Original Article

Rate of Prophylaxis Oophorectomy and Associated Factors at the Time of Hysterectomy in Premenopausal Women with Benign Diseases

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Objective: To determine the rate of oophorectomy and associated factors at the time of hysterectomy in premenopausal women with benign diseases.

Materials and Methods: The medical records of the premenopausal women that underwent hysterectomy with or without oophorectomy due to benign gynecologic conditions between January 1, 2012 and December 31, 2017 at Khon Kaen University Hospital (Thailand) were retrospectively reviewed. The data collected included age, BMI, parity, indication for surgery, family history of carcinoma, route of hysterectomy, procedure, specialization of the surgeon, operative notes, and histopathological reports of the ovaries.

Results: Six hundred thirty-eight subjects underwent hysterectomy due to benign gynecologic conditions. Bilateral salpingo-oophorectomy (BSO) was performed in 57.37% (366) of the cases. In 81.97% (300) of these cases, either one or both patient's ovaries were grossly normal. The rate of prophylactic oophorectomy among all cases was 47.02% (300 in 638). The strongest associated factor with BSO was age (odds ratio 8.421, 95% CI 5.488 to 12.921). Other associated factors were irregular menstrual history, the surgeon being a gynecologic oncologist, and abdominal hysterectomy. No cases of ovarian cancer were found.

Conclusion: Nearly half of premenopausal women that underwent hysterectomy due to benign conditions underwent prophylactic oophorectomy. Associated factors were age, irregular menstruation, the surgeon being a gynecologic oncologist, and abdominal hysterectomy.

Keywords: Hysterectomy, Premenopausal women, Prophylactic oophorectomy

Hysterectomy is the most commonly performed major gynecologic operation. Bilateral salpingo-oophorectomy (BSO) of normal ovaries is often concurrently performed at the time of hysterectomy in benign diseases to prevent ovarian cancer or to avoid future adnexal surgery[1]. The lifetime risk of developing ovarian cancer in the general population is 1 in 70 or 1.4%[2]. In women whose ovaries are retained at the time of hysterectomy, the chance of developing secondary ovarian tumors is 5.1% and

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the reoperation rate is 2.8% to 3.8%[3,4].

The American College of Obstetricians and Gynecologists (ACOG) recommends that the option of BSO be offered to premenopausal women with *BRCA*1 and *BRCA*2 gene mutations after completion of childbearing or by age 40, and women with a history of hereditary breast and ovarian cancer. This could reduce the risk of ovarian cancer by 80% to 90% and breast cancer by 50% to 60%[2]. By contrast, strong consideration should be made to retain normal ovaries in premenopausal women who are at the low risk of ovarian cancer[2]. Although the recommendation has been launched for many years, concomitant BSO is still practiced at the time of hysterectomy in women with benign conditions. Mahal et al[5] reported that between 2005 and 2011, the proportion of inappropriate oophorectomy remained relatively stable, ranging from 36% to 38%.

The median age at menopause is 49.5±3.6 years in Thai women[6] and 51.3 years in women in western countries[7]. Estrogen deficiency can accelerate atherosclerosis and increase the risk of coronary heart disease. Advanced age at natural menopause has

been associated with reduced risk of mortality from cardiovascular, ischemic heart disease, and stroke and associated with longer life expectancy[8-10]. Surgical removal of both ovaries causes abrupt cessation of estrogen, which could harm the patient in various ways. Studies found that 15,000 women in the U.S. die from ovarian cancer, but 350,000 subjects die from coronary heart disease[11,12]. Although estradiol levels decrease dramatically during natural menopause, the ovaries continue to produce androgens, testosterone, and androstenedione, which can be peripherally converted into estrone and may last as long as 10 years after menopause[13].

The authors hypothesized that the rate of premenopausal women with benign conditions undergoing prophylactic salpingo-oophorectomy in the present study setting would be higher than that in the U.S. The authors also attempted to identify associated factors for bilateral oophorectomy and review the histopathologies of ovaries that were removed.

Materials and Methods

The present study was retrospectively conducted at Khon Kaen University Hospital (Thailand). Prior approval was obtained from the Institute Review Board for Human Research (HE611041). The authors identified the relevant cases from the operative records using the following keywords, hysterectomy either abdominal, vaginal, or laparoscopic, hysterectomy with salpingo-oophorectomy, salpingo-oophorectomy, adnexectomy, and adnexal surgery. The authors reviewed the patients' medical records. Malignancy cases or cases in which the patient had previously undergone BSO or hysterectomy were excluded. The medical records of premenopausal women who underwent hysterectomy with or without oophorectomy due to benign gynecologic conditions between January 1, 2012, and December 31, 2017 were reviewed. The data collected included age, body mass index (BMI), parity, indication for surgery, family history of carcinoma, route of hysterectomy, procedure, specialization of the surgeon, operative notes, and histopathological reports of the ovaries.

