



OOPHORECTOMY: When and Why? A Novel Risk Stratification Tool as an Aid to Decision Making at Gynecological Surgeries

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Abstract

The decision regarding oophorectomy during gynecological surgeries, especially in perimenopausal and postmenopausal women, has historically posed a significant dilemma. Traditionally, it was widely believed that conserving the ovaries held no benefits, leading to a common practice of recommending bilateral salpingo-oophorectomy alongside hysterectomy for benign conditions in women aged 40–45 and above. Given our evolving comprehension of postmenopausal ovarian function and the genetic susceptibility to ovarian epithelial cancers, the decision regarding oophorectomy poses a dilemma. Oophorectomy is recommended for women with a higher risk of ovarian cancer and ovarian conservation is necessary with women with higher risk of co-morbidities. This paper reviews the available literature on these aspects of oophorectomy. Despite a wealth of literature narrating the advantages and disadvantages of oophorectomy, covering various aspects such as ovarian cancer risk, myocardial infarction incidence, and post-oophorectomy peritoneal cancer, there is a notable absence of a comprehensive evaluation system for risk stratification. The objective of the present paper is to address this gap by consolidating existing literature into a risk stratification system. This system will provide treating physicians a tool that facilitates more informed, case-specific decisions in collaboration with patients and their families. While recognizing that the ultimate decision must be tailored to the individual case and agreed upon mutually by the surgeon, patient, and family, the proposed system seeks to streamline risk stratification. This, in turn, should aid in determining the most suitable course of treatment that maximizes benefits for the patient.

Keywords Oophorectomy · Risk stratification · Decision making tool · Ovarian conservation · Menopausal hormone therapy · Scoring system

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Introduction

There is an ongoing debate on decision to do Oophorectomy at gynecological surgeries. Historically, there was assumed to be no benefit in ovarian conservation in perimenopausal/postmenopausal women. Thus, women older than 40–45 years of age, were advised to go Bilateral Salpingo-oophorectomy (BSO) concomitantly with hysterectomy for benign causes. The overall lifetime risk of developing ovarian cancer in the population is 1.4% [1]. BSO had been used as a risk reduction in patients with significant family history or a proven genetic predisposition (e.g., BRCA

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gene carriers, Lynch syndrome, Peutz-Jeghers syndrome). Increased risks for cancers of the ovary, fallopian tube, and peritoneum are observed in carriers of a Pathogenic/ Likely Pathogenic (P/LP) BRCA1/2 (Breast CAncer gene 1 & 2) variant. A P/LP BRCA1 variant has been found in 3.8% to 14.5%, and a P/LP BRCA2 variant has been found in 4.2% to 5.7% of patients of invasive ovarian cancer. BRCA1 variants have an estimated 48.3% cumulative risk of ovarian cancer by age 70, while the cumulative risk by age 70 is 20.0% for carriers of a P/LP BRCA2 variant [2]. Obesity and endometriosis are other non-heritable risk factors for ovarian malignancy. In a study by Lim, M. et al., the hazard ratio for ovarian cancer was 1.7, in women with surgically diagnosed endometriosis [3] (*95% Confidence Interval (CI)).

While a large body of literature exists as regards pros and cons of oophorectomy like ovarian cancer risk, incidence of myocardial infarction, post oophorectomy peritoneal cancer, collation of the data to help the treating doctors to arrive at the most appropriate case-based decision has not been undertaken. This paper aims at putting together the available literature in an evaluation system of risk stratification. While the final decision remains case based, mutually arrived at, between the surgeon patient and the family, the proposed system is expected to help risk stratification and arrive at the most appropriate line of treatment which will be most beneficial to the patient.

