

Elective oophorectomy for benign gynecological disorders

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Abstract

Objective: To review the risks and benefits of elective oophorectomy and to make a clinical recommendation for an appropriate age when benefits of this procedure outweigh the risks.

Design: The risks and benefits of oophorectomy as detailed in published articles are reviewed with regard to quality-of-life issues and mortality outcomes in oophorectomized versus nonoophorectomized women from five diseases linked to ovarian hormones (coronary heart disease, ovarian cancer, breast cancer, stroke, and hip fracture).

Results: Numerous reports link oophorectomy to higher rates of cardiovascular disease, osteoporosis, hip fractures, dementia, short-term memory impairment, decline in sexual function, decreased positive psychological well-being, adverse skin and body composition changes, and adverse ocular changes, as well as more severe hot flashes and urogenital atrophy. The potential benefits associated with oophorectomy include prevention of ovarian cancer, a decline in breast cancer risk, and a reduced risk of pelvic pain and subsequent ovarian surgery. In our study of long-term mortality after oophorectomy using Markov modeling, preservation of ovaries until women are at least aged 65 years was associated with higher survival rates. For women between ages 50 and 54 with hysterectomy and ovarian preservation, the probability of surviving to age 80 was 62% versus 54% if oophorectomy was performed. This 8% difference in survival is primarily due to fewer women dying from cardiovascular heart disease and/or hip fracture. This survival advantage far outweighs the 0.47% increased mortality rate from ovarian cancer prevented by oophorectomy. If surgery occurred between ages 55 and 59, the survival advantage was 4%. After age 64 there were no significant differences in survival rates. Prior literature supports our conclusion of a benefit over risk for ovarian conservation.

Conclusions: Elective oophorectomy is associated with short- and long-term health consequences that merit serious consideration. For women with an average risk of ovarian cancer, ovarian conservation until at least age 65 seems to benefit long-term survival.

Key Words: Elective oophorectomy – Osteoporotic hip fracture – Mortality – Cardiovascular disease.

The average life expectancy of U.S. women is now 78 years, making quality of life as well as long-term health even more important to menopausal women. Despite this fact, there is continued controversy about the long-term risks and benefits of elective oophorectomy during hysterectomy for benign disease.^{1,2} Reported elective oophorectomy rates are between 50% and 66% in women undergoing hysterectomy between ages 40 and 64.³⁻⁵ This rate rises to 78% for those between ages 45 and 64.⁶

Generally, most elective oophorectomies are done to reduce the risk of ovarian cancer. It is estimated that approximately 1,000 cases of ovarian cancer can be

prevented if prophylactic oophorectomy is performed in all women older than 40 years who undergo hysterectomy in the United States.⁷ This estimate assumes an incidence of 24,000 new cases of ovarian cancer per year and does not take into account the incidence of peritoneal carcinoma. The underlying question is whether the estimated number of ovarian cancer cases prevented (1,000) is worth the risk associated with 300,000 elective oophorectomies.⁷

BENEFITS OF OOPHORECTOMY

Ovarian cancer prevention

In the United States, 1.4% of women will develop ovarian cancer in their lifetime. At age 50, this number is 1 in 1,500. At age 70, the age of peak incidence, 1 woman in 400 will be found to have ovarian cancer.⁸ If women with known BRCA1 or BRCA2 germ-line mutations or those from high-risk families are excluded, ovarian cancer is even more uncommon. Of importance, hysterectomy alone is associated with a 50% less risk for ovarian cancer.^{9,10}

Of women with ovarian cancer, between 4% and 14% have had an antecedent hysterectomy with ovarian conservation.¹¹ Current screening techniques for detecting

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ovarian cancer, including the use of tumor markers and ultrasound, are neither sensitive nor specific enough to detect early cancer as part of a general screening program. Unfortunately, most ovarian cancer is detected when it is in an advanced stage. Oophorectomy does not completely eliminate the risk of subsequent ovarian cancer, because peritoneal carcinoma can still develop, although it is rare.

