ORIGINAL ARTICLE

Effect of Hysterectomy on Ovarian Reserve in the Early Postoperative Period Based on the Type of Surgery

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Objectives: This study aimed to evaluate the influence of simple hysterectomy on the ovarian reserve based on the type of surgery.
Methods: Eighty-six premenopausal women between 31 and 48 years who underwent hysterectomy for benign gynecologic disease without additional adnexal surgery at a university hospital participated in this study. Seventy-one patients underwent laparoscopy-assisted vaginal hysterectomy (LAVH), and 15 patients underwent abdominal hysterectomy (AH). Blood samples were obtained from all study participants on preoperative day and 3 days after the operation to determine the anti-Müllerian hormone (AMH) levels.
Results: The postoperative reduction of the mean serum AMH level in the LAVH group (0.42 ± 0.76 ng/mL) was greater than that in the AH group, although the difference was not statistically significant (0.01 ± 0.60 ng/mL) (P = 0.053). The mean baseline AMH level (2.59 ± 2.33 ng/mL) was significantly reduced to 2.24 ± 2.08 ng/mL at 3 days after hysterectomy, and the mean rate of decline of AMH levels after surgery was 13.61% ± 30.81%. In subgroup analysis based on the type of surgery, the mean serum AMH level decreased significantly after surgery in the LAVH group, but no significant changes were found in serum AMH levels before and after the surgery in the AH group.
Conclusions: These preliminary results suggest that simple hysterectomy affects the early postoperative decline of ovarian reserve, and these results might vary depending on the type of surgery.

Key Words: Anti-Müllerian hormone, Hysterectomy, Ovarian reserve

INTRODUCTION

Ovarian reserve refers to the size of the non-growing or resting primordial follicle population in the ovaries [1,2], and it represents the potential ovarian function at a given time point [3]. Among a variety of methods used to assess ovarian reserve (including serum follicle-stimulating hormone [FSH] and inhibin B level assessments [1,3]), anti-Müllerian hormone (AMH) is known to be the most improved and informative marker among these ovarian reserve tests [3-6]. Particularly, serum AMH measurement is helpful for counseling patients regarding ovarian reserve change after gynecologic surgical interventions for benign gynecologic conditions [3].

Hysterectomy is known as one of the most common surgical procedures performed [7]. Some authors have reported that hysterectomy, even if the ovaries are preserved, might antedate ovarian failure [8-10], but whether ovary-sparing hysterectomy influences ovarian reserve postoperatively remains unclear [3,11-15]. In addition, studies regarding the difference of the influence of hysterectomy on ovarian function based on the type of surgery are still lacking.

This study aimed to assess the effect of simple hysterectomy with ovarian conservation on the serum AMH level based on the type of surgery.

MATERIALS AND METHODS

Participants

This study was approved by the Institutional Review Board (IRB) of Inje University Haeundae Paik Hospital (IRB No. 129792-2014-091), and the written informed consent was waived by the IRB. Patients aged 31 to 48 years with regular menstrual cycles undergoing hysterectomy for benign gynecologic disease without additional adnexal surgery between January 2011 and December 2013 at Inje University Haeundae Paik Hospital participated in this study. Those who underwent radical or laparoscopic radical hysterectomy for malignancy were excluded. Additional exclusion criteria were as follows: history of previous uterine or adnexal surgery for gynecologic pathology (except cesarean section); suspicion of ovarian malignancy based on clinical or ultrasonographic evidence; any hormone treatment during the previous 6 months; or menopause symptoms or oligo-amenorrhea. The present study included 86 patients; 71 and 15 patients underwent laparoscopy-assisted vaginal hysterectomy (LAVH) and abdominal hysterectomy (AH), respectively.

Operative techniques

All types of hysterectomy, including LAVH and AH, were performed by the same gynecologist who has been engaged in laparoscopic surgery with more than 10 years of experience. No additional procedures on the adnexa, including oophorectomy, ovarian cystectomy, or salpingectomy, were performed in any of the participants in this study.

LAVH

After three-trocar insertion with carbon dioxide (CO_2) gas insufflation and entrance to the peritoneal cavity, the round ligaments and peritoneum of both sides are dissected and coagulated using monopolar forceps. Subsequently, the ovarian ligaments and salpinges were cut bilaterally with the LigaSure device (Medtronic, Minneapolis, MN, USA). A circular incision is made around the region approximately 2 cm from the external cervical os, and the vaginal wall is dissected. After entry of the anterior peritoneal reflection, the posterior peritoneal sac is opened between the uterosacral ligaments. The uterosacral and cardinal ligaments are individually clamped, divided, sutured, and ligated using Vicryl suture (Ethicon, Somerville, NJ, USA). After the uterus is removed through the vaginal canal, the anterior and posterior mucosae are closed by interlocking suture.