Ovaries were categorized based on histopathological reports as 1) normal when stated as normal, unremarkable, cystic follicle, follicular cyst, corpus luteal cyst, hemorrhagic corpus luteum, theca lutein cyst, 2) benign ovarian tumors when stated as endometriosis or endometriotic cyst, mucinous cystadenoma, serous cystadenoma, mature teratoma, and others, 3) malignant ovarian tumors when stated
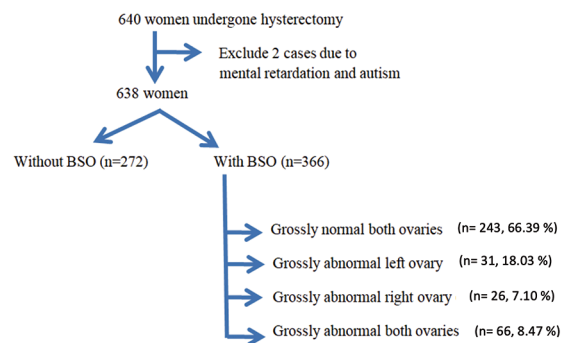
Figure 1. Study flowchart.

as mucinous carcinoma, serous carcinoma, immature teratoma, and others.

The main outcomes were the rate of oophorectomy and associated factors at the time of hysterectomy in premenopausal women with benign diseases. Based on a study by Mahal et al[5], the study needed at least 576 subjects to achieve 80% power at a 5% significance level. The categorical data were presented as frequency and percentage. Associated factors were compared using the chi-square test or Fisher exact test, as appropriate. Univariate analysis was performed using logistic regression. Multivariate analysis was performed to assess the effects of possible associated factors. Multiple logistic regression was used for variables that were found to be significant according to univariate analysis. A p-value of less than 0.05 was considered statistically significant. Associated factors were expressed as adjusted odds ratio with 95% confidence intervals (CIs). The authors used Stata/SE, version 10.1 (StataCorp LP, College Station, TX, USA) to analyze all data.

Results

Six hundred forty premenopausal women that underwent hysterectomy due to benign gynecologic conditions during the study period were identified. The authors excluded two patients who underwent hysterectomy due to mental retardation and autism. BSO was performed in 57.37% (366 of 638) of the cases, and unilateral salpingo-oophorectomy or ovarian conservation was performed in the remaining 42.63% (Figure 1). The demographic data of the patients are shown in Table 1. Most patients had regular menstruation before surgery. Most of the subjects in the BSO group were older than 45 years old. The most common indication for hysterectomy in both groups was myoma uteri. The most common route of hysterectomy was the abdominal approach.

Table 1. Participant data (n=638)

	Hysterectomy with unilateral salpingo-oophorectomy (n=272); n (%)	Hysterectomy with bilateral salpingo-oophorectomy (n=366); n (%)
Age (years)		
<40	16 (5.88)	11 (3.01)
40 to 45	135 (49.63)	46 (12.57)
46 to 50	97 (35.66)	189 (51.64)
>50	24 (8.82)	120 (32.79)
Menstrual history		
Regular	259 (95.22)	298 (81.42)
Irregular	13 (4.78)	68 (18.58)
Parity		
0	53 (19.49)	60 (16.39)
1	36 (13.24)	41 (11.20)
2	111 (40.80)	162 (44.26)
>2	72 (26.47)	103 (28.14)
BMI (kg/m^2)		
<30	252 (92.65)	330 (90.16)
>30	20 (7.35)	36 (9.84)
Preoperative diagnosis		
Myoma uteri	204 (75.00)	229 (62.57)
Adenomyosis	50 (18.38)	54 (14.75)
Endometrial hyperplasia without atypia	9 (3.31)	15 (4.10)
Endometrial hyperplasia with atypia	3 (1.10)	4 (1.09)
Endometriosis/ endometriotic cyst	14 (5.15)	42 (11.48)
Other benign ovarian tumors	9 (3.31)	50 (13.66)
Heavy menstruation/dysfunctional uterine bleeding	3 (1.10)	28 (7.65)
Abnormal Pap smear	8 (2.94)	26 (7.10)
Tubo-ovarian abscess	1 (0.37)	2 (0.55)
Past illness/underlying disease		
No	197 (72.43)	221 (60.38)
DM	15 (5.51)	30 (8.20)
HT	20 (7.35)	61 (16.67)
Breast cancer	0 (0.00)	8 (2.19)
Others	49 (18.01)	83 (22.68)
Family history of carcinoma		
No	247 (90.81)	330 (90.16)
Yes	25 (9.19)	36 (9.83)
Surgeon		
Non-gynecologic oncologist	245 (90.07)	251 (68.58)
Gynecologic oncologist	27 (9.92)	115 (31.42)
Type of hysterectomy		
Abdominal hysterectomy	209 (76.84)	341 (93.17)
Laparoscopic hysterectomy	63 (23.16)	25 (6.83)
Vaginal hysterectomy	0 (0.00)	0 (0.00)

