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Changes of Ovarian Reserve after Hysterectomy for Non-oncologic Conditions in Reproductive-aged Women: A prospective study

Natcha Silpaibulpanich, M.D.*,
Pruttaporn Maneerat, M.D.*

** Department of Obstetrics and Gynecology, Rajavithi Hospital, Bangkok, Thailand*

ABSTRACT

Objectives: To assess the impact of hysterectomy on the ovarian reserve markers in reproductive-aged women.

Materials and Methods: This prospective cohort study was conducted from May 2021 to April 2022. Reproductive-aged women who underwent hysterectomy without ovarian surgery due to benign conditions at Rajavithi Hospital were recruited. Ovarian reserve markers were compared between the date before surgery and 12 weeks following hysterectomy by measurement of serum anti-Müllerian hormone (AMH), antral follicle count (AFC) and ovarian volume (OV).

Results: Fifty-five reproductive-aged women were enrolled. Different proportion (DP) between serum AMH at preoperative and 12 weeks postoperative was decreased after hysterectomy (DP 22.5%, $p = 0.001$). The antral follicle count (AFC) and ovarian volume (OV) were also decreased (DP 33.3%, $p < 0.001$, and 20.0%, $p < 0.001$, respectively). Nonetheless, surgical outcomes and menopausal symptoms were not different.

Conclusion: Hysterectomy without ovarian surgery affects the ovarian reserve at 12 weeks post operation without significantly changing of menopausal symptoms. However, other long-term consequences from accelerated ovarian aging should be investigated.

Keywords: ovarian reserve, anti-mullerian hormone, ovarian volume, antral follicle count, hysterectomy.

Correspondence to: *Natcha Silpaibulpanich, M.D., Department of Obstetrics and Gynecology, Rajavithi Hospital, Bangkok, Thailand. E-mail: natchasilp1234@gmail.com*

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การทำงานของรังไข่ที่เปลี่ยนไปหลังการผ่าตัดมดลูกด้วยภาวะที่ไม่ใช่มะเร็งในสตรีวัยเจริญพันธุ์: การศึกษาแบบไปข้างหน้า

ณัชชา ศิลป์ไพบูลย์พานิช, พฤฒพร มณีรัตน์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลกระทบของการตัดมดลูกต่อค่าการทำงานของรังรังไข่ในสตรีวัยเจริญพันธุ์*

วัสดุและวิธีการ: *การศึกษาวิจัยแบบไปข้างหน้าดำเนินการในสตรีวัยเจริญพันธุ์ที่เข้ารับการผ่าตัดมดลูกโดยไม่มีการผ่าตัดรังไข่เนื่องจากสาเหตุที่ไม่ใช่มะเร็งในโรงพยาบาลราชวิถี ตั้งแต่เดือนพฤษภาคม พ.ศ. 2564 ถึงเดือนเมษายน พ.ศ. 2565 โดยเปรียบเทียบค่าการทำงานของรังไข่วันก่อนการผ่าตัดและ 12 สัปดาห์หลังการตัดมดลูก โดยวัดระดับฮอร์โมนแอนตี้มูลเลอเรียน (anti-Müllerian hormone: AMH) ในเลือด และตรวจอัลตร้าซาวด์ทางช่องคลอดเพื่อวัดจำนวนฟองไข่ (antral follicle count: AFC) และวัดปริมาตรของไข่ (ovarian volume: OV)*

ผลการศึกษา: *จากการศึกษาในสตรีวัยเจริญพันธุ์จำนวน 55 คน พบว่าฮอร์โมนแอนตี้มูลเลอเรียนลดลงเมื่อเปรียบเทียบก่อนผ่าตัดและหลังผ่าตัด 12 สัปดาห์ โดยสัดส่วนที่แตกต่างกัน (Different proportion: DP) เฉลี่ยอยู่ที่ร้อยละ 22.5 ($p = 0.001$) เช่นเดียวกับจำนวนฟองไข่ และปริมาตรของไข่ ที่ลดลงด้วยโดยมีสัดส่วนที่แตกต่างกัน ร้อยละ 33.3% และร้อยละ 20.0 ($p < 0.001$ และ $p < 0.001$) ตามลำดับ อย่างไรก็ตาม ผลข้างเคียงจากการผ่าตัด และอาการของการหมดประจำเดือนไม่ได้เปลี่ยนแปลงอย่างมีนัยสำคัญ*

