CONTEMPORARY OB/GYN®

Grand Rounds: Hysterectomy sans oophorectomy: The case for leaving a woman's ovaries alone

If there's no cancer present, why remove a woman's ovaries during hysterectomy? Does the reduced risk of ovarian cancer outweigh the consequences of eliminating the protective hormones secreted by a healthy pair of ovaries? A team of researchers offers some thought-provoking conclusions.

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TABLE 1
Annual incidence of ovarian cancer by age group

At age 40	1 of 2,500
At age 50	1 of 1,500
At age 60	1 of 600
At age 70	1 of 400
At age 80	1 of 400

Table 1. Annual incidence of ovarian cancer by age group

Gynecologists have long suggested that prophylactic oophorectomy is the best way to decrease the rate of ovarian cancer.[1] In fact, calculations suggest that routine oophorectomy for women over 40 years old who are having a hysterectomy for benign conditions would save about 1,000 US women per year from getting ovarian cancer.[2] With the general acceptance of this notion, the percentage of hysterectomies accompanied by bilateral oophorectomies more than doubled from 25% in 1965 to 55% in 1999. Of the 600,000 hysterectomies performed yearly in the US, approximately 300,000 are accompanied by prophylactic bilateral oophorectomy.

Ovarian cancer is a difficult disease to manage because it's hard to diagnose before it metastasizes, and late-stage disease is too often fatal. But excluding women from high-risk families—those with known *BRCA1* or *BRCA2* germ-line mutations, for example—ovarian cancer is a relatively uncommon malignancy. At age 50, only about one in 1,500 women will be diagnosed with ovarian cancer and at age 70, the age of peak incidence, only one in 400 will be found to have ovarian cancer (Table 1). In fact, ovarian cancer is much less common than lung, colon, or breast cancer. Although about 15,000 women die of ovarian cancer every year, 68,000 die of lung cancer, 28,000 die of colon cancer, and 42,000 die of breast cancer. And, significantly, 479,000 women die of heart disease every year and about 48,000 women die within 1 year following hip fracture (Table 2).


Number of women dying per year

Table 2. Number of women dying per year

The cumulative lifetime mortality rate for women from ovarian cancer after hysterectomy for benign disease is 0.47%, or fewer than one in 200. This is lower than the often-stated lifetime risk of one in 70, a number that includes women with *BRCA1* or *BRCA2* mutations or other high-risk germ-line mutations.

Women are living longer, with an average life expectancy of 78 years, and long-term health issues are important. When considering any potential benefits of removing a patient's ovaries, one has to also consider the benefits of preserving them, which include lower risks of osteoporotic fracture and coronary heart disease, as we'll discuss further on.

Despite these important health concerns, many women feel that they do not have enough information about long-term risks and benefits to help them make a decision regarding the prophylactic removal of ovaries when they are having a hysterectomy for benign disease.[3] A recent decision analysis for women with inherited *BRCA1/2* mutations and at high risk for ovarian cancer (and breast cancer) found that prophylactic oophorectomy was clearly beneficial after completion of childbearing.[4] But a recommendation for women

with average risk of ovarian cancer has not been established.

The ideal way to study this issue would be with a prospective, randomized trial. However, to be statistically valid and yield meaningful outcomes, such a study would require 8,000 women randomized to oophorectomy or ovarian conservation and then followed for 40 years. So it's unlikely that outcomes will ever be studied in this way.

Why preserve the postmenopausal ovary?

