits for cancer risk reduction in women at average risk of ovarian cancer.

Keywords

prophylactic bilateral oophorectomy; surgical menopause; estrogen deficiency; aging; mortality; estrogen treatment

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Introduction

Approximately 1 in 8 women above age 55 years has undergone bilateral oophorectomy before reaching natural menopause.[1,2] Bilateral oophorectomy may be performed for a benign disease or for prophylaxis against ovarian cancer, and is usually performed along with hysterectomy (in nearly 90% of cases).[3] Of the more than 600,000 hysterectomies performed annually in the United States, approximately half include bilateral oophorectomy.[4] In addition, the practice of prophylactic oophorectomy has increased over time and more than doubled between 1965 and 1990.[5] Meanwhile, reports now link premenopausal 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. For women undergoing hysterectomy who are not known to be at increased risk for cancer,[6,7] these consequences need to be carefully weighed against the potential benefits of preventing ovarian cancer.

Most studies that compared outcomes after surgical menopause with outcomes after natural menopause were observational studies with less than 10-years of follow-up.[8] By contrast, the Mayo Clinic Cohort Study of Oophorectomy and Aging involved a follow-up of approximately three decades. That study evaluated a population-based sample of women who underwent unilateral or bilateral oophorectomy between 1950 and 1987 in Olmsted County, Minnesota, U.S.A., and compared them with a cohort of referent women from the same defined population who did not undergo oophorectomy during the 38-year period. These 4,780 women were followed with a combination of active methods (direct or proxy interview and examination) and passive methods (review of medical records in a records-linkage system and review of death certificates). Women were evaluated to assess the incidence of neurologic and psychiatric disease as well as mortality through 2001–2006. Results from these landmark studies,[9–13] along with results from other shorter-term studies,[8] provide important information to guide decision-making for or against prophylactic bilateral oophorectomy before the onset of natural menopause.

Methods

A literature review of studies related to outcomes following surgical menopause and prophylactic bilateral oophorectomy was completed through 2007. In addition, results from the Mayo Clinic Cohort Study of Oophorectomy and Aging related to bilateral oophorectomy were compared with other studies with regard to overall mortality, cardiovascular, neurologic, and psychiatric outcomes.

Results

Overall mortality

Oophorectomy is associated with increased overall mortality - not limited to cardiovascular disease. In a study using a Markov decision analysis model to assess mortality attributable to oophorectomy at the time of hysterectomy, women undergoing oophorectomy before age 55 years were reported to have an 8.6% excess mortality by age 80 years.[14] Even women with oophorectomy up to age 59 years were predicted to have an excess mortality of 3.9%. So, the risk is not confined to premenopausal oophorectomy. Parker and colleagues concluded that women at average risk of ovarian cancer who undergo hysterectomy for a benign disease benefit from ovarian conservation until at least age 65 years.[14–16] The Mayo Clinic Cohort Study of Oophorectomy and Aging empirically verified these predictive models by showing that overall mortality was increased in women who underwent prophylactic bilateral oophorectomy before age 45 years compared with referent women (HR 1.67; 95% CI 1.16–2.40).[9] The increased mortality in this group of women was mainly observed in those who did not take estrogen up

to the age of 45 years (HR 1.93; 95% CI 1.25–2.96). These findings are also consistent with several studies that showed increased overall mortality in women who underwent natural menopause at younger age.[17–20]

Cardiovascular disease

In 2006, a meta-analysis evaluated 11 studies of postmenopausal status and age at menopause in relation to cardiovascular disease. The study showed that the pooled relative risk of cardiovascular disease in women who underwent bilateral oophorectomy was 2.62 (95% CI 2.05–3.35) compared with women who were premenopausal.[21] This compared with a relative risk of 1.14 (95% CI 0.86–1.51) for natural menopause versus premenopausal status. The pooled effect of bilateral oophorectomy before age 50 years was 4.55 (95% CI 2.56–8.01) compared with bilateral oophorectomy after age 50 years. This compared with a relative risk of 1.27 (95% CI 1.14–1.43) for natural menopause before age 50 years versus natural menopause after age 50 years.[21]

