Comparison of serum anti-Mullerian hormone level following hysterectomy and myomectomy for benign gynaecological conditions

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Condensation

Hysterectomy may have a more lasting adverse effect on ovarian reserve measured by serum AMH level, when compared with myomectomy.

Abstract:

Objective: The aim of this study was to compare serum anti-Mullerian hormone (AMH) levels following hysterectomy and myomectomy.

Study design: This is a prospective longitudinal observational study. Serum AMH, follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were measured prior to the operation (T1), 2 days (T2), 3 months (T3) following hysterectomy and myomectomy in 70 women aged from 36 to 45 years. Hysterectomy (laparoscopy-assisted vaginal hysterectomy=10; total abdominal hysterectomy=25) with conservation of both ovaries for benign diseases of the uterus were performed in 35 women whereas myomectomy (laparoscopy myomectomy=15; open myomectomy=20) was performed in another 35 women. The time of follow-up was 3 months after operation. The results were analyzed using repeated measure ANOVA and using t test or one-way analysis of variance.

Results: The serum AMH level in the hysterectomy group was 1.08±0.77 ng/ml at T1, 0.78±0.58 ng/ml at T2 and 0.81±0.58 ng/ml at T3 and was significantly lower at T2 and T3 when compared with T1. The corresponding serum AMH level in the myomectomy group was 1.54±0.95ng/ml, 1.18±0.77ng/ml and 1.50±0.58ng/ml respectively and was significantly lower at T2 only. There were no significant differences in serum FSH and LH levels in both hysterectomy and myomectomy groups among these three time points.

Conclusions: Serum AMH levels were significantly lower 2 days and 3 months

following hysterectomy when compared with the pre-operative level. In the myomectomy group, serum AMH levels were only significantly lower 2 days following operation but were similar to the preoperative levels 3 months after operation. Hysterectomy may have a more lasting adverse effect on ovarian reserve. A long term study to follow-up on the AMH level is needed.

~~**Key Words:** AMH, hysterectomy, myomectomy, ovarian reserve~~

Introduction:

Hysterectomy is a commonly performed gynecologic operation but it may adversely affect the ovarian function (1). After hysterectomy, patients experience ovarian failure and menopausal symptoms at a younger age (2). A transient decrease in plasma estradiol (E2) and progesterone has been reported after hysterectomy (3). Elevated follicle-stimulating hormone (FSH) levels were noted in some studies (4-5). On the other hand, several studies (6-7) found no evidence of loss of ovarian function following hysterectomy, as shown by the serum FSH level.

One of the difficulties in studying these patients after hysterectomy is the lack of cycle day when the assessment of ovarian function performed because of the absence of menstruation. In many of the above studies, serum FSH levels were checked at random, rather than in the early phase of follicular development. One study (8) investigated both early follicular FSH level and antral follicle count, but transvaginal ultrasound and repeated scanning were needed.

A cycle-independent marker of ovarian function such as anti-Mullerian-hormone (AMH) is desirable in these studies. AMH is a promising predictor for the occurrence of the menopausal transition (9). AMH in women reaches its highest level after puberty and gradually decreases over time in normal ovulatory women (10). Furthermore, AMH is cycle independent (11-12) and can reflect the quantity of remaining follicles in the ovaries (9, 13).

The effect on the ovarian function following myomectomy is largely unknown. In one study (14), no significant change in serum FSH and estradiol levels between pre- and post-operation in those with myomectomy who served as controls. Blood loss can be severe in the myomectomy operation. Whether blood loss will also affect ovarian function needs to be further investigated. The aim of this study was to compare abdominal hysterectomy and abdominal myomectomy in serum AMH levels.

Materials and methods

~~Subjects~~

~~–~~Women were eligible for inclusion if they had regular menstrual cycles and no history of pelvic surgery and were not taking any hormonal preparation for the recent two months. Any subject who had irregular cycles, history of ovarian surgery or pregnancy now was excluded. If ovaries are removed or ovarian cystectomy is done during hysterectomy or myomectomy, the patients were retrospectively excluded from the study. The study was approved by the Institutional Review Board of GuangDong General People Hospital. Written informed consent was obtained from all subjects prior to the participation into this study.

