Elective oophorectomy in the gynecological patient: when is it desirable?

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Purpose of review
Oophorectomy is electively performed in approximately 300 000 US women per year who are having hysterectomy for benign disease.
Recent findings
New studies have suggested that elective oophorectomy may not be advisable for the majority of women, as it may lead to a higher risk of death from cardiovascular disease and hip fracture, and may result in a higher incidence of dementia and Parkinson's disease. Women with known BRCA 1/2 germ-line mutations clearly benefit from oophorectomy after childbearing.
Summary
Prophylactic oophorectomy should be undertaken with caution in the majority of women with an average risk of ovarian cancer who are having a hysterectomy for benign disease.

Keywords
elective oophorectomy, hysterectomy, oophorectomy, prophylactic oophorectomy

Curr Opin Obstet Gynecol 19:350–354. © 2007 Lippincott Williams & Wilkins.

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Current Opinion in Obstetrics and Gynecology 2007, 19:350–354

Abbreviations

CHD coronary heart disease
WHI Women's Health Initiative

1040-872X

Introduction

Gynecologists have long suggested that prophylactic oophorectomy is the best strategy to decrease the rate of ovarian cancer [1]. With the general acceptance of this theory, the percentage of hysterectomies accompanied by bilateral oophorectomy has more than doubled, from 25% in 1965 to 55% in 1999. Of the 600 000 hysterectomies performed yearly in the United States, approximately 300 000 are accompanied by prophylactic bilateral oophorectomy.

Ovarian cancer is hard to diagnose before it has metastasized, and late stage disease is associated with a high mortality rate. Excluding women with known BRCA 1 or 2 germ-line mutations, ovarian cancer is an uncommon malignancy. At 50 years of age, only approximately one in 1500 women, and at 70 years of age, the age of peak incidence, only one in 400 women will be found to have ovarian cancer (Table 1). Although approximately 16 000 women die of ovarian cancer every year, 70 000 die of lung cancer, 28 000 die of colon cancer, 40 000 die of breast cancer, 490 000 women die of heart disease, and 48 000 women die after hip fracture.

Benefits of ovarian conservation

After the menopause there is a loss of follicular development and a resultant drop in estrogen levels, but the ovarian stroma remains an important source of androgens, producing androstenedione and testosterone in significant amounts until 80 years of age [2]. These androgens are converted in fat, muscle and skin into estrone, the primary estrogen in postmenopausal women. Menopausal women with intact ovaries have significantly higher plasma levels of androstenedione and testosterone than oophorectomized menopausal women [3,4]. The benefits of preserving ovarian function include a lower risk of coronary heart disease (CHD), osteoporotic fracture, dementia, Parkinson's disease, sexual function and a lower incidence of menopausal symptoms.

Cardiovascular disease

Oophorectomy in both premenopausal and postmenopausal women is linked to an increased risk of cardiovascular disease, the major cause of death for all women. Data from the Women's Health Initiative (WHI) showed that hysterectomy with oophorectomy is an independent predictor of myocardial infarction or coronary death [5].

Table 1 Annual incidence of ovarian cancer by age group

At age 40 years – 1 in 2500
At age 50 years – 1 in 1500
At age 60 years – 1 in 600
At age 70 years – 1 in 400
At age 80 years – 1 in 400

Source: SEER database.

Earlier natural or surgical menopause is associated with more subclinical atherosclerosis compared with age-matched controls [6,7]. Oophorectomy after 50 years of age increases the risk of developing a first myocardial infarction by 40% [relative risk 1.4; 95% confidence interval (CI) 1.0–2.0] compared with controls. The Nurses' Health Study (121 700 women) reported a 2.2-fold greater relative risk of CHD in oophorectomized, non-estrogen-treated women compared with naturally menopausal women [8].

Hip fracture

Both estrogens and androgens inhibit bone resorption, and androgens increase bone formation [9]. In a study following women for 16 years, those women who had undergone an oophorectomy during their postmenopausal years had 54% more osteoporotic fractures than women with intact ovaries [10]. A prospective study found that oophorectomized women older than 60 years had a twofold increase in mortality [odds ratio 2.18; 95% CI 2.03–2.32] after low trauma hip fractures [11].

Dementia

In a recent study from the Mayo Clinic [12••], researchers reported an increased risk of dementia, cognitive impairment and neurological disturbances, such as Parkinson's disease, in elderly women who had previously undergone oophorectomy. Many studies report significant declines in cognitive ability after oophorectomy [13]. These findings are supported by a large number of studies linking normal brain function and endogenous ovarian hormones [14].