Ovarian Function Pre and Around Menopause [1, 4]

The actual endocrine effect of the postmenopausal ovary may be related to its contribution of androgens to the plasma pool of estrogens through extragonadal conversion. Patients going through menopause who have healthy ovaries have increased levels of androgens (androstenedione and testosterone). This ovarian production of androgens appears to persist even 10 years beyond the onset of menopause. Aromatase enzyme in the adipose tissue converts the androgens into estrone which is then converted to estradiol. The hormone levels in menopause are shown in Table 1. Expression of aromatase is associated with body fat and tumor development. The hypo-estrogenic state is associated with glucose and lipid metabolism dysregulation, obesity, metabolic disorders and their associated complications. Thus, ovarian preservation is beneficial to the overall health and longevity of postmenopausal women and ovarian preservation should be considered in appropriately selected women who may benefit from the effects of endogenous hormone production. However to date there is no guidance

or any objective way to make the decision of oophorectomy at surgery for benign conditions, in literature.

The average reduction in blood testosterone and serum estradiol concentrations in premenopausal women who undergo oophorectomy is 50% and 80%, respectively [5]. More frequent and severe symptoms are linked to a sudden fall in estradiol necessitating menopausal hormone treatment (MHT). These include hot flashes, sexual dysfunction, depression, migraine headaches, vaginal dryness, and cardiac symptoms. Due to the recurrence of severe symptoms, many women who have bilateral oophorectomy find it difficult to discontinue using MHT at any age. Contrarily, as part of the physiology of the process, women going through natural menopause experience a slow-onset ovarian hormone deficit after a protracted period of intermittent and erratic ovarian function. MHT is given to these women to treat their symptoms, not to replace the deficient ovarian hormones.

Beneficial Effects of Ovarian Conservation (OC)

1. *Overall life expectancy*: Elective oophorectomy (EO) is related with the risks of coronary artery disease, osteoporotic hip fracture, cerebrovascular accident, breast cancer, death from other causes, and add-back estrogen therapy (ET). A woman's chance of dying from coronary artery disease and from osteoporotic hip fracture by age 80 increases from a baseline risk of 7.57% to 15.95% and from a baseline risk of 3.38% to 4.96% respectively if EO is done before the age of 55. The risk of all-cause mortality is also noticeably greater in younger women who received EO before the ages of 45 to 50 and did not begin on ET [6]. A study showed a more than 10% increase in all-cause mortality and composite morbidity following EO between the ages of 50 and 54 [1].
2. *Cognitive benefits*: Studies documenting the decline in cognitive abilities after EO demonstrate the neuroprotective effects of estrogen. These effects are more pronounced in patients under the age of 50 and occurs due to decrease in serum estradiol [6].
3. *Prevention of osteoporosis and hip fracture*: Even in the absence of ET, OC has been proven to slow bone loss in postmenopausal women because of the modest levels of

Table 1 Levels of steroid hormones (in pg/mL) in natural vs surgical menopause [5]

	Reproductive Age (luteal phase levels)	Natural Menopause	Surgical Menopause
Estradiol	150	10–15	10
Testosterone	400	290	110
Progesterone	12,000–20,000	< 100	< 100

estrogen generated. In a study by Melton et al., there was a 32% increase in overall fracture risk in women with postmenopausal EO when compared with postmenopausal women with their ovaries intact [6].

4. *Sexual function* [1, 6]: EO causes concerns with quality of life that can result in unhappy relationships, impaired sexual function, hypoactive sexual drive disorder, low self-esteem, and depression. Serum levels of both estrogen and androgen fall after surgical menopause. Androgens released by the postmenopausal ovaries are involved in sexual desire, arousal and orgasm. As it relates to female sexual function, estrogen prevents vulvovaginal atrophy, lowers the incidence of vaginal and urinary infections, and helps provide lubrication during arousal.
5. *Risk of an unindicated surgery*: There may be an increased risk of organ injury circulatory or bleeding complications, and postoperative gastrointestinal complications.
6. *Cardio-vascular disease*: EO before the age of 45 was linked to a 1.5 times increased total mortality from cardiovascular disease [1]. Reduction in endogenous estrogen increases serum lipids, reduce carotid artery blood flow and increases subclinical atherosclerosis. Women with surgical menopause have elevated subclinical atherosclerosis compared with same-age women who had natural menopause [7].
7. *Prevention of ovarian remnant syndrome*: It is the condition in which remnants of ovarian cortex left behind after surgical removal of the ovaries become functional and cystic. Increased vascularity causing difficulty in achieving hemostasis, pelvic adhesions, and alterations in anatomy as seen with neoplasms, are the major factors which predispose the surgeon to leave an ovarian remnant at the time of surgery. This can be a source of postoperative chronic pain. Symptoms usually occur within weeks to 5 years after bilateral oophorectomy [8]. The pain could be brought on by an ovarian remnant that was left behind in hemorrhagic tissue and eventually formed adhesions. The remnant is encased by the scar tissue and continues to function there.