Also in 2006, Lokkegaard and colleagues reported on the Danish Nurse Cohort Study, a prospective cohort study of nearly 20,000 women above 44 years of age who were followed for 5 years.[22] In this study, the adjusted risk of ischemic heart disease among women who underwent bilateral oophorectomy before age 40 years was 8.7 (95% CI 2.0–38.1) compared to women with oophorectomy after age 45 years. This compared with a much smaller increased risk for ischemic heart disease among women who experienced natural menopause before age 40 years (HR 2.2; 95% CI 1.0–4.9). Among the women who experienced menopause as a result of bilateral oophorectomy, estrogen therapy was associated with significant protection against ischemic heart disease (HR 5.5 among ever users, versus 16.2 among never users). The benefit from estrogen therapy was most pronounced for women who were current users or who started treatment within 1 year after onset of surgical menopause.

Overall, the preponderance of evidence suggests that bilateral oophorectomy is associated with increased cardiovascular risk and premature death, and that oophorectomy at a young age further increases this risk.[23] Estrogen therapy started early after surgical or natural menopause at a young age appears to reduce this risk.[22–25]

Cognitive impairment or dementia

Current evidence on the association between oophorectomy and cognitive performance comes from observational studies and from small-scale clinical trials. In the Mayo Clinic Cohort Study of Oophorectomy and Aging, women who underwent bilateral oophorectomy before the onset of menopause had an increased risk of cognitive impairment or dementia compared with referent women (HR 1.33; 95% CI 0.98–1.81; $P = 0.07$). The risk increased with younger age at oophorectomy, and women under age 43 years had the greatest risk (HR 1.74; 95% CI 0.97–3.14; $P = 0.06$). The trend of increasing risk with younger age at oophorectomy was significant ($P=0.01$). Interestingly, the risk was restricted to women who underwent oophorectomy before age 49 years and were not treated with estrogen until at least age 50 years (HR 1.89; 95% CI 1.27–2.83; $P = 0.002$).[10]

Nappi and colleagues evaluated neuropsychological tasks in 27 surgically menopausal women following hysterectomy with bilateral oophorectomy and 76 naturally menopausal women at a mean age of 52 years. Women who underwent oophorectomy scored significantly worse on recency items from a word-list memory task. Additionally, the recency scores tended to be lower when oophorectomy occurred at younger ages.[26] In a longitudinal study from Egypt, 35 premenopausal women at a mean age of 41 years underwent neuropsychological testing before and after oophorectomy with hysterectomy, and results were compared with those of 18 premenopausal women matched for age, education, parity, weight, and height. Surgically

menopausal women had significant decreases in global cognitive functioning scores and Wechsler Memory Scale subtests 6 months after oophorectomy, compared with the premenopausal women who experienced no decline. Women with greater declines in estradiol levels had greater declines in performance on one of two verbal memory tasks and two of the four other cognitive tests.[27]

In the Rancho Bernardo Study, which evaluated older postmenopausal women at a mean age of 74 years in a southern California community, women with prior bilateral oophorectomy with hysterectomy performed significantly poorer on certain memory tests (serial sevens and Trails B), but the difference was reported to be of unlikely clinical significance.[28] There were no differences in mean cognitive function scores between women in this cohort who underwent bilateral oophorectomy (n = 190) versus hysterectomy with conservation of one or both ovaries (n = 225), and no differences compared with women who were naturally menopausal (n = 470). Although women who had undergone hysterectomy (with or without oophorectomy) were more likely to be using estrogen at the time of cognitive testing than women who were naturally menopausal, there was no significant difference in cognitive function tests after adjusting for current and past estrogen use. Likewise, in a British cohort of 1,261 women with a mean age of 53 years, there were no significant differences in mean cognitive test scores between women who had undergone hysterectomy, bilateral oophorectomy, or natural menopause.[29] However, women who underwent hysterectomy or bilateral oophorectomy and were not taking estrogen therapy had the lowest reading ability scores.