Breast cancer protection

Numerous population-based studies reported an apparent protective effect of oophorectomy for breast cancer, which was strongest among women who are both premenopausal and younger than age 50 or are at high risk for breast cancer.^{12,13} Before age 50 these women may have up to a 50% reduction in breast cancer for 10 years after surgery. No reduction in risk has been reported in those women having an oophorectomy after age 50.¹⁴

Decreased risk of future oophorectomy

Oophorectomy may prevent pelvic pain, residual ovary syndrome, ovarian cyst formation, or endometriosis. Benign ovarian cysts, however, are common among postmenopausal women and rarely require surgical intervention. Multiple studies of postmenopausal women with a sonographically benign adnexal cyst and normal CA-125 levels reported no malignancy upon removal.¹⁵ In one study, sonographic screening of 7,705 asymptomatic postmenopausal women showed unilocular cysts in 3.3%, and none of these women were subsequently found to have cancer.¹⁶ The current recommendation is expectant management for postmenopausal women with no increase in cyst size or CA-125 levels.¹⁷ In a study by 'Dekel et al'¹⁸ of 2,561 women who had undergone a hysterectomy without oophorectomy, after 20 years of follow-up, only 2.8% required subsequent oophorectomy.

BENEFITS OF OVARIAN CONSERVATION

The beneficial effects of estrogen on lipid metabolism, vascular integrity, and bone remodeling remain the primary argument for retention of the ovaries in premenopausal women. Although there is a loss of follicular development and a resultant drop of both androgen and estrogen levels during the menopausal transition, the ovarian stroma remains an important source of androgens that are peripherally converted to estrogens.¹⁹⁻²² Menopausal women with intact ovaries have significantly higher plasma levels of androstenedione and testosterone than oophorectomized menopausal women.²³⁻²⁶ The benefits of endogenous androgens (and their derivatives) and the consequences of removal are discussed below.

Cardiovascular disease and risk factors

Oophorectomy in both premenopausal and postmenopausal women is linked to an increased risk of cardiovascular disease,²⁷⁻³⁵ the major cause of death for women. Oophorectomy after age 50 increases the risk of developing a first myocardial infarction by 40% (relative risk, 1.4; 95% CI, 1.0-2.0) compared with control subjects.^{34,35} The

Nurses' Health Study (a prospective study of 121,700 women) reported a 2.2-fold greater relative risk for coronary heart disease in oophorectomized, non-estrogen-treated women compared with naturally menopausal women.³⁶ Data from the Women's Health Initiative showed that hysterectomy with oophorectomy is an independent predictor of myocardial infarction or coronary death.³⁷ Earlier natural or surgical menopause is associated with more subclinical atherosclerosis compared with age-matched control subjects.^{38,39}

Type 2 diabetes and cardiovascular diseases were more prevalent in postmenopausal women than in premenopausal age-matched counterparts.⁴⁰ After menopause, dyslipidemias are more frequent, especially reduced levels of high-density lipoprotein and adverse changes in apolipoprotein A and B. Other adverse cardiovascular risk factors, including worse fibrinogen and insulin resistance, are more prevalent.⁴¹⁻⁴⁴ In one study, surgical oophorectomy was linked to higher salt sensitivity, a risk factor for development of hypertension.⁴⁵ Multiple studies document adverse changes in cardiovascular risk factors in premenopausal women after oophorectomy.⁴⁶⁻⁴⁸

Osteoporosis and hip fracture

Both estrogens and androgens inhibit bone resorption, and androgens increase bone formation.^{49,50} Early oophorectomy (before age 45) has been an accepted risk factor for the development of osteoporosis.⁵¹ In a study following postmenopausal women for 16 years, those women who had undergone oophorectomy (during their postmenopausal years) had 54% more osteoporotic fractures than women with intact ovaries.⁵² A prospective study found oophorectomized women older than age 60 had a twofold increase in mortality (odds ratio, 2.18; 95% CI, 2.03-2.32) after low-trauma hip fractures.⁵³

Dementia

In a recent study from the Mayo Clinic, researchers reported an increased risk of dementia, cognitive impairment, and neurological disturbances, such as Parkinson disease, in elderly women who had previously undergone oophorectomy.⁵⁴ Multiple studies report significant declines in cognitive ability within the weeks⁵⁵⁻⁵⁷ or years⁵⁸ after oophorectomy. These findings are supported by a large number of studies linking normal brain function and endogenous ovarian hormones.⁵⁹⁻⁶¹

Feeling of well-being/depression

After early bilateral oophorectomy, some women may experience a decline in feelings of well-being or report a negative affect.⁶²⁻⁶⁵ Population studies⁶⁶ and clinical studies link a higher frequency of depression in women following surgical compared to natural menopause.⁶⁷ Randomized trials to explore this link are lacking.