BMI=body mass index; DM=diabetes mellitus; HT=hypertension

Table 2. Factors associated with bilateral salpingo-oophorectomy (n=366)

	BSO (%)	p-value	95% CI	Multivariable odds ratio	95% CI
Age >45 years	84.43	<0.01	4.725 to 9.912	8.421	5.488 to 12.921
Irregular menstruation	18.58	<0.01	2.648 to 9.433	2.158	1.064 to 4.376
BMI >30	9.84	0.285	0.771 to 2.415	0.858	0.429 to 1.716
History of breast cancer	2.19	0.023	1.294 to >999	NA	NA
Family history of CA	9.83	0.804	0.626 to 1.830	0.995	0.522 to 1.897
Gynecologic oncologist	31.42	<0.01	2.618 to 6.498	6.122	3.546 to 10.571
Abdominal hysterectomy	93.17	<0.01	2.385 to 6.346	5.381	2.983 to 9.707

BMI=body mass index; BSO=bilateral salpingo-oophorectomy; CI=confidence interval; NA=not available

Table 3. Histopathological report of grossly abnormal ovaries (189 specimens)

Histopathological report	Left ovary (97 specimens); n (%)	Right ovary (92 specimens); n (%)
Mature teratoma	8 (8.25)	18 (19.57)
Serous cystadenoma	8 (8.25)	6 (6.52)
Mucinous cystadenoma	6(6.19)	8 (8.70)
Tubo-ovarian abscess	2 (2.06)	0 (0)
Epithelial cyst	1 (1.03)	1 (1.09)
Parovarian cyst	0 (0.00)	1 (1.09)
Cystic follicle	4 (4.12)	5 (5.43)
Follicular cyst	3 (3.09)	3 (3.26)
Corpus luteal cyst	7 (7.22)	1 (1.09)
Hemorrhagic corpus luteum	3 (3.09)	2 (2.17)
Unremarkable	9 (9.28)	11 (11.96)

Table 4. Histopathological report of grossly normal ovaries (543 specimens)

Histopathological report	Left ovary (269 specimens); n (%)	Right ovary (274 specimens); n (%)
Unremarkable	178(66.17)	174 (63.50)
Cystic follicle	27 (10.04)	26 (9.49)
Follicular cyst	18 (6.69)	17 (6.20)
Corpus luteal cyst	24 (8.92)	30 (10.95)
Hemorrhagic corpus luteum	1(0.37)	4 (1.50)
Theca lutein cyst	2 (0.74)	2(0.73)
Epithelial cyst	3 (1.12)	5 (1.82)
Cortical cyst	0 (0)	1 (0.36)
Endometriosis/endometriotic cyst	8 (2.97)	9 (3.28)
Serous cystadenoma	6 (2.23)	4(1.46)
Mature teratoma	1 (0.37)	2 (0.73)
Microscopic Brenner tumor	1 (0.37)	0 (0.0)

In the BSO group, both ovaries were grossly abnormal in only 18.03% (66 in 366) of the cases. Either one or both ovaries were grossly normal in 81.97% (300 in 366) of the cases. The overall rate of prophylactic oophorectomy was 47.02% (300 in 638), as shown in Figure 1.

According to univariate analysis, there were five significant associated factors for BSO, which were age older than 45 years, history of dysfunctional uterine bleeding (DUB) or heavy menstrual bleeding, history of breast cancer, the surgeon being a gynecologic oncologist, and abdominal hysterectomy (Table 2). The significant associated factors according to multivariate logistic regression were the same, with the exception of history of breast cancer, which not applicable due to the small sample size. The most strongly associated factor with BSO during hysterectomy in the cases of benign disease was age older than 45 years (odds ratio 8.421; 95% CI 5.488 to 12.921).