สรุป: *การตัดมดลูกโดยไม่ได้ผ่าตัดรังไข่มีผลต่อค่าการทำงานของรังไข่หลังการผ่าตัด 12 สัปดาห์ โดยไม่มีการเปลี่ยนแปลงของอาการของการประจำเดือนอย่างมีนัยสำคัญ อย่างไรก็ตามควรมีการศึกษาผลจากการผ่าตัดในระยะยาวต่อไป*

คำสำคัญ: *ค่าการทำงานของรังไข่, ฮอร์โมนแอนตี้มูลเลอเรียน, จำนวนฟองไข่, ปริมาตรของไข่, การตัดมดลูก*

Introduction

Hysterectomy is the most common gynecologic surgery nowadays. The mean age of patients who underwent hysterectomy was 40.5 years old[1] and tends to increase in older ages. The most common indications for hysterectomy are symptomatic leiomyoma (51.4%), abnormal uterine bleeding (41.7%) and endometriosis (30%)[2]. The surgical approaches to hysterectomy comprise total abdominal hysterectomy, vaginal hysterectomy and minimally invasive procedures such as laparoscopic hysterectomy, robotic-assisted laparoscopic hysterectomy and vaginal natural orifice transluminal endoscopic surgery (vNOTES)[2]. The optimal route of surgery is justified according to the suitability and benefit of each patient, the shape and size of the vagina and accessibility to the uterus, the extent of extrauterine disease, the size and shape of the uterus, comorbidity, preference of the informed patient, hospital devices and surgeon experience. Laparoscopic hysterectomy has a faster return to normal activity, shorter hospital stays, and fewer wound infections than laparotomy. Surgical complications, for example, surgical site infection, blood loss and adjacent organ injury were not significantly different between the open and laparoscopic approaches[2].

Another consequence of hysterectomy is the deterioration of ovarian function, even though the ovaries were preserved[3]. The etiology is believed to result from the ovarian branches of the uterine artery being damaged after hysterectomy, which leads to the disturbance of blood supply to the ovaries[4]. Advancing of ovarian aging would result in not only postmenopausal symptoms, but also long-term health effects from hypoestrogenism, such as, coronary artery disease, dementia and osteoporosis which negatively impact on the quality of life[5].

Ovarian function composes of reproductive and endocrine functions. Ovarian reserve markers are widely used to predict fertility outcomes of infertile patients, such as follicle stimulating hormone (FSH), estradiol (E2), inhibin B, anti-Müllerian hormone (AMH) and ultrasound for antral follicle count (AFC) or ovarian volume (OV)[6]. However, AMH was little intracycle variation and predicted ovarian reserve independent of menstrual cycle[7]. The previous study showed that AMH levels decreased up to 30% after three months of hysterectomy (1.08 ± 0.77 ng/ml and 0.78 ± 0.58 ng/ml respectively)[8].

The purpose of this study was to compare the different proportions (DP) or percentage changes of individual ovarian reserve markers, including serum levels of AMH combined with ultrasound measurements of AFC and OV in premenopausal women who underwent hysterectomy without oophorectomy.

Materials and Methods

Subject recruitment

This was a prospective cohort study that recruited reproductive-aged women from 25 to 50 years old who visited Rajavithi Hospital, Bangkok, Thailand, and underwent hysterectomy for non-oncologic conditions from May 2021 to June 2022. This study was approved by the Institutional Review Board of Rajavithi Hospital. (EC number 64067) No protocol amendments were made after the trial started.