Sexual function

Some oophorectomized women are more likely to report a worsening of sexual function after hysterectomy compared with women who retain their ovaries. Adverse changes in libido and orgasmic response may be more likely in oophorectomized women [15].

Menopausal symptoms and urogenital atrophy

Oophorectomy in premenopausal and some postmenopausal women may lead to the sudden onset of hot flushes and mood disturbances [16]. Symptoms of urogenital atrophy are increased in women following oophorectomy.

Overall effects of oophorectomy on long-term mortality

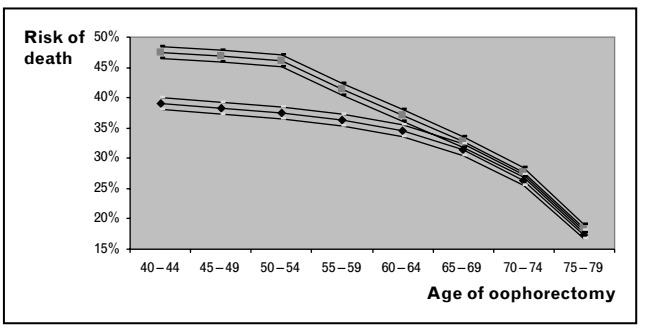
We published a study using the Cochrane database and PubMed to select articles reporting disease and mortality in women having oophorectomy or ovarian conservation from CHD, ovarian cancer, breast cancer, stroke or hip fracture [17]. Mortality rates in the general population were derived from the Surveillance, Epidemiology and End Results (SEER) database and the National Center for Health Statistics [18,19]. All-cause mortality rates in women were obtained from National Vital Statistics Reports [20]. These data were entered into a Markov decision model for purposes of calculating mortality risk estimates at 5-year intervals for women having oophorectomy between the ages of 40 and 75 years.

In our model, hysterectomy alone was assumed to reduce the risk of developing ovarian cancer by 46% [21]. Although not well understood, this reduced risk may be a result of a decreased number of carcinogens reaching the ovaries such as talc, endometrial tissue, and human papillomavirus, or the formation of antibodies to ovarian cancer cells after injury to tissue in the reproductive tract [22]. The risk of ovarian cancer after bilateral oophorectomy was assumed to be 0% (primary peritoneal cancer is a distinct disease).

In that study, women at average risk of ovarian cancer who have had hysterectomy and ovarian conservation between 50 and 54 years have a probability of surviving to the age of 80 years of 62% compared with 54% if oophorectomy was performed (Figure 1). This difference in survival is primarily the result of fewer women dying of cardiovascular heart disease (16 versus 8%) and hip fracture (5 versus 3%).

Hypothetically, if 10 000 women undergo oophorectomy with hysterectomy (versus ovarian conservation) between the ages of 50 and 54 years, our model predicts that by the age of 80 years, forty-seven fewer women will have died from ovarian cancer; however, 838 more women will have died from cardiovascular disease and 158 more from hip fracture. When all-cause mortality is factored, excess mortality is 858 per 10 000 women after oophorectomy.

Figure 1 Risk of death by age 80 years for non-estrogen replacement therapy users as a function of age at oophorectomy with 95% confidence interval



—◆— Ovarian conservation; —■— oophorectomy.

Our study included probability estimates mainly derived from case–control studies that may include selection bias, information bias or confounding bias. Our study was constructed from data derived from different studies with disparate populations.

The Mayo study evaluated a population-based sample of women in Minnesota who had an oophorectomy between 1950 and 1987, and compared them with age-matched controls. The authors reported that prophylactic oophorectomy before the age of 45 years significantly increased a woman's chance of death (1.67; 95% CI 1.16–2.40), particularly from estrogen-related cancers and neurological disorders.

Benefits of oophorectomy

The benefits of oophorectomy include the prevention of ovarian cancer, a short-term reduction of breast cancer and a 2.8% reduction in subsequent ovarian surgery.

Ovarian cancer prevention

Current screening techniques for detecting 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 programme. Unfortunately, most ovarian cancer is detected when it is in an advanced stage.

Approximately 1.4% of women will develop ovarian cancer in their lifetime. At the age of 50 years one in 1500 and at the age of 70 years, the age of peak incidence, one in 400 women will be found to have ovarian cancer. If women with known BRCA 1 or 2 germ-line mutations are excluded, ovarian cancer is even more uncommon. Although hysterectomy alone is associated with 50% less risk of ovarian cancer, bilateral oophorectomy reduces the risk to essentially nil [23].