Clinical trials evaluating the effects of oophorectomy and estrogen therapy on cognitive function have reported contrasting results. Sherwin reported a greater decline in cognitive function tests in 40 premenopausal women who underwent hysterectomy with bilateral oophorectomy and were randomized to placebo compared with women randomized to estrogen or testosterone therapy for 3 months following surgery.[30] In a subsequent randomized controlled trial evaluating 19 premenopausal women before and after surgical menopause with a larger battery of neuropsychological tests, women were randomized to estradiol versus placebo. The women given estradiol following hysterectomy with oophorectomy performed significantly better on tests of verbal memory than women given placebo.[31]

Four other randomized controlled trials reported no cognitive benefit of estrogen after surgical menopause, but the trials were not well controlled in that oophorectomy was inferred and not confirmed, estrogen was not given immediately after surgery, and baseline testing before surgical menopause was not performed.[32–35]

Finally, a series of case-control and cohort studies evaluated the effect of estrogen treatment after menopause, regardless of the cause of menopause. They reported a 20–40% reduction in the risk of Alzheimer's disease for women starting estrogen therapy early after menopause compared with those not taking estrogen.[36–38]

Evidence to date suggests that there may be a neuroprotective effect of estrogen on the brain, and that the effect may be age-dependent. For women undergoing surgical menopause as a result of oophorectomy before the age of natural menopause, estrogen therapy may be particularly important for neuroprotection.[10,39]

Parkinsonism and Parkinson's disease

In 2001, investigators from the Mayo Clinic reported preliminary associations of Parkinson's disease with type of menopause, age at menopause, and post-menopause estrogen therapy.[40] In that case-control study evaluating 72 patients with Parkinson's disease and 72 matched controls, women with a history of hysterectomy (but without bilateral oophorectomy) were at significantly increased risk of Parkinson's disease (OR 3.36; 95% CI 1.05–10.77; $P = 0.04$) as

well as women with menopause before age 47 years (OR 2.18; 95% CI 0.88–5.39; *P* = 0.09). Finally, there was a trend toward protection against Parkinson's disease in postmenopausal estrogen therapy users for women who were naturally menopausal as well as surgically menopausal.[40] However, other studies did or did not confirm these associations.[41,42]

In the Mayo Clinic Cohort Study of Oophorectomy and Aging, women who underwent bilateral oophorectomy before the onset of menopause had an increased risk of parkinsonism compared with referent women (HR 1.80; 95% CI 1.00–3.26; *P* = 0.05), and the risk increased with younger age at oophorectomy (test for linear trend; *P* = 0.02). The findings were similar regardless of the indication for the oophorectomy (benign condition vs. prophylactic). The findings were also consistent for Parkinson's disease alone, but did not reach statistical significance.[11,12]

Psychological well-being and sexual function

While recent data report that hysterectomy performed for a benign disease is generally associated with improved psychological well-being and quality of life,[43–49] hysterectomy with bilateral oophorectomy is more commonly associated with worsened psychological well-being. In fact, the link between oophorectomy and depression has been recognized for many years.[50–53]

However, prospective evaluation of this association has been limited. Nathorst-Boos and colleagues evaluated 101 women following hysterectomy, of whom 35 had their ovaries preserved and were not taking estrogen, 33 underwent bilateral oophorectomy and were not taking estrogen, and 33 underwent oophorectomy and were taking estrogen.[54] 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 preserved. Oophorectomized women taking estrogen reported less anxiety and depression, and their psychological well-being was similar to women whose ovaries had been preserved. Similarly, oophorectomized women reported more impaired sexual function compared to women with intact ovaries; however, sexual symptoms were not ameliorated by taking estrogen.

In contrast, a more recent prospective study evaluating psychological well-being and sexual function in 323 women at baseline and one year after simple hysterectomy versus hysterectomy with oophorectomy found no difference in psychological well-being changes and no overall difference in reported sexual function changes from baseline between the two groups.[55] Of note, 98% of women who underwent hysterectomy with bilateral oophorectomy were taking estrogen at the time of testing while only 26% of women in the simple hysterectomy group were taking estrogen, and estradiol levels in the simple hysterectomy group declined significantly following surgery suggesting a decline in ovarian function in these women.

The Mayo Clinic Cohort Study of Oophorectomy and Aging followed 666 women with bilateral oophorectomy and 673 referent women using structured questionnaires and telephone interviews to assess depressive and anxiety symptoms. Women who underwent premenopausal bilateral oophorectomy were found to have an increased risk of developing *de novo* depressive symptoms (HR 1.54; 95% CI 1.04–2.26) and *de novo* anxiety symptoms (HR 2.29; 95% CI 1.33–3.95) compared with referent women.[13] This increase in depressive and anxiety symptoms occurred in women who did not suffer from depression or anxiety before the surgery, and persisted even many years after surgery.