The most common histopathological result in ovaries with grossly abnormal appearance was endometriosis (Table 3). There were no cases in which there was an incidental finding of carcinoma of the ovary in the present review. Of the cases in which the ovaries were grossly abnormal in appearance, 25.40% (48 in 189) were reported as normal. In cases that the ovaries were grossly normal in appearance 7.37% (40 in 543) had incidental abnormal histopathology, which was benign in all cases. The most common benign pathology was endometriosis (3.13%, 17 of 543 specimens) (Table 4). Of the 732 removed ovaries, 75.27% (551 in 732) of normal ovaries were removed.

Discussion

The present study revealed that nearly half of premenopausal women underwent hysterectomy due to benign conditions also underwent prophylactic oophorectomy. The rate of prophylactic oophorectomy

was consistent with those found in other studies (37% to 52%)[5,14,15].

Of the various associated factors for BSO, age is the factor most strongly associated with BSO, which is consistent with the findings of other studies[15,16]. This might be because the incidence of ovarian cancer increases with age. The authors found that gynecologic oncologists were more likely to perform BSO in hysterectomies of benign tumors than non-gynecologic oncologists. This might be due to severe adhesion or difficult case. The abdominal approach tended to be used in difficult hysterectomies or severe pathology then concomitant BSO was more significantly performed than the laparoscopic approach.

There were no incidental findings of ovarian carcinoma in the present study. This could be explained by the lower prevalence of ovarian cancer in Asia than in North America and Central Europe[17]. In Thailand, the incidence of ovarian cancer is approximately 5.4 to 6.8 per 100,000 women (0.005% to 0.007%)[18]. Three-fourth of normal ovaries were removed in the present study, which was higher than in a previous study conducted by Karp et al[19]. This finding suggests that gynecologists should carefully consider whether BSO is necessary before performing the operation in premenopausal women. Prophylactic or concurrent bilateral oophorectomy at the time of hysterectomy to prevent ovarian cancer should not be a routine procedure and should only be performed after in-depth counseling with the patient and careful assessment of risk. The risk, benefit, and cost of hormonal therapy post oophorectomy should be included in patient's decision-making process. Prophylactic oophorectomy should be reserved for the cases in which there is a high risk of develop ovarian cancer (*BRCA*1/2 mutation, postmenopausal stage, or abnormal CA 125 levels or transvaginal examination)[20]. In addition, in the case of unilateral benign ovarian tumors, preservation of one ovary or conservative surgery should be offered. Jitkunnatumkul et al[21] reported a low incidence of subsequent oophorectomy in cases of prior hysterectomy with ovarian preservation and that the pathologic diagnoses in these cases were all benign.

There are many procedures that could reduce the risk of epithelial ovarian cancer (EOC) at the time of hysterectomy by blocking carcinogens from the lower genital tract and fallopian tube without damage to the ovaries[22]. Hysterectomy alone has also been associated with a protective effect against EOC (relative risk [RR] 0.78; 95% CI 0.60 to 0.96)[23].

A previous meta-analysis showed that tubal ligation reduced endometrioid (RR 0.40) and serous (RR 0.73) but not mucinous cancers[24]. Bilateral salpingectomy (BS) has been associated with a 40% to 65% decrease in the incidence of EOC when performed at the time of benign hysterectomy in premenopausal women at low risk for EOC[25].

Although all ovarian specimens had histological reports to confirm gross pathology, the limitation of the present study was lack of data regarding the reasons for oophorectomy in normal looking ovary at the time of hysterectomy.

Conclusion

Nearly half of premenopausal women underwent hysterectomy due to benign conditions and underwent prophylactic oophorectomy. Associated factors were age, DUB or heavy menstrual bleeding, the surgeon being a gynecologic oncologist, and abdominal hysterectomy. The present study contribution may convince the gynecologists to save the normal ovaries at the time of hysterectomy in premenopausal women with benign conditions.

What is already known on this topic?

The ACOG recommends that the option of BSO be offered to premenopausal women who are high risk of breast and ovarian cancer.

Surgical removal of both ovaries causes abrupt cessation of estrogen from the ovaries, which could harm the patient in various ways such as vasomotor symptoms, risk of mortality from cardiovascular, ischemic heart disease, and stroke.

However, prophylactic BSO of normal ovaries is still often concurrently performed at the time of hysterectomy in benign diseases to prevent ovarian cancer or to avoid future adnexal surgery in low-risk cases.

What this study adds?

The rate of prophylactic oophorectomy in premenopausal women undergoing hysterectomy due to benign conditions was high. Two-thirds of normal ovaries were removed.

Prophylactic oophorectomy to prevent ovarian cancer should not be a routine procedure and should only be performed after in-depth counseling with the patient and careful assessment of risk.

Acknowledgement

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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