[Nevertheless, there's strong evidence that the risk of developing ovarian cancer after hysterectomy performed for benign disease is 40% lower than expected based on its prevalence in the general population.[5-7]] Because the reduction in risk of ovarian cancer persists for 10 to 20 years after surgery, this effect is not the result of screening bias. Theories to explain the decreased risk include blocking reflux of carcinogens, such as endometrial tissue, human papilloma virus, or talc[8,9] through the reproductive tract to the ovaries, and destruction of reproductive-tract tissue during surgery with release of antigens that cause the formation of antibodies (MUC1) to ovarian cancer cells.[10]

Premenopausal oophorectomy causes an immediate and significant loss of all ovarian hormones. Following menopause, a normal ovary continues to produce androstenedione and testosterone in significant amounts until age 80.[11] These androgens are converted in fat, muscle, and skin into estrone, the primary estrogen in postmenopausal women. As you might expect, following oophorectomy, menopausal women have significantly lower plasma levels of androstenedione and testosterone than naturally menopausal women.[12]

Both estrogens and androgens inhibit bone resorption, and androgens increase bone formation. Blood levels of testosterone and estradiol are correlated with hip fractures in postmenopausal women.[13,14] One study found that after 16 years of follow-up (median), women who were postmenopausal at the time of oophorectomy had 54% more osteoporotic fractures than women with intact ovaries.[15] A prospective study found women older than 60 had a twofold increase in mortality (OR 2.18; CI 2.03–2.32) following low-trauma hip fractures.[16]

[Oophorectomy also increases the risk of cardiovascular disease, the major cause of death for women. Oophorectomy after age 50 increases risk of developing a first myocardial infarction by 40%] (RR 1.4; CI 1.0–2.0) compared to controls.[17] Other, indirect findings support this conclusion. Data from the Women's Health Initiative (WHI) showed that hysterectomy with oophorectomy is an independent predictor of Framingham risk of myocardial infarction or coronary death.[18] More severe coronary atherosclerosis has been found at autopsy in women with prior bilateral oophorectomy.[19] And earlier menopause, either natural or surgical, is associated with more sub-clinical atherosclerosis, and this finding has been related to the risk of clinical cardiac events.[20,21]

Designing a study that compares benefits and risks

Weighing the benefits of ovarian hormones against the risk of ovarian cancer has been a difficult task for women and their doctors. Usually, any long-term health benefits have been overshadowed by the specter of ovarian cancer.

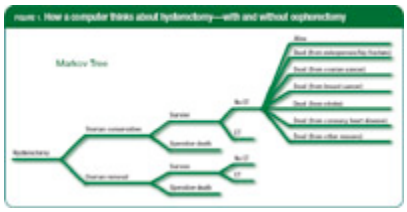

Figure 1. How a computer thinks about hysterectomy—with and without oophorectomy

To clarify the risks and benefits of oophorectomy, we used a Markov decision analytic computer model that helps make complex medical decisions when there are uncertain conditions.[22] We first reviewed the medical literature and found studies that examined the incidence of disease and mortality from five conditions that appear to be related to ovarian hormones: coronary heart disease (CHD), ovarian cancer, breast cancer, stroke, and hip fracture, as well as data for death from all other causes (Figure 1). We then searched for data for the relative risk of developing these five conditions for women having either oophorectomy or ovarian conservation between the ages of 40 and 75. Next, we calculated risk estimates for these conditions for every 5-year interval until women in our model either died or reached the age of 80. We deliberately chose to measure mortality because good data for quantifying morbidity or quality of life are lacking.

Data for the incidence of and mortality in the general population from the five selected conditions were derived from the Surveillance, Epidemiology and End Results (SEER) database and the National Center for

Health Statistics.[23,24] Data for all-cause mortality for women (excluding our five specific conditions) were derived from the National Vital Statistics Reports.[25] The difference in surgical mortality following hysterectomy alone and hysterectomy with oophorectomy was negligible and was omitted from the model.

The relative risks of dying from the five conditions following oophorectomy or ovarian conservation was calculated from published studies. Hysterectomy alone has been shown to reduce the risk of developing ovarian cancer by an average of 46%.[5-7] The risk of ovarian cancer following bilateral oophorectomy is 0%. The risk of myocardial infarction for women following oophorectomy up to age 55 is double the baseline risk (RR = 2.2; CI 1.2–4.2). [For ages 55 to 65, the risk of CHD was found to decrease 6% for each year oophorectomy is delayed after menopause.[26]] Since no applicable data were found for women older than 65, the relative risk of MI for these women was conservatively assumed to be 1.0.