AH

After skin incision and entrance into the peritoneal cavity, both the round ligaments and infundibulopelvic ligaments are clamped, incised, and ligated using Vicryl suture. The bladder flap is dissected, and both uterine arteries are clamped twice, incised, and double suture-ligated on the isthmic portion. After anterior entrance into the vagina, the uterus is excised by completely circumscribing the cervix. The vaginal vault is closed with locking suture with Vicryl. After controlling pelvic floor bleeding, pelvic peritonization is performed, and the abdominal wall is closed layer by layer.

Measurement of serum AMH levels

Serum samples were collected on preoperative day and 3 days after scheduled hysterectomy from all subjects in obedience to the Declaration of Helsinki guidelines. The serum AMH levels were determined using the AMH Gen II assay (Beckman Coulter, Brea, CA, USA). The intra- and inter-assay coefficients of variation were both < 5.0% with the lowest detection limit of 0.08 ng/mL.

The formula for the rate of decline of AMH levels is as follows:

[(preoperative AMH – postoperative day 3 AMH) / (preoperative AMH)] × 100.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics (ver. 25.0; IBM, Armonk, NY, USA). All data were presented as mean ± standard deviation. Differences of clinical variables between LAVH and AH group were assessed using unpaired t tests for continuous variables and chi-square statistics for categorized data, and pre- and postoperative serum AMH levels were compared using paired samples t tests. A one-sample t test was used to determine the statistical significance of the rate of decline of AMH levels. For all analyses, $P < 0.05$ was considered significant.

RESULTS

Table 1 showed the baseline clinical characteristics of the study participants. No significant differences were observed in the clinical variables between the two groups.

Table 1. Comparison of baseline clinical characteristics between the two study groups according to the type of surgery

Variable	LAVH group (n = 71)	AH group (n = 15)	*P* value
Age (y)	43.67 ± 3.32	43.73 ± 2.58	0.950[a]
Height (cm)	158.46 ± 5.46	157.57 ± 4.79	0.559[a]
Weight (kg)	59.29 ± 8.32	61.75 ± 8.47	0.317[a]
Body mass index (kg/m^2)	23.57 ± 2.82	24.83 ± 2.94	0.121[a]
Surgical indications			0.360[b]
Bleeding (including HMB)	31 (43.7)	7 (46.7)	
Pain (including dysmenorrhea)	20 (28.2)	3 (20.0)	
Mass itself (or pressure symptoms)	11 (15.5)	5 (33.3)	
CIN 3	7 (9.9)	0	
Others	2 (2.8)	0	
Preoperative serum AMH levels (ng/mL)	2.69 ± 2.46	2.12 ± 1.56	0.397[a]

Data are presented as mean ± standard deviation or number (%).
LAVH: laparoscopy-assisted vaginal hysterectomy, AH: abdominal hysterectomy, HMB: heavy menstrual bleeding, CIN: cervical intraepithelial neoplasia, AMH: anti-Müllerian hormone.
P values by [a]unpaired *t* test or [b]chi-square test.

Table 2. Comparison of surgical outcomes between the two study groups according to the type of surgery

Variable	LAVH group (n = 71)	AH group (n = 15)	*P* value
Uterine weight (g)	305.41 ± 142.34	751. 43 ± 736.09	< 0.001[a,*]
Surgery time (min)	88.38 ± 22.94	95.33 ± 17.38	0.272[a]
Δ Hemoglobin (g/dL)	1.29 ± 0.80	1.15 ± 0.71	0.529[a]
Postoperative histology			0.205[b]
Myoma or adenomyosis	64 (90.1)	15 (100)	
CIN 3	7[c] (9.9)	0	
Δ AMH (ng/mL)	0.42 ± 0.76	0.01 ± 0.60	0.053[a]
Rate of decline of AMH levels (%)	14.62 ± 32.74	8.81 ± 19.35	0.510[a]

Data are presented as mean ± standard deviation or number (%). Δ means the postoperative blood level changes compared to the preoperative ones.
LAVH: laparoscopy-assisted vaginal hysterectomy, AH: abdominal hysterectomy, CIN: cervical intraepithelial neoplasia, AMH: anti-Müllerian hormone.
P values by [a]unpaired *t* test or [b]chi-square test. [c]Coexistence of myoma or adenomyosis in 3/7 resected specimens. *$P < 0.05$.

In Table 2, the size of uterus of the patients who underwent AH is larger compared with those who underwent LAVH (751.43 ± 736.09 g vs. 305.41 ± 142.34 g, respectively), but there were no significant differences in terms of surgery time or postoperative change in hemoglobin level between the two groups. Mean postoperative reductions of serum AMH levels in LAVH group (0.42 ± 0.76 ng/mL) were greater than those in AH group (0.01 ± 0.60 ng/mL), but this difference did not reach statistical significance ($P = 0.053$).