Benefits of Elective Oophorectomy

1. *Cancer prevention in high-risk population* [2]: The need for bilateral RRSO (Risk Reducing Salpingo-Oophorectomy) in high-risk population, after childbearing is supported by the lack of effective early detection tools and the poor prognosis associated with advanced ovarian cancer. The NCCN Guidelines Panel recommends RRSO between 35 and 40 years of age for carriers of a BRCA1 P/LP variant. Since the carriers of the BRCA2 P/LP variant tend to experience later onset of ovarian cancer, it is fair to postpone RRSO for the management of ovarian cancer risk until between the ages of 40 and 45, unless the age at which the family member was diagnosed with the disease justifies consideration of this preventative surgery at an earlier age, immediately after child bearing function is over. Studies have demonstrated a 80- 85% reduction in risk of ovarian cancer when RRSO is performed in carriers of a BRCA1/2 P/LP variants. Studies have also shown RRSO to reduce the incidence of breast cancer, but the age-dependent benefit is still unknown. Thus, consensus on the effect of RRSO on breast cancer risk in BRCA1/2 germline pathogenic variant has not yet been reached [9]. For other P/ LP variants associated with breast/ ovarian cancer, the NCCN panel recommends RRSO when risk of developing ovarian cancer exceeds that of the average-risk population. The panel uses a threshold of 10% for a recommendation to discuss RRSO. Example, PALB2, for which lifetime risk estimates are approximately 5%, RRSO may be considered based on family history. Given the effects of early menopause, the choice to perform RRSO should not be taken lightly. NCCN also recommends RRSO in carriers of RAD51C and RAD51D P/LP variants at 45 to 50 years of age.
2. *Cancer prevention in general population*: The other risk factors for ovarian cancer in general population are race, nulligravida, late menopause and long estimated years of ovulation. Various screening methods such as CA-125 levels, yearly transvaginal ultrasounds, symptom indexes, or any combination of these have been used for early detection of ovarian cancer and to reduce the 5-year mortality rate. For postmenopausal women with an average risk of ovarian cancer, these screening techniques have no demonstrable predictive value.
3. *Repeat surgery*: When hysterectomy is performed with OC, the risk of repeat adnexal surgery for benign and malignant indications has been consistently reported to be between 2.4 and 7.6% [6].
4. *Other benefits*: When previous therapies have failed, EO plus hysterectomy has been demonstrated to reduce severe premenstrual symptoms and pelvic pain. EO can significantly reduce the anxiety and depression in many women who believe they have a higher risk of developing ovarian cancer. In severe endometriosis, BSO may result in improved pain relief and reduce the chance of future surgery [1].
5. *Estrogen therapy after EO*: MHT prevents the negative side effects of oophorectomy. It decreases vasomotor symptoms and improves sexual function in natural and surgical postmenopausal women. It also prevents and treats bone loss in peri- and postmenopausal women.
6. *As an adjuvant treatment of breast cancer in hormone receptor positive patients in premenopausal age group*

[10]: A meta-analysis supported the addition of ovarian ablation in premenopausal women with hormone receptor positive breast cancer, with persisting benefit compared with observation, or when added to tamoxifen, or when added to chemotherapy and tamoxifen. Ovarian function can be suppressed either with gonadotrophin-releasing hormone agonists, by ovarian irradiation, or surgical BSO. Some patients may opt for definitive surgical ablation because of the implications for fertility and family planning.

