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Oophorectomy: the debate between ovarian conservation and elective oophorectomy

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Abstract

Ovarian cancer remains the fifth deadliest cancer among women due to its early asymptomatic nature and lack of efficacious screening methods leading to frequent late-stage diagnosis. Elective oophorectomy (EO) is an option for women undergoing benign hysterectomy as a means of reducing their ovarian cancer risk. Benefits also include reduced risk of repeat surgery due to adnexal masses and reduced anxiety related to perceived risk of ovarian and breast cancer. The potential negative side effects of EO, such as decreased cognition and sexual function and increased risk of osteoporosis and cardiac mortality, offer support for ovarian conservation. The implications of this elective procedure and the possible consequences without it require physicians to review the pros and cons with patients in light of the patient's individual circumstances and ovarian cancer risk.

Keywords

cognitive function; oophorectomy; osteoporosis; ovarian cancer prevention; sexual function

INTRODUCTION

Despite improvements in treatment in recent years, ovarian cancer has maintained its status as the fifth deadliest cancer in women with 15,500 estimated deaths this year in the United States.[1] One option for reducing the risk of ovarian cancer is prophylactic oopherectomy. Elective bilateral salpingectomy oophorectomy/remaining oophorectomy (EO) often occurs at the time of hysterectomy and occurs in almost half of all hysterectomies for benign reasons performed in the United States.[2] However, a debate exists regarding risks and benefits of this elective procedure. The current recommendation by the American College of Obstetricians and Gynecologists (ACOG) on EO is that "strong consideration should be made for retaining normal ovaries in premenopausal women who are not at increased genetic risk of ovarian cancer. [However,] given the risk of ovarian cancer in

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Conflicts of Interest
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postmenopausal women, ovarian removal at the time of hysterectomy should be considered for these women."[3] This statement highlights the considerable debate between ovarian conservation and EO.

This review will discuss literature to support both the case for ovarian conservation and EO. Articles were identified for inclusion in this review based on a PubMed search conducted November 2011 with key words "oophorectomy," "elective oophorectomy," "prophylactic oophorectomy," and "risk-reducing oophorectomy."

IN SUPPORT OF OVARIAN CONSERVATION

The risk of developing ovarian cancer after hysterectomy with ovarian conservation performed for benign disease is 40% lower than with women who do not undergo hysterectomy.[4,5] However, performing EO to reduce cancer risk at the time of hysterectomy may unintentionally cause more deaths from all causes by age 80 than the number of lives saved from ovarian cancer.

Overall life-expectancy

EO can be detrimental to the life expectancy rate for women with average risk. Multiple studies have shown an association between oophorectomy and decreased overall health and life expectancy, most notably due to coronary heart disease, the primary cause of death among women in the United States.[6-9] In a landmark study, Parker et al[6] used data from the Surveillance, Epidemiology, and End Results (SEER) database, the National center for Health Statistics, the Women's Health Initiative, and the National Inpatient Sample with Markov decision analytic models to model the risks and benefits of EO in women aged 40 to 80 years. Risks of ovarian cancer, coronary artery disease, osteoporotic hip fracture, cerebrovascular accident, breast cancer, death from other causes, and add-back estrogen therapy (ET) were considered. The model demonstrated no clear benefit of EO at any age. EO prior to the age of 65 was associated with an increase risk of death from coronary artery disease and after the age of 65 EO was associated with a increased risk of death from osteoporotic hip fracture, although the latter association was not statistically significant. EO before the age of 55 increased a woman's risk of dying by the age of 80 from coronary artery disease to 15.95% from a baseline risk of 7.57%. EO before age 55 increased a woman's risk of dying by the age of 80 from osteoporotic hip fracture to 4.96% from a baseline risk of 3.38%.[6]

While the risk of death from coronary artery disease may be lessened with estrogen therapy (ET), this reduction depends largely on a woman's age at the time of EO and the timing of estrogen treatment. In a retrospective study, Rivera et al[8] found no statistically significant increase in coronary artery disease mortality in premenopausal women after oophorectomy when they were treated continuously with ET through at least age 45. This differs from the Nurses' Health study, however, that noted variations in age or estrogen treatment among women with bilateral oopherectomy did not greatly reduce risk of death from coronary artery disease and other causes. Among nurses who currently or previously used ET, a multivariable analysis showed oophorectomy to be associated with an increased risk of death from coronary artery disease and, interestingly, lung cancer for women of all ages.[7] The risk of all-cause mortality is also significantly higher in younger women who underwent EO before ages 45–50 and did not start on ET when compared to women who retained their ovaries.[7,10]

Cognitive benefits

Bilateral salpingo-oophorectomy/remaining oophorectomy (BSO) has been linked to cognitive impairment caused by estrogen deficiency. The neuroprotective effects of estrogen

can be seen in studies showing the deterioration of cognitive functions following surgery, and is particularly evident among women with BSO under 50 years old.[11,12] Diminished cognitive functioning has been tied to the decrease in serum estradiol. Cognitive decline was demonstrated among women following EO when given cognitive tests preoperatively, 3- and 6-month postoperatively and when compared to tests taken by control subjects over the same time period. In this investigation, women with a serum estradiol decrease of greater than 50% 6 months postoperatively were found to perform worse in all cognitive function testing when compared with women whose estradiol decreased by less than half.[13] This discovery was supported by later studies showing that even unilateral oophorectomy can be harmful to cognitive function.[12,14] Cognitive impairment has been shown to be mitigated with immediate and continuous estrogen treatment until at least age 50, though ET has not been approved solely for this reason.[11,14,15]