Inclusion and exclusion criteria

The inclusion criteria consisted of female patients aged 25-50 who visited the Rajavithi hospital for a hysterectomy without ovarian surgery for non-oncologic conditions, were able to communicate in Thai, and were willing to participate in the research. If transvaginal sonography revealed dominant follicle, the participant was not included, because measurement of AFC is cycle dependent. Exclusion criteria were as follows: women who had amenorrhea for more than one year, had a history of salpingo-oophorectomy or ovarian surgery, had gynecologic malignancy, genetic or autoimmune diseases, received chemotherapy, brachytherapy

or radiation and received hormonal contraception within one year. Moreover, participants with an initial AMH lower than 0.05 ng/ml were also excluded because changes in AMH could not be compared.

Based on a previous study, a comparison of the AMH values before and after hysterectomy was used to calculate the sample size[8]. The mean difference of AMH was about 30%, therefore we determined that if the difference between AMH before and 3 months post-operation was exceeded 30%, it was significantly different. Using an alpha of 0.05 and a beta of 80%, the minimal sample size was 51 patients. On account of the 30% dropout rate and low level of AMH, 66 patients were enrolled in the study.

Data collection and ovarian reserve measurement

Enrolled participants were first interviewed by a researcher for demographic and relevant data, including previous pregnancy history, maternal menopausal age, menstrual characteristics, underlying diseases, current medication, smoking and previous surgical history. At one day before surgery patients' blood sample was collected in a lithium heparin tube for AMH and delivered to the laboratory department of Rajavithi Hospital to measure AMH level using chemiluminescent immunoassay system (MAGLUMI 2000; Snibe Co., Ltd). Transvaginal sonography for the antral follicle count and ovarian volume was performed by the investigator (Voluson S6, GE Healthcare Support Services) and ovarian volumes were the sum of both ovaries, calculated using the formula length × width × depth × 0.52. If preoperative AMH is less than 0.05 ng/ml and/or transvaginal sonography reveals a dominant follicle, the patients were excluded.

The surgical technique of the hysterectomy

Procedures for total abdominal hysterectomy (TAH) consisted of clamping of the round ligament, cut and ligated. Each utero-ovarian ligament was clamped, cut and ligated. The broad ligament was separated downward, and bladder was mobilized. The uterine artery was skeletonized and clamped at the isthmic portion of the uterus. The pedicle was cut, and suture ligated to ensure hemostasis. The cardinal ligament and uterosacral ligament were all clamped, and suture ligated consequently. The cervicovaginal angle was accessed and hysterectomy was done. Following the removal of the uterus, the vaginal stump was closed using the continuous lock technique. Finally, the abdominal wall was closed layer by layer[4].

The total laparoscopic hysterectomy (TLH) was performed using the same steps as TAH. The pneumoperitoneum was created by Veres needle, and the trocars were placed. Round ligaments, uteroovarian ligaments, uterine arteries, cardinal ligaments and uterosacral ligaments were coagulated and cut by bipolar electrocauterization. The uterus was removed through the vagina and the vaginal stump was closed via laparoscopy[4].

Postoperative data collection

Enrolled participants were undergoing surgery, and information about the surgery was recorded by the doctor who attended the surgery using a data record form. Prior to the surgery, they were informed and trained to record the form precisely. Afterwards, the patients were appointed in the 2nd week postoperatively to inquire about complications from surgery and menopausal symptoms. If the pathology results were malignant, they were excluded from further analysis. The final appointment was on the 12th week to reevaluate postmenopausal symptoms, receive blood tests for AMH and transvaginal sonography to measure AFC and OV. Owing to the absence of uterus, the exact date of the menstrual cycle was unpredictable. If the follow-up sonography revealed a dominant follicle, the patients were scheduled to repeat sonography in three weeks.