Sexual function

Some oophorectomized women are more likely to report worsening of sexual function after hysterectomy compared

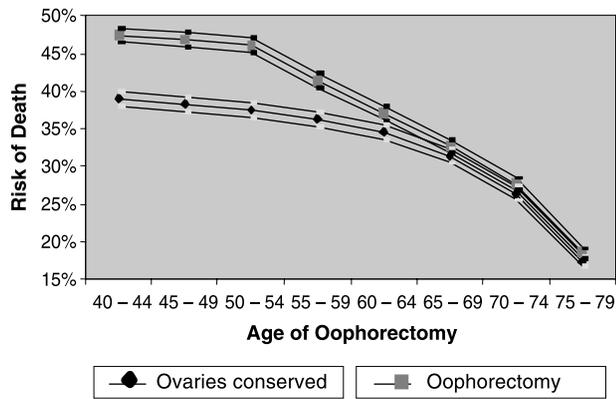


FIG. 1. Risk of death ($\pm 95\%$ CI) in women from ages 40 through 80 for women with and without oophorectomy. Adapted from Parker et al.¹

with women who retain their ovaries.⁶⁸ Adverse changes in libido and orgasmic response may be more likely in oophorectomized women. Studies of both the consequences of oophorectomy and the beneficial effects of testosterone replacement are evidence of the important role of androgens in female sexual function and psychological well-being.⁶⁹⁻⁷³

Lens opacities and macular degeneration

Surviving members of the original cohort of the Framingham Heart Study who also participated in the Framingham Eye Study (1986-1989) were examined for the absence or presence of lens opacities. The risk of posterior subcapsular opacities was significantly increased for women who had undergone surgical menopause compared with women who experienced natural menopause (odds ratio, 2.2; 95% CI, 1.1-4.3).⁷⁴ Early menopause is linked with higher rates of macular degeneration.⁷⁵

Skin and body composition

The distribution of body fat and body fat composition may be affected by menopausal hormones.⁷⁶⁻⁸² Postmenopausal women, particularly those who underwent surgical menopause, might have a greater risk for lowered overall muscle mass and development of central adiposity as detected by both waist circumference and waist-to-hip ratio.

Menopausal symptoms and urogenital atrophy

Oophorectomy in premenopausal and some postmenopausal women may lead to the sudden onset of hot flashes and mood disturbances.⁸³⁻⁸⁶ Other problems include poor-quality sleep, headaches, and depression. The frequency and severity of these symptoms along with problems associated with urogenital atrophy are increased in oophorectomized women compared with naturally menopausal women.⁸⁷

OVERALL EFFECTS OF OOPHORECTOMY ON LONG-TERM MORTALITY

Despite a long list of negative quality-of-life issues after oophorectomy, a benefit of survival has not been documented for oophorectomy in women with an average risk of ovarian cancer. Before publication of the results of our

study¹ and a recent report from the Mayo Clinic,⁸⁸ no reports had directly addressed this issue. In the Mayo Clinic study, researchers reported that prophylactic ovarian removal before age 45 significantly increased a woman's chance of death (hazard ratio, 1.67; 95% CI, 1.16-2.40). In this study approximately 4,800 women were evaluated between 1950 and 1987.

In our study,¹ the Cochrane database and PubMed were used to select articles that reported occurrence of and mortality from coronary heart disease, ovarian cancer, breast cancer, stroke, or hip fracture in oophorectomized and nonoophorectomized women. Mortality rates in the general population were derived from the Surveillance, Epidemiology and End Results⁹ database and the National Center for Health Statistics.⁸⁹ All-cause mortality rates in women were obtained from National Vital Statistics Reports.⁹⁰ These data were entered into a Markov decision model for the purpose of calculating mortality risk estimates at 5-year intervals for women aged 40 through 80.