Mortality rates for osteoporotic hip fractures in the general population were calculated by multiplying annual incidence rates by the case-fatality rates.[27] Women having oophorectomy after age 49 have been shown to have a 50% increased risk of hip fracture and, because we could not find any relevant studies for women aged 40 to 49, we conservatively assumed that the RR was similar.[15] Mortality rates in the general population from stroke are known, but no studies have examined relative risk following oophorectomy, and we assumed the risk to be equal in both groups. Women who had oophorectomy prior to age 50 have a 50% reduction in breast cancer for 10 years following surgery, but no reduction in risk has been found in women who had surgery after the age of 50.[28]

The effects of estrogen therapy on the five conditions were based on the estrogen-only arm of the Women's Health Initiative (WHI).[29] WHI studies have not reported risks based on presence or absence of ovaries, so we used the data equally for both groups of women. However, the WHI found that ET use reduced hip fractures by 6 per 10,000 women-years, increased the risk of stroke 12 per 10,000 women-years and was associated with no increased risk of breast cancer and these data were used in our model.

What our research revealed

[For women who have a hysterectomy with ovarian conservation at ages 50 to 54, for example, and who are at average risk of ovarian cancer, coronary heart disease, osteoporosis, breast cancer, and stroke, the probability of surviving to age 80 was 62.46% (without ET) compared to 53.88% if oophorectomy was also performed (without ET)]. This 8.58% difference in survival is primarily due to fewer women dying of CHD (15.95% vs. 7.57%) and hip fracture (4.96% vs. 3.38%), far outweighing the 0.47% mortality rate from ovarian cancer after simple hysterectomy for benign disease. If surgery occurs at ages 55 to 59, the survival advantage is 3.92%. After age 64 there was no significant difference in survival. A sensitivity analysis was performed by varying the RR based on the range of data we found in the literature, and no analysis showed that oophorectomy improved survival.

For a hypothetical group of 4,000 women ages 50 to 54 undergoing hysterectomy with oophorectomy (assuming they don't receive estrogen therapy), our analysis predicts 343 excess deaths (largely from CHD). For the risk of ovarian cancer to outweigh the risks of CHD and hip fracture following oophorectomy, CHD deaths would need to be less than 5% of our estimates, or hip fracture mortality would need to be less than 70% of our estimates. (While ET improves survival in oophorectomized women, it still doesn't equal the survival rates found in women who retained their ovaries.)

Summing up the data

[Because ovarian cancer is a relatively uncommon cause of death and heart disease a relatively common one, our data show that for women of average risk of ovarian cancer, it's better to spare a woman's ovaries at the time of hysterectomy for benign disease.]

Although quality of life issues are of great importance to women, insufficient data were available to include these in our model. For premenopausal women, and some who are postmenopausal, oophorectomy may lead to the sudden onset of hot flushes and mood disturbances if estrogen is not taken. Other problems may include a decline in well-being, a decline in cognitive functioning, poor sleep quality, depression, and a decline in sexual desire and frequency.[30]

While estrogen therapy may reduce both risks and symptoms, many women discontinued hormone therapy after the WHI and fewer now start hormones at the time of menopause.[21,31]

Studies also show that the number of patients still taking either statins or bisphosphonates after 12 months is less than 20%. Therefore, any assumption that medical treatment can ameliorate these conditions following oophorectomy is questionable.

Our research suggests that surgeons should be very cautious about performing prophylactic oophorectomy in the majority of women who are at low risk of developing ovarian cancer and who are under the age of 65. Clinical management guidelines published by the American College of Obstetricians and Gynecologists in 1999 recommended that "the decision to perform prophylactic oophorectomy should be based not only on the patient's age but also on other factors that weigh individual risk for developing ovarian cancer against loss of ovarian function."[32] Hopefully, our results will encourage a dialogue between women and their doctors regarding the potential risks that may result from oophorectomy and aid women who are considering ovarian conservation or oophorectomy.

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