Prevention of osteoporosis and hip fracture

Another drawback to EO is an increased risk of hip fracture. Hip fracture risk rises due to the decrease in bone mineral density (BMD) when estrogen levels drop following natural or surgical menopause.[16,17] The value of ovarian conservation and the presence of estrogen in premenopausal women can be seen when considering the rise in hip fractures following the mass discontinuation of ET among postmenopausal women in light of the initial Women's Health Initiation trial publication.[18] More importantly, however, ovarian conservation in postmenopausal women has been shown to reduce the rate of bone loss due to the small amounts of estrogen produced, even in the absence of ET.[19] This point is emphasized in a population-based study by Melton et al[16] in which women who received postmenopausal oophorectomies were followed for fracture incidents over a median of 16 years. Their analysis found a 32% increase in overall fracture risk in this group when compared with postmenopausal women with their ovaries intact.

Sexual function

An additional drawback of EO is decreased sexual function and hypoactive sexual desire disorder, quality of life issues that can lead to dissatisfied relationships, low self-esteem, and depression.[20–23] Long after menopause, the female ovaries have been demonstrated to produce both testosterone and androstenedione that are peripherally converted to estrogens.[24] Following surgical menopause, both serum estrogen and androgen levels decrease.[25] Estrogen's role in female sexual function helps maintain genital tissue, reduces vulvovaginal atrophy, reduces rates of vaginal and urinary infections, and aids in the manufacture of lubrication with arousal.[26]

EO is implicated in a reduction of sex steroid levels and subsequent decline in sexual function. A recent prospective study found that premenopausal women had a significant decrease in sexual pleasure, comfort, and frequency following EO when compared to pre-surgery ratings.[20] Even with the addition of postoperative ET, women experienced a significant decline in sexual pleasure and comfort when compared to their pre-surgery levels, though their reports of dyspareunia was significantly less than women undergoing EO who did not use postoperative ET. Among postmenopausal women undergoing EO, a significant decrease in the Female Sexual Function Index scores was noted before and after surgery.[21] Additionally, overall sexual function (sexual desire, vaginal dryness, and avoidance of intimacy) declined significantly when pre- and post-oopherectomy sexual function was compared.

Risks of unintended procedure

Any surgical procedure has risks. In an analysis of the National Inpatient Sample of all hysterectomies performed for benign indications between 1979 and 2004, women who

underwent EO at the time of hysterectomy had an increased risk of organ injury (Adjusted odds ratio [AOR] 1.35, 95% confidence interval [CI] 1.02 – 1.70), circulatory or bleeding complications, (AOR 1.34, 95% CI 1.05–1.70), and postoperative gastrointestinal complications (AOR 1.76, 95% CI 1.31–2.37) compared with women undergoing hysterectomy alone.[2] In sum, the benefits of EO at the time of hysterectomy in women with average risk of ovarian cancer may not outweigh the increased risks of cardiac mortality, hip fracture, cognitive impairment, and loss of sexual function. Therefore, women may elect for ovarian conservation at the time of hysterectomy at any age.

IN SUPPORT OF ELECTIVE OOPHORECTOMY

With over 22,000 estimated new cases and 15,500 estimated deaths for 2012, ovarian cancer is the fifth leading cause of death among U.S. women and the fourth leading cause of death among women ages 40–59.[1] An astounding 63% of cases are diagnosed in late stages due to its early asymptomatic nature, leading to a dismal 44% 5-year survival rate for all stages.[1] A woman's lifetime risk of ovarian cancer is 1 in 70 or 1.4%.[27] Screening methods for ovarian cancer have failed to result in decreased mortality or increased diagnosis of early stage disease. Because there is no recommended screening method for ovarian cancer, EO at the time of hysterectomy is a good option to prevent subsequent ovarian cancer. It has been estimated that as many as 1,000 cases of ovarian cancer could be avoided annually or a 12% reduction in the total cases diagnosed if EO was performed during the time of hysterectomy in women 40 years and older.[28,29]

Cancer prevention

High risk population—In the absence of a proven screening method for ovarian cancer, the recommended procedure for ovarian cancer prevention for women at high-risk for ovarian cancer, especially with familial history or genetic predisposition, is a risk-reducing oophorectomy (RRO).[3] RRO in women with either *BRCA1* or *BRCA2* mutations reduced ovarian cancer-specific mortality (3% vs. 0.4%, Hazard ration [HR] 0.2, 95% CI 0.06–0.80) and all-cause mortality (10% vs. 3%, HR 0.40, 95% CI 0.26–0.61).[30] For women with *BRCA1* or *BRCA2* mutations, RRO also reduces their breast cancer risk. Kauff and colleagues[31] reported a 72% decrease in *BRCA2* associated breast cancer risk in addition to an 85% decrease in *BRCA1* associated gynecologic cancer.