Among women at increased risk for ovarian cancer, such as a woman with a family history of ovarian cancer or with a *BRCA* mutation, several studies have reported on the negative psychosocial and sexual consequences of prophylactic oophorectomy. Madalinska and colleagues compared quality of life after prophylactic oophorectomy versus surveillance in

their survey of 846 women, and found that the most common adverse effects of surgery were an increase in hot flashes, dyspareunia, and a decrease in sexual satisfaction.[56] In other smaller cohort studies, prophylactic oophorectomy has also been associated with a decrease in sexual satisfaction and dyspareunia.[57–62]

In 2006, Dennerstein and colleagues reported that in their survey of 1,345 European women aged 20–70 years, women who underwent bilateral oophorectomy were twice as likely to meet diagnostic criteria for hypoactive sexual desire disorder compared with women who were premenopausal or experienced natural menopause.[63]

Osteoporosis

Numerous studies through the years have shown that bone loss accelerates following menopause. The earlier in life that menopause occurs, the lower the bone density will be later in life.[64] Oophorectomy before age 45 is a well-established risk-factor for osteoporosis.[65] In addition, even in women who undergo bilateral oophorectomy after natural menopause, the risk of osteoporotic fracture may be increased compared with women with intact ovaries.[66] Estrogen therapy reduces this risk, and there are now also numerous non-estrogen treatment options for postmenopausal osteoporosis.[67] The frequency of use of these non-estrogen treatments in women discontinuing estrogen therapy following surgical menopause is unknown.

Discussion

Women facing the decision to undergo prophylactic bilateral oophorectomy at the time of hysterectomy are confronted with a difficult dilemma. Guidance regarding the decision generally focuses on a reduction in risk for ovarian cancer. But, evidence shows that a woman's lifetime risk for premature death, cardiovascular disease, cognitive impairment or dementia, symptoms of parkinsonism, and osteoporosis may be adversely impacted by premature loss of ovarian function. Additionally, the potential adverse effects on quality of life, sexual function, and mental health are rarely discussed with women considering this surgical procedure. The risk-benefit balance for prophylactic bilateral oophorectomy in younger women is outlined schematically in Figure 1.

Premature loss of ovarian function by elective oophorectomy before natural menopause is associated with an increased risk for premature death, cardiovascular disease, cognitive impairment or dementia, parkinsonism, a decline in psychological well-being and, in some studies, a decline in sexual function. Whether these consequences are due to the abrupt drop in estrogen, testosterone, or progesterone levels, or whether the changes might be mediated through effects on the hypothalamic-pituitary axis via an increase in gonadatropins remains unknown. Estrogen levels are higher in women with ovaries intact than in women after bilateral oophorectomy, even in older women.[68,69] Now that women are discouraged from initiating estrogen therapy, those who undergo oophorectomy at a young age and do not initiate or continue estrogen therapy until at least the age of natural menopause are at significantly increased risk for several chronic diseases of aging.

In the specialty of Obstetrics and Gynecology, the predominant teaching in recent years has been that prophylactic bilateral oophorectomy should be avoided in women under the age of 40 years, should routinely be performed above age 55 years, and should be considered and discussed with the patient in the interval between.[70] More research is needed to appropriately inform women between the ages of 40 and 55 years about the risks and benefits of prophylactic oophorectomy. The findings summarized in this review argue for thoughtful scrutiny of the practice of prophylactic oophorectomy at all ages, for women who are not known to be at increased risk for ovarian cancer. Additionally, more research is needed to determine the

relative benefits and risks of hormone therapy for this group of women. The studies summarized in this review article argue for caution against thoughtlessly applying the results of the Women's Health Initiative clinical trials to hormone therapy decisions for women with prophylactic bilateral oophorectomy.[71]

Finally, the primary consideration favoring prophylactic bilateral oophorectomy is the lack of effective screening tools for ovarian cancer. When diagnosed early, cure rates for ovarian cancer are as high as 90% to 95%. However, this disease has appropriately earned a dreaded reputation because vague and non-specific symptoms lead to late stage diagnosis in 75% of patients.[72] Unfortunately, advanced ovarian cancer has a low cure rate in spite of aggressive medical and surgical therapy. An effective and affordable screening test that allows early diagnosis, when ovarian cancer is most treatable, will eliminate the justification for prophylactic bilateral oophorectomy. Fortunately, considerable research is being directed toward that goal.[73]

In the meantime, elective oophorectomy in women not known to be at increased risk for ovarian or breast cancer needs to be carefully considered in the context of each woman's health risks, goals, and personal preferences.