In Table 3, the baseline serum AMH level of all study participants was 2.59 ± 2.33 ng/mL. Postoperative day 3 serum AMH levels (2.24 ± 2.08 ng/mL) significantly declined compared with baseline AMH levels ($P < 0.001$). The rate of decline of AMH levels after hysterectomy was 13.61% ± 30.81% ($P < 0.001$). In subgroup analysis based on the type of surgery (Table 3, Fig. 1), day 3 postoperative serum AMH levels in the LAVH group (2.26 ± 2.20 ng/mL) were significantly different from preoperative levels (2.69 ± 2.46 ng/mL), and the rate of decline of AMH levels after hysterectomy was 14.62% ± 32.74% ($P < 0.001$). However, serum AMH level before surgery was not significantly different from the AMH levels at 3 days after operation in the AH group (2.12 ± 1.56 ng/mL and 2.11 ± 2.07 ng/mL, respectively).

Table 3. Changes of serum anti-Müllerian hormone (AMH) levels after hysterectomy based on the type of surgery

Variable	Value	P value
All participants receiving hysterectomy (n = 86)		
Preoperative AMH (ng/mL)	2.59 ± 2.33	
Postoperative AMH (ng/mL)	2.24 ± 2.08	< 0.001[a,*]
Rate of decline of AMH levels (%)	13.61 ± 30.81	< 0.001[b,*]
Participants receiving LAVH (n = 71)		
Preoperative AMH (ng/mL)	2.69 ± 2.46	
Postoperative AMH (ng/mL)	2.26 ± 2.20	< 0.001[a,*]
Rate of decline of AMH levels (%)	14.62 ± 32.74	< 0.001[b,*]
Participants receiving AH (n = 15)		
Preoperative AMH (ng/mL)	2.12 ± 1.56	
Postoperative AMH (ng/mL)	2.11 ± 2.07	0.956[a]
Rate of decline of AMH levels (%)	8.81 ± 19.35	0.099[b]

Data are presented as mean ± standard deviation.
LAVH: laparoscopy-assisted vaginal hysterectomy, AH: abdominal hysterectomy.
P values by [a]paired t test (compared to preoperative AMH levels) or [b]one-sample t test. *P < 0.05.

Fig. 1. Serum anti-Müllerian hormone (AMH) levels between the two groups before and after hysterectomy. LAVH: laparoscopy-assisted vaginal hysterectomy, AH: abdominal hysterectomy, pre: preoperative, post: postoperative. *P < 0.05.

DISCUSSION

Hysterectomy is major surgical procedure which is the second most frequently conducted following cesarean section in the United States [1,2]. The first aim of the present study was to evaluate whether ovarian reserve was immediately reduced after hysterectomy with bilateral ovarian preservation by assessing serum AMH levels, and the result is that AMH levels significantly decreased after postoperative day 3 when compared with preoperative ones in all the participants. The second aim of this study was to assess whether the postoperative change of ovarian reserve was different based on the type of surgery, and we found that serum AMH levels significantly decreased postoperatively compared with baseline serum levels before surgery in the LAVH group, but not in the AH group.

It is controversial whether hysterectomy with ovarian preservation affects ovarian reserve [3]. The assessment of the ovarian reserve using serial AMH level measurement is considered a useful tool for evaluating the ovarian function after hysterectomy [3,11], and several studies have been conducted to ascertain whether the postoperative AMH level decreases when compared with the preoperative level, but the results are conflicting [11-17]. Some authors reported that hysterectomy
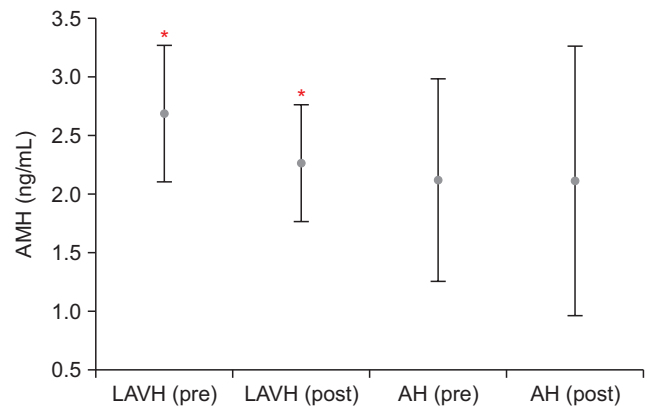
with ovarian conservation could accelerate ovarian failure [8-10]. Ahn et al. [10] reported that the mean age of women who underwent hysterectomy (46.3 ± 3.0 years) was significantly lower than that of those in the control group (48.1 ± 3.2 years).