Considerations for Ovarian Preservation [1]

Bilateral salpingectomy with ovarian preservation should be considered in:

1. Premenopausal women without genetic predisposition to cancer
2. No significant family history of ovarian cancer
3. No adnexal pelvic pathology
4. Postmenopausal women with no additional risk factors.

Indications of Bilateral Oophorectomy [1]

1. Suspected or confirmed Gynecological malignancy
2. Risk reduction surgery (RRSO): see “Cancer prevention in high-risk population” above.
3. Other indications (i) Chronic pelvic pain (ii) Pelvic inflammatory disease (iii) Severe endometriosis.

Other Interventions Not Involving Elective Oophorectomy

1. *Opportunistic salpingectomy (OS)* [11]: It is the removal of the fallopian tubes for the primary prevention of ovarian cancer in a woman already undergoing pelvic surgery for another indication. OS is safe, does not add to pre or postoperative morbidity and mortality, and does not affect ovarian function. However, consents for salpingectomy should be taken and the decision for OS should not alter the route of hysterectomy. It also has a protective effect specifically against endometrioid and clear cell carcinomas of the ovary. According to a meta-analysis of three studies on women having hysterectomies for benign reasons, those who also had bilateral OS at the same time, had a decreased risk of developing ovarian cancer than those who did not. However, it is not a substitute for oophorectomy in high-risk population.
2. *Prophylactic salpingectomy with delayed oophorectomy (PSDO)* [12]: In BRCA mutation (mBRCA) carriers, preventive salpingectomy after the end of childbearing

with delayed oophorectomy is being advocated as a less morbid option to RRSO. Data on PSDO's clinicopathological outcomes in mBRCA carriers, however, are scarce.

3. *Reduction of number of lifetime ovulations* [1, 2]: Ovulation suppression with combined hormonal contraception (CHC) reduces the risk of ovarian cancer in proportion with the duration of use. CHCs reduced the risk for ovarian cancer by 45% to 50% in carriers of a P/LP BRCA1 variant and by 60% in carriers of a P/LP BRCA2 variant. A considerable risk reduction is linked to pregnancy and breastfeeding (especially for longer than 12 months).
4. *Other preventive strategies* [12]: NSAIDs, aspirin, Vitamin D, have shown promise in prevention, but further studies are warranted. Fenretinide (4-HPR), a synthetic vitamin A analog, has antitumor properties both in vivo and in vitro and only one study has documented a lower incidence of ovarian cancer in women with prior breast cancer.
5. *Ovarian transposition* [13]: The most common indication of ovarian transposition in women of reproductive age is cervical carcinoma. It is done in young premenopausal women (desiring future fertility) proceeding to pelvic radiotherapy. Despite a high frequency of symptomatic ovarian cysts, it achieves great ovarian function preservation and has a very low risk of metastases to the transferred ovaries. Serial AMH levels can be used to monitor ovarian function.

A Novel Risk Stratification Tool as an Aid to Decision Making

From above discussion it can be appreciated that the individual pros and cons of oophorectomy need to be integrated in an evaluation system for ovarian conservation/elective oophorectomy for pre-surgical assessment of women undergoing hysterectomy/surgery for a gynecological condition. To address this need, authors developed a new risk stratification tool based on review of literature, taking into account the interplay of factors in a given case scenario.

This risk stratification tool is validated from experts as a delphi consensus document after procuring ethical committee waiver certificate. This scoring system (Tables 2, 3) guides surgeons to grade women as having low, intermediate, or higher need for bilateral elective oophorectomy so that an appropriate decision can be taken. Recent ICMR consensus document [14] also is in line with various views and reviews presented here.