Acknowledgements

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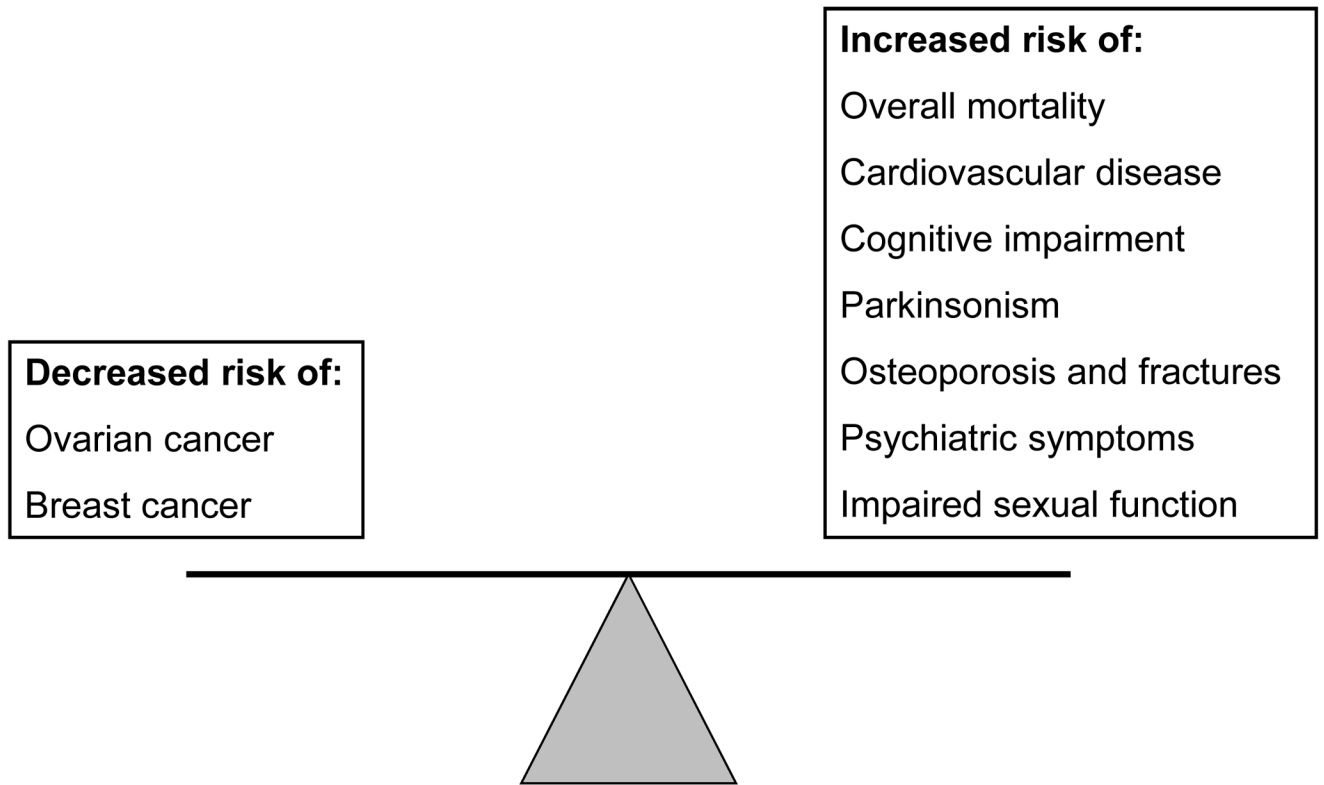
Figure 1.
The risk-benefit balance for prophylactic bilateral oophorectomy in younger women.