In our model, hysterectomy alone was assumed to reduce the risk of development of ovarian cancer by 46%.^{10,11,91} Although not well understood, this reduced risk may be a result of decreased levels of carcinogens, such as talc, endometrial tissue, and human papilloma virus, reaching the ovaries or the formation of antibodies to ovarian cancer cells.⁹² The risk of ovarian cancer after bilateral oophorectomy was assumed to be 0%. Women who had oophorectomy before age 50 were assumed to have a 50% reduction in breast cancer rates for 10 years after surgery.¹⁴

The risk of myocardial infarction for women after oophorectomy up to age 55 was assumed to be double the baseline risk.³⁴⁻³⁶ For women aged 55 to 65 years, the risk was assumed to decrease 6% for each year in menopause that oophorectomy was delayed.⁹³

TABLE 1. Factors to consider when discussing the risks of an elective oophorectomy

Risks linked to oophorectomy
Body composition changes
Higher percentage of adipose tissue and lower muscle mass
Cardiovascular disease
Higher rates of myocardial infarction
Higher rates of atherosclerosis
Adverse changes in multiple cardiovascular risk factors
Increase in risk of mortality
Central nervous system
Short-term memory declines
Dementia
Declines in sense of well-being
Len opacities and macular degeneration
Menopausal symptoms
Osteoporosis and fractures
Increased risk of mortality
Sexual dysfunction and loss of desire
Skin changes
Loss of collagen
Urogenital atrophy

Surgical removal of ovaries in premenopausal women is often associated with sudden changes in ovarian hormones and can result in a sudden onset of symptoms that can be more severe than in women undergoing natural menopause. Surgical menopause through age 65 is linked to multiple adverse conditions.

Women having oophorectomy after age 49 were assumed to have a 50% increased risk of hip fracture and associated mortality.^{52,53} Women who had a hip fracture between ages 60 and 64 were determined to have lost 11 years of life, and for those with a fracture between ages 70 and 74, a 4.4-year loss was assumed.⁹⁴

In our hypothetical cohort, women with an average risk of ovarian cancer who had hysterectomy and ovarian conservation between ages 50 and 54 have a probability of surviving to age 80 of 62% versus 54% if oophorectomy was performed (Fig. 1). This difference in survival is due primarily to fewer women dying of cardiovascular heart disease (16% vs 8%) and hip fracture (5% vs 3%). The survival advantage from these two causes is much greater than the small (0.47%) increased mortality rate from ovarian cancer after simple hysterectomy and ovarian conservation. If surgery occurs between ages 55 and 59, this model predicts a survival advantage of 4%. After age 64, there is no significant difference in survival.

Hypothetically, if 10,000 women undergo oophorectomy with hysterectomy (vs ovarian conservation) between the ages of 50 to 54, our model predicts that by age 80, 47 fewer women will have died from ovarian cancer; however, 838 more women will have died from cardiovascular disease and 158 more from hip fracture. The excess mortality is 858 per 10,000 women.

Our study has several inherent weaknesses. Our probability estimates are derived mainly from case-control studies, and case-control studies are prone to selection bias, information bias, or confounding bias. Our study, of necessity, combines data from several different studies with disparate populations. Further studies to more accurately identify risks and benefits of elective oophorectomy are clearly needed. A randomized, long-term study, although ideal, would be very difficult to complete.

The effects of exogenous estrogen use or of bisphosphonate or statin therapy were not directly addressed in this study. Population-based studies, however, include a certain percentage of women taking these medications, and the published results would reflect the benefit of their use in the general population. Overall, the continuation rate for all of these products remains low. The use of long-term estrogen therapy fell from 12% to 9% after the publication of the Women's Health Initiative.^{95,96} Overall continuation rates for osteoporosis medications including bisphosphonates for 12 months have been reported to be less than 25%.⁹⁷ Statin adherence rates are documented to be as low as 18% at 1 year.⁹⁸ Early and sustained use of these products in appropriate candidates would be expected to beneficially affect survival in both naturally and surgically menopausal women.

CONCLUSIONS

Numerous reports link oophorectomy to higher rates of cardiovascular disease, osteoporosis, hip fracture, dementia, short-term memory impairment, declines in sexual function, decreased positive psychological well-being, adverse skin

and body composition changes, and adverse ocular changes, as well as more severe menopausal symptoms and urogenital atrophy. The results of our ovarian conservation modeling study and the current literature suggest that there is no survival benefit with oophorectomy. However, for women younger than age 65 years who have an average risk for ovarian cancer, there seems to be an overall decline in long-term survival.

The decision whether or not to have an elective oophorectomy is an important medical decision that warrants a thoughtful dialogue between a woman and her doctor about the potential risks and benefits (Table 1). Ovarian conservation should be strongly considered in women younger than age 65 who have an average or low risk for ovarian cancer.

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