General population—RRO is an ideal treatment for the prevention of ovarian cancer in other women with increased risk due to the lack of proven alternatives in ovarian cancer screening. Risk factors for development of ovarian cancer include being white, never having been pregnant, late age of menopause, and a long estimate number of years of ovulation.[32] Numerous studies have investigated the efficacy of various screening methods such as CA-125 serum screening, yearly transvaginal ultrasounds, symptom indexes, or any combination of these. The overall purpose of these screening methods is to improve the rate of early stage diagnosis of ovarian cancer, thereby increasing the 5-year mortality rate. Unfortunately however, these screening methods lack proven predictive value for postmenopausal women with average risk of ovarian cancer. Regular screening with ultrasound and CA-125 still results in the majority of ovarian cancers cases being diagnosed in late stages and does not decrease the 5-year mortality rate.[33–36] There are also risks associated with the current ovarian cancer screening methods that should be considered, such as false positives resulting in unnecessary gynecologic surgeries, increased healthcare costs, and emotional stress. To illustrate the drawback of inefficient screening methods, one should consider the results of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, a large randomized controlled trial conducted over the course of 8 years. In addition to not showing improvement in early diagnosis rates, the authors note that in this

study the screening methods had a high rate of false-positives, leading to invasive surgical procedures which may result in serious surgical complications.[34]

Estrogen therapy after elective oophorectomy

One of the greatest arguments against EO is the loss of benefits from natural hormone production. However, estrogen therapy (ET) is a viable option for preventing the negative side effects of oophorectomy. First, ET has been shown to decrease vasomotor symptoms and improve sexual function in natural and surgical postmenopausal women.[20] Regarding sexual function in particular, there is no significant difference in pre- and postoperative scores for sexual desire, arousal, orgasm, and pain among postmenopausal women receiving ET after EO.[21] Likewise, EO with ET does not have the same link to increased mortality that EO and no ET has. In an analysis of age-specific data for absolute and relative risk by Parker et al[6] the proportion of women ages 50–54 with oophorectomy and ET alive at age 80 was similar to the proportion of women alive with ovarian conservation. When broken down by specific condition, the proportion of women deceased by age 80 from hip fracture, breast cancer, stroke, coronary heart disease, or other was similar between women with ET after oophorectomy and women with ovarian conservation and no ET. The fear of coronary heart disease following oophorectomy can also be dispelled if the patient is provided ET, as shown by results from Women's Health Initiative studies. Coronary-artery calcium levels are not significantly increased in women taking estrogen after oophorectomy when compared to the levels in women with their ovaries intact.[37] In addition, among women who underwent EO between ages 45 and 50 and received ET had a significantly lower number of deaths related to cardiovascular disease than in women with intact ovaries.[7] Finally, the benefit of ET for the prevention and treatment of bone loss in peri- and postmenopausal women is well documented and clinically recommended.[18,38,39]

Repeat surgery

When hysterectomy is performed and the ovaries are retained, there is a risk of repeat surgery due to adnexal masses or other adnexal disease later in life. The risk of repeat adnexal surgery after hysterectomy with ovarian conservation (for benign and malignant indications) has been consistently reported to be between 2.4% and 7.6%.[40]

Secondary benefits

Other secondary benefits of oophorectomy at the time of hysterectomy should also be acknowledged. In some cases, EO with hysterectomy has been shown to decrease pelvic pain and severe premenstrual symptoms when other treatments have failed.[41,42] More common, however, is the positive psychological effect EO brings. For many women at increased risk of developing ovarian cancer, the removal of their ovaries can lead to a significant decrease in anxiety and depression related to their perceived cancer risk.[43–45] In one prospective study including women not considered at increased risk of ovarian cancer, an impressive 97% felt satisfied with their oophorectomy and hysterectomy 3 years post-operation, and there was a significant increase in the percentage of participants who reported their health status as good or very good.[43] Overall, it has been shown that women undergoing a EO do not have a decrease in quality of life compared to women undergoing less invasive gynecologic screening for cancer.[44]

CONCLUSIONS

EO is something that should be considered on an individual basis given a women's unique risk of ovarian cancer. The fear of potential negative consequences should not overshadow the benefits of this prophylactic procedure. With the availability of ET and lack of efficacious ovarian cancer screening methods, prophylactic oophorectomy is a viable option

for many women undergoing hysterectomy. Additionally, age at hysterectomy should also be considered in the decision to proceed with EO or to elect for ovarian conservation. In 2010, recommendations from the Society of Gynecologic Oncologists state “Ovarian conservation before menopause may be especially important in patients with a personal or strong family history of cardiovascular or neurological disease. Conversely, women at high risk of ovarian cancer should undergo risk-reducing bilateral salpingo-oophorectomy.”[40] Weighing a women’s risk of cardiovascular disease, dementia, osteoporosis, and family history must be used to guide decisions for EO and ovarian conservation when a woman is considering hysterectomy.

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