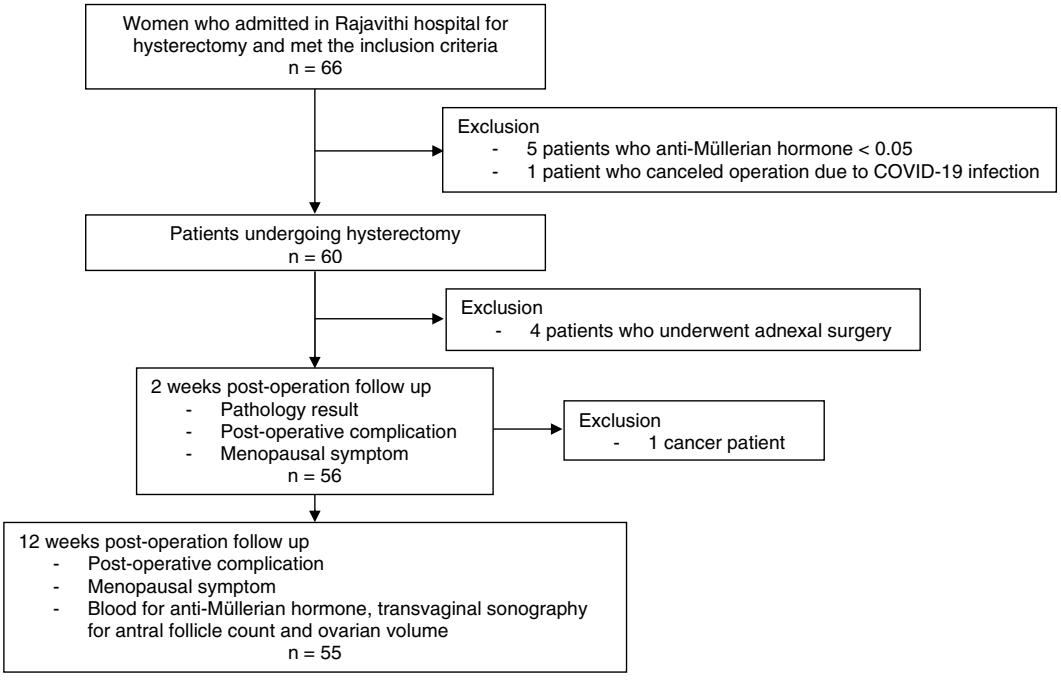

Fig. 1. Study flow diagram.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 26.0, SPSS Inc., IBM New York, USA). Numerical data were presented as the mean with standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of each variable. The categorical data were presented by proportion and percentage. The independent t-test, Wilcoxon signed rank test and McNemar test were used to compare continuous variables. A p value of < 0.05 was determined to be statistically significant.

Results

A total of 66 participants were enrolled between May 2021 and June 2022. Five participants were excluded due to AMH < 0.05 ng/ml and another patient that the operation was cancelled due to COVID-19 infection were excluded. From 60 patients who underwent surgery, four patients were excluded because an oophorectomy was performed, and another was excluded after the pathology result was cancer. Finally, 55 participants were eligible for the analysis. (Fig. 1.)

The demographic characteristics of patients in this study and information about the surgery are shown in Table 1. The average age of participants was 40.67 ± 4.51 years, with a mean body mass index (BMI) of 26.11 ± 7.5 kg/m^2. Twenty percent had a history of cesarean section and 16.4% had postpartum tubal sterilization. Regarding the operation, forty-seven patients (85.5 %) underwent hysterectomy with bilateral salpingectomy. Classified by surgical approach, 34 participants (61.8%) were undergoing TAH, and 21 participants (38.2%) were undergoing TLH. Uterine leiomyoma was the most common pathological diagnosis in 35 patients (63.6%). For the type of operation, 8 patients (14.5%) were hysterectomy, and 47 patients (85.5%) were hysterectomy with BS. During the operation, three patients experienced surgical complications; two patients had bladder injuries and excessive blood loss of more than 1,000 ml.

Table 1. Baseline characteristics of the patients.