Breast cancer protection

Population-based studies have reported that oophorectomy has an apparent protective effect against the development of breast cancer. Oophorectomy before the age of 50 years may result in a 50% reduction in breast cancer for 10 years after surgery; however, no reduction in risk has been reported in women having an oophorectomy after the age of 50 years [24].

Decreased risk of subsequent ovarian surgery

Benign ovarian cysts are common among postmenopausal women and rarely require surgical intervention. In one study [25], sonographic screening of 7705 asymptomatic postmenopausal women found unilocular cysts in 3.3% and none of the women were subsequently found to have ovarian cancer. Many studies of postmenopausal women with sonographically benign adnexal cysts and normal CA-125 levels have reported no malignancy upon removal [26]. For postmenopausal women with no increase in cyst size or abnormal CA-125 levels, the current recommendation is expectant management [27].

Concern about the subsequent need for surgery for pelvic pain or ovarian cysts often leads to elective oophorectomy at the time of hysterectomy. After 20 years of follow-up for 2561 women who had undergone a hysterectomy without oophorectomy, only 2.8% had required subsequent oophorectomy [28].

Medical therapy after oophorectomy

The assumption that medical treatment can ameliorate heart disease or osteoporosis after oophorectomy is not convincing. In 1999, before publication of the WHI, only 31% of women continued to use estrogen therapy for 5 years or longer after hysterectomy and oophorectomy [29]. In the 6 months after the publication of the WHI both continuation rates and new starts of estrogen therapy decreased [30]. A study of women with documented osteoporosis and beginning treatment with either estrogen therapy, estrogen and progestin, bisphosphanates or raloxifene ($n = 58\,109$) found medication continuation rates of less than 25% at 12 months [31]. Likewise, statin continuation rates are 18% at the end of one year [32]. Women may have side effects, cost-related issues, or fears about medications that preclude use despite a physician's recommendation. Furthermore, such studies do not include women who never see a doctor, who never get a prescription, or who get a prescription but choose not to fill it. Therefore, the subsequent risk of untreated disease for large numbers of women is underestimated.

When is oophorectomy appropriate?

Oophorectomy is appropriate for women with BRCA 1/2 mutations, and may be appropriate for women with severe endometriosis or who want oophorectomy on the basis of their personal weighing of the risks and benefits of this procedure.

BRCA 1/2 mutation carriers

Women with BRCA 1 and 2 mutations have a lifetime risk of ovarian cancer of 39% and 11%, respectively [33]. A number of studies have shown clear benefits of oophorectomy for women who carry the BRCA 1/2 mutations. In a study of 259 carriers electing for oophorectomy compared with 292 carriers not having oophorectomy, the risk of ovarian cancer was reduced by 96% (4% developed primary peritoneal cancer) and the risk of breast cancer was reduced by 53% over the 8-year follow-up period [34].

A decision analysis found that a cohort of women with documented mutations who had prophylactic oophorectomy after completing childbearing would be expected to increase life expectancy by 3–5 years depending on the

age when oophorectomy was performed [35]. Therefore, prophylactic oophorectomy is advised in women with these mutations after the completion of childbearing.

Severe endometriosis

Women with symptomatic severe endometriosis, who have not responded to conservative medical or surgical therapy, may choose hysterectomy with ovarian conservation if the ovaries are normal. If the ovaries are severely affected, however, bilateral oophorectomy can be appropriate. Surgery should also include the resection of all peritoneal lesions to ensure successful pain relief. In that oophorectomy causes the estrogen deficiency long-term health conditions noted above, it should be undertaken with caution. The patient should understand the potential risks, and be agreeable to long-term estrogen therapy.

Oophorectomy by patient choice

Some women may choose oophorectomy on the basis of their personal weighing of the risks and benefits. A woman who has experienced a relative or friend dying of ovarian cancer may choose to avoid that disease at any cost. Others, with a family history of CHD, may choose conservation. An active dialogue between each woman and her doctor regarding the risks and benefits of ovarian conservation/oophorectomy will best inform this decision.

Conclusion

Approximately 300 000 US women are subjected to incidental oophorectomy annually. Up until now, this decision was based on one factor alone – the risk and fear of ovarian cancer. Clearly, that is inappropriate. Hopefully, our study and the Rocca study will raise awareness among women and their gynecologists regarding the public health consequences of routinely performed oophorectomy. We wish to allow individual women to determine their own particular risks and concerns regarding the related conditions. We are presently undertaking a collaboration with the Nurse's Health Study to analyse the health outcomes, with regards to ovarian conservation/oophorectomy, of the 122 000 women enrolled in their database. Hopefully, the study will shed more light on the risks and benefits of ovarian conservation.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 409).

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