The reasons for the effect of a simple hysterectomy on the decrease of postoperative ovarian reserve even if the both ovaries are preserved are unclear. One generally accepted hypothesis is that the decrease of ovarian reserve after hysterectomy may be attributed to the interruption of the ovarian branch of the uterine artery that leads to the disturbance of blood supply to the ovaries [3,11,12]. Atabekoğlu et al. [11] suggested that the decrease of ovarian reserve after hysterectomy may be attributed to the acute hypoxia in the ovaries after the interruption of the uterine arteries during operation. However, this explanation is in contrast with the result by Lee et al. [12] who revealed that hysterectomy did not affect ovarian arterial blood flow indices (pulsatile and resistance indices) based on Doppler ultrasonography findings. In addition, this hypothesis hardly explains why the postoperative change of ovarian reserve is different according to the type of hysterectomy in our study.

The second hypothesis is that the electro-thermal energy from the devices used during laparoscopic surgery, such as bipolar forceps or LigaSure, can lead to deleterious effects on the ovarian tissue and vessels, leading to additional loss of ovarian function. To the best of our knowledge, only one study reported the comparison of changes of ovarian reserve after laparoscopic hysterectomy (LH) and non-laparoscopic hysterectomy

(non-LH). Cho et al. [18] measured serum AMH levels preoperatively, and at 7 days, 2 months, and 6 months after LH (total LH or LAVH) and non-LH (vaginal hysterectomy or AH), and they found that the incidence of a significant decrease of serum AMH levels at postoperative 2 months was considerably higher in the LH group compared with that in the non-LH group (43.9% vs. 20.0%). They suggested that electro-thermal devices used for bleeding control during laparoscopic surgery can lead to additional loss of ovarian function, and this result is comparable to ours. Two studies reported that the rate of decline of AMH levels in the bipolar group was significantly higher than that in the suture group after laparoscopic cystectomy for endometrioma [19,20], which supports this hypothesis. In the present study, postoperative decline of serum AMH level in LAVH group was greater than that in AH group which is partially consistent with the results of Cho et al. [18], but regrettably, this difference of ours did not reach statistical significance. In fact, most important drawback of our study was mostly attributable to the relatively small sample size, and in particular, the difference in sample sizes between the two groups is too large (71 vs. 15). If our study had had a larger and more even sample size, this insignificant difference between the two groups in our study would have reached statistical significance.

A prospective cohort study of 83 patients with symptomatic uterine fibroids who underwent LH with conservation of both ovaries reported that serum AMH levels were decreased significantly at 4 months after LH [15], On the contrary, Abdelazim et al. [16] reported that the preoperative AMH level (1.75 ± 4.61 ng/mL) of the 220 studied women was not significantly different compared with the AMH level 6 and 12 months after AH (1.78 ± 2.45 ng/mL and 1.81 ± 2.19 ng/mL, respectively). The results from these two studies are in agreement with our results that serum AMH levels significantly decreased immediately after surgery in the LAVH group, but not in the AH group.

In our study, only AMH levels were assessed as an indicator of ovarian reserve. Of course, AMH is known to be the most informative marker of ovarian reserve, and serum AMH measurement is helpful for counseling patients regarding ovarian reserve change after gynecological surgery, but it would have been better if we had added other indicators of ovarian reserve such as FSH or antral follicle counts in our study.

Determining the optimal time to assess early postoperative decline of ovarian reserve after gynecologic surgery is difficult. There may be questions about whether an AMH measurement 3-days postoperatively was too early to assess the impact of surgery on the ovarian reserve. Most previous studies performed postoperative serial AMH measurements at least 1 week after surgery [21]. Griesinger et al. [22], however, reported that the length of time for serum AMH levels to decrease by the minimum detection limit after bilateral oophorectomy is within 84 hours postoperatively. This finding supports the suggestion of a previous study that 3 days after surgery could be an effective time point to assess early postoperative reduction of the ovarian reserve.

Besides relatively small sample size with uneven sample size between two groups and short-term study design, this study had some serious limitations as follows: First, the mean age of the patients in our study is 43 years old at which serum AMH levels has already reduced, and it may be an another drawback in the present study. Another limitation of our study was the inability to conduct an age-matching comparison between the two groups in a sub-group analysis because of the small sample size and the relatively higher age of the target patients of our study. Furthermore, AMH is known to be recovered at 3 months postoperative after ovarian surgery [23], and for this reason, we might as well checked the serum AMH level at least one more time around 3 months after the surgery. Finally, variables, such as unexpected events in the operative field, which was difficult to compare semiquantitatively, may be additional critical confounding factors in our study.

In summary, our results suggest that hysterectomy has an effect on the decline of ovarian reserve immediately, and this result might be influenced by the type of surgery. Electro-thermal energy from the laparoscopic surgical devices may lead to additional damage to the ovarian reserve. Further prospective large-scale trials are needed to confirm these preliminary findings.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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