Characteristics	
Age (years), mean ± SD	40.67 ± 4.51
BMI, (kg/m^2), mean ± SD	26.11 ± 7.5
- BMI > 30, n (%)	15 (27.3%)
Parity	
- Nulliparity, n (%)	24 (43.6%)
Maternal menopause age, (years), mean ± SD	50.82 ± 2.3
Previous surgery, n (%)	
- Cesarean section	11 (20.0%)
- Tubal resection	9 (16.4%)
Type of operation, n (%)	
- TAH	34 (61.8%)
- TLH	21 (38.2%)
Operation, n (%)	
- Hysterectomy	8 (14.5%)
- Hysterectomy with BS	47 (85.5%)
Operation time (minutes), mean ± SD	147.67 ± 41.89
Blood loss (ml), median (IQR)	200 (250)
Complication, n (%)	
- Blood loss > 1000 ml	2 (3.6%)
- Bladder injury	2 (3.6%)
Pathological diagnosis, n (%)	
- Myoma uteri	35 (63.6%)
- Adenomyosis	19 (34.5%)
- CIN 3	1 (1.8%)

Data were presented as mean ± standard deviation (SD), median (interquartile range (IQR)) and number (%)
BMI: body mass index, TAH: total abdominal hysterectomy, TLH: total laparoscopic hysterectomy, BS: bilateral salpingectomy, CIN: cervical intraepithelial neoplasia

The ovarian reserve markers revealed an AMH of 0.58 (18.1) ng/ml, an AFC of 7 (5) follicles, and an OV of 13.2 (8.2) ml as the median (IQR). Postoperative ovarian markers of AMH, AFC and OV were 0.4 (1.46) ng/ml, 4 (3) follicles and 9.2 (7.6) ml, respectively.

Overall changes in postoperative ovarian markers are shown in Fig. 2. AMH levels were significantly decreased with a median (IQR) DP of 22.47% (68.68), p = 0.001. Twenty-five patients (45.5%) had AMH level decreased ≥ 30%. In addition, AFC and OV were also significantly decreased by the median (IQR) DP of 33.33% (43.33) and 20.0% (25.95) respectively, p < 0.05.

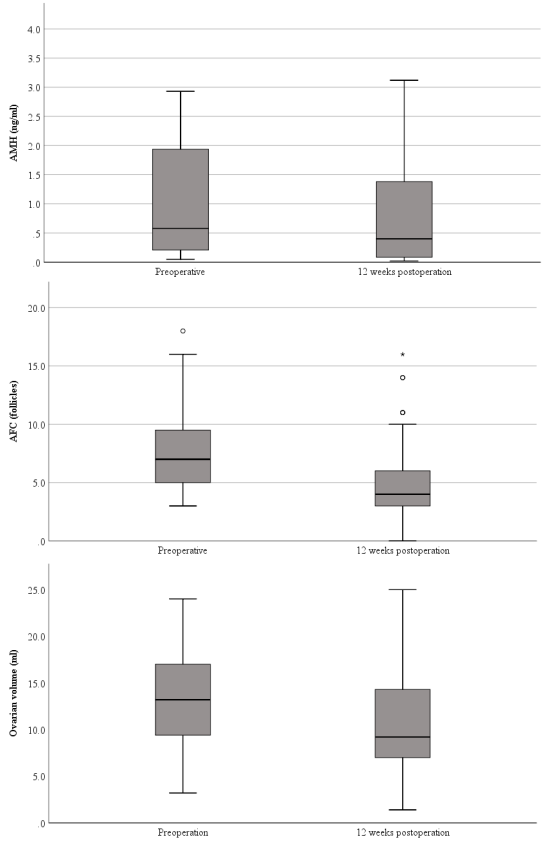

Fig. 2. Changes of ovarian reserve markers between preoperative and 12 weeks after hysterectomy.

Subgroup analysis was performed using logistic regression to estimate the factors associated with diminished AMH of more than 30% and found that BMI ≥ 28 kg/m^2 was the only factor that correlates with significantly declined AMH (odds ratio 1.11, p = 0.025). Subgroup analysis by the age of hysterectomy was not significant. Also, surgical variations such as surgical approach or opportunistic salpingectomy were not correlated with significantly diminished AMH. Nine participants (16.4%) and 10 participants (18.2%) had menopausal symptoms in the 2nd and 12th weeks, respectively. Postoperative wound infection occurred in two participants at two weeks with ongoing infection at 12 weeks and two participants had a wound dehiscence at two weeks.

Discussion

Hysterectomy has a significant effect on ovarian reserve markers with a median DP of 22.47%. 45.5% of them had AMH level decreased ≥ 30%. According to a previous study, AMH was considered to have significantly decreased by 0.27 ng/ml, or approximately 30% after three months of hysterectomy (1.08 ± 0.77 ng/ml and 0.81 ± 0.58 ng/ml, respectively). Furthermore, in another study, the mean AMH level after hysterectomy was 1.08 ± 0.94 ng/mL, which was significantly lower than the level in the control group (1.54 ± 1.10 ng/mL) (p = 0.016)[9]. The laboratory variation of AMH during the menstrual cycle is up to 30%[10]. Therefore, we determined that the reduction of AMH at least 30% was a significant level of DP[8]. The duration of our

study was 12 weeks, which was comparable with some previous studies[8], and another study showed no significant difference in AMH at 6 months compared with 2 months[11].

Not only AMH but also AFC and OV were affected. The AFC and OV were significantly lower, with median DP of 33.33% and 20%, respectively. Nevertheless, the previous study indicated that ovarian volume was unchanged after hysterectomy[9].

Higher BMI correlated with significantly lower AMH. It could be assumed that women with higher BMI might have endocrine disruptions including, steroidogenesis, metabolism, and inflammation, impaired folliculogenesis, and ovulatory potential, which affect the production of the AMH[12]. In addition, abnormal vascular function might potentiate the effects of vascular compromise after hysterectomy. However, participants of study had lower BMI, higher age and high baseline AMH could affect the changes of AMH after hysterectomy themselves. Due to the smaller sample size after subgroup analysis, the power of the study to determine each factor might be lacking.

Opportunistic salpingectomy was not correlated with significantly decreased AMH. According to the recommendation[2], bilateral salpingectomy was planned to prevent epithelial ovarian cancer, but in some patients, it was complicated by severe adhesion. The opportunistic salpingectomy was discontinued. The previous study showed no correlation between significantly decreased AMH and hysterectomy with or without BS after subgroup analysis[13]. Also, the surgical approach was not found to be associated with lower AMH in this study. Nevertheless, according to Cho et al, laparoscopic hysterectomy resulted in a reduction of AMH at two months after surgery (hazard ratio 4.147, 95% confidence interval 1.139-15.097)[11].

Short-term adverse events related to decreased ovarian function were reflected by menopausal symptoms. However, our study showed no significant correlations between significantly decreased AMH and menopausal symptoms. There has been reported that the lower AMH was associated with increased risk of vasomotor symptoms in postmenopausal women, but data regarding changes in AMH were not collected[14]. Vasomotor symptoms are caused by the fluctuation of estrogen, that correlation with dynamic change of AMH and vasomotor symptoms might be plausible. However, the incidence of postoperative vasomotor symptoms was low and the power to determine the correlation was lacking.

For the strength of the study, this is the first prospective cohort trial that investigated the effects of hysterectomy on AMH might be useful to validate the marker of ovarian endocrine factors to monitor patients underwent hysterectomy in the future. AMH was used as the primary outcome measure to avoid intracycle variation from other markers and it was objectively reliable. All patients had a complete blood test protocol to compare the differences in ovarian reserve markers individually. Nonetheless, owing to the conditions of the COVID-19 pandemic, the duration of the study was limited to only 12 weeks, which reflects only the effect of hysterectomy, but the consequences of decreased ovarian function might be in the long run. Thus, the long-term sequelae of hysterectomy on ovarian function could not be justified. AFC and OV exhibit intracycle variation. The exact date of the ultrasonographic evaluation was uncertain, particularly after the procedure.

Conclusion

Hysterectomy significantly decreased ovarian reserve markers; AMH, AFC and OV. However, even with significantly depleted AMH after hysterectomy, short term sequelae from hypoestrogenism were not increased. Further studies to monitor the long-term consequences of hysterectomy on decreased ovarian function should be explored.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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