Between January 2011 and November 2011, 92 women aged from 36 to 45 who attended the Guangdong General Hospital were enrolled in this prospective study: the hysterectomy group (n=43) and the myomectomy group (n=49). Totally 22 women were lost to follow up or withdrew consent. Thus, 35 women in the hysterectomy group (laparoscopy-assisted vaginal hysterectomy [LAVH]=10; total abdominal hysterectomy [TAH]=25) and another 35 subjects in the myomectomy group (laparoscopy myomectomy=15; open myomectomy=20) completed the follow-up appointments.

~~Study design~~

A complete medical history was obtained, and physical and gyneacological

examination was performed at baseline. The data included information on age, menstrual cycle, parity, weight. The follow-up period was 3 months. Blood samples were obtained at three time points: prior to the operation (T1), 2days (T2) and 3 months (T3) following operation. Difference in serum AMH, FSH and LH levels at various time points were compared in both groups.

~~Surgical procedure~~

Hysterectomies and myomectomies were performed by the same team of gynecologists in our center. –All the surgeries were performed in the early stage of the menstrual cycles.

Hysterectomies were performed using laparoscopy-assisted vaginal or trans-abdominal approaches. No additional procedures on the adnexa were performed on any of the patients in this study. In the case of LAVH, after a 15mm subumbilical incision was made and a pneumoperitoneum was established with CO2 gas, two additional 10-mm incisions were made in the right and left lower quadrants. After entering the peritoneal cavity, the round and ovarian ligaments and tubes were transected bilaterally, and the uterus was removed vaginally. Cutting and hemostasis were achieved with bipolar or monopolar coagulation.

Myomectomies were performed using laparoscopic or trans-abdominal approaches. The myometrium overlying the fibroids is injected with a diluted solution of vasopressin (20 units in 100mL of normal saline) using a laparoscopic needle. The myometrial incisions were made with monopolar electrode. Fibroid removed with the

morcellator. The myometrium was closed in layers using 0 or 2-0 absorbable suture on a large needle. Haemostasis was checked after intraabdominal pressure reduced to 6mm Hg.

No surgical complication was founded in both groups.

~~Hormonal measurement~~

Ten ml of blood were taken each time and blood samples were allowed to clot, centrifuged, serum collected, frozen at -22 °C within 2 hours and stored until assayed. The samples for AMH were assayed using an enzyme-immunometric assay (DSL Webster, TX, USA). Inter- and intra-assay coefficients of variation were below 5% at the level of 3 mg/l, and below 11% at the level of 13 mg/l. The detection limit of the assay was 0.026 mg/l. FSH and LH were assayed by immunometric technique.

~~Statistical analysis~~

If a 30% reduction in serum AMH level after hysterectomy was considered as significant, 30 subjects had to be recruited in order to achieve a 80% power at 5% significance level. Statistical analysis were performed using a commercially available software (SPSS13.0).Variables with a normal distribution were compared by t-test or analysis of variance by repeated measures ANOVA. For the variables that did not have a normal distribution, a Wilcoxon's test was used. A p-value<0.05 was considered significant.

Results

The demographic characteristics of patients in this study are presented in Table 1. There were no significant differences between the hysterectomy and myomectomy groups in age, weight, cycle length and blood loss during the operation. Significantly higher parity was found in hysterectomy group.

Table 2 summarized serum AMH, FSH and LH levels at the three time points. In the hysterectomy group, serum AMH level was significantly lower at T2 (P value<0.01) and T3 (P value<0.01) when compared with that at T1 and there was no significant difference between T2 and T3 (Figure 1). In the myomectomy group, serum AMH level was lower at T2 when compared with T1 (P value<0.01) but was comparable between T1 and T3 (P value=0.07). There were no significant differences in serum FSH and LH levels in both hysterectomy and myomectomy groups among these three time points.

Comments~~Discussion~~

To the best of our knowledge, this is the first study assessing the effect of myomectomy on the ovarian reserve using AMH. It is also the study on the effect of hysterectomy on the ovarian reserve. In the hysterectomy group, serum AMH level was found to be reduced 2 days after operation and remained at the lower level 3 months after operation. In the myomectomy group, serum AMH level was also significantly reduced 2 days after operation but was comparable to the pre-operative level 3 months after operation.

The results of our study demonstrate a trend towards decrease ovarian reserve in the hysterectomy group. There was a significant difference between the pre-operative and 2 days postoperative levels or 3 months postoperative levels. The AMH level descended sharply post-operation and ascend slightly after 3 months, but still lower than baseline significantly. However, we also observe the AMH level of 2 days post-operation was lower than pre-operation's significantly in myomectomy group. Iwase et al. (15) also found that there was a small, but significant decrease in serum