Total score is calculated separately for all the four columns (Table 2). In first column total score can be 0 and hence decision for OC is suggested. In last column, all

Table 2 The risk stratification tool: major parameters

Number	Factors	Unlikely-0	Less likely-1	More likely-2	Most likely -3
1	Age	≤50 years	51- 65	66–80	> 80
2	Age of ovaries	Reproductive years	Perimenopause	5 years post menopause	10 years post menopause
3	Indication for primary surgery	Benign: fibroid, AUB, prolapse	Colonic cancer	PID, endometriosis	Malignancy in reproductive tract
4	Surgical history: ovarian cancer risk reduction	Salpingectomy	Tubal ligation, hysterectomy	–	–
5	Surgical history: breast cancer risk reduction	Bilateral mastectomy	Unilateral mastectomy, breast cancer operated in remission	Metastatic breast cancer operated	Early ER, PR positive tumors, diagnosed or operated
6	Family history of cancer ovary and breast	No	Second degree relative	–	First degree relative
7	Family history of colonic cancer (HNPCC syndrome+)	No	Yes	–	–
8	Personal primary cancer breast	ER, PR negative		–	ER, PR positive
9	BRCA 1& 2 status	Negative	Not known	–	BRCA 1 positive/BRCA 2 positive
10	Family or personal history of comorbidities (Dyslipidemia, diabetes, hypertension, osteoporosis, dementia, Parkinson’s disease)	Personal	Family	No	–
Column wise Total score:	–	When score = 0 Decision in favour of ovarian conservation	When added score of 1 overrides or is equal to added score of 2, Proceed as per foot note*	When added total score of 2 overrides added score of 1 decision in favour of oophorectomy	When score ≥ 3, decision in favour of oophorectomy

AUB Abnormal Uterine Bleeding, ER Estrogen Receptor, PR Progesterone Receptor, PID: Pelvic Inflammatory Diseases

*Calculate the integrated score as follows: Add the combined score of minor criteria (Table 3) to the combined score of major criteria of column of scores 1 and 2. If integrated score is more or equal to 13, decision in favour of oophorectomy if integrated score is less than 13 then, decision against oophorectomy

Table 3 The risk stratification tool: minor parameters

Number	Factors	0	½	1
1	Parity	Multiparity (> 3)	1–2	Nulliparity
2	Breast feeding practices	Prolonged	Short	Never breastfed
3	Ethnicity	Asian??	African/ American	Caucasian
4	Drug history	CHC pills > 5 years	CHC pills < 5 years	Ovulation inducing agents
Total score			02	04

factors bear a score of 3 indicating stronger risk for current or future malignancy or other pathology, hence EO is suggested if score is ≥ to 3. For second and third column the decision needs to be a balanced one. For column 3 bearing score of 2 each, if total score overrides the total score of column 2 bearing score of 1 each, the decision favours EO. However if total score of column 2, is more than total score of column 3, then add total score of minor criteria (Table 3) to this score and obtain Integrated score. If this

score is more than or equal to 13, decision favors EO. If it is less than 13, then decision favors OC.

The strength of this system is that this is unique and more objective way of decision making. The weakness of the evaluation system is that this is based on retrospective data from literature, and the prospective clinical validation has not been done. We suggest that this can be undertaken by readers and clinicians and publish their results.

Conclusion

Given each woman's distinct risk of ovarian cancer, elective oophorectomy (EO) should be considered on an individual basis. The advantages of this preventative measure shouldn't be overshadowed by concern over potential unwanted effects. Since there is lack of effective ovarian cancer screening tools, prophylactic oophorectomy is a reasonable choice for many women with high risk factors who are undergoing hysterectomy. In deciding whether to move forward with EO or choose for ovarian conservation, age at hysterectomy should also be considered. When a woman is considering a hysterectomy, her risk of cardiovascular disease, dementia, osteoporosis, and family history must be taken into consideration while deciding EO. The productive function of ovaries continues several years after menopause which is beneficial to health so injudicious decisions may harm the body [15, 16]. Hence this novel evaluation system for risk stratification was designed to aid the gynecologists in taking a decision for or against ovarian conservation.

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Disclaimer It represents a general guidance for easy objective decision making for or against oophorectomy based on available evidence on the topic. It does not in any way bind a clinician to follow this evaluation system, and use the risk stratification tool. One can take decision based on discussions with the patient and institution, national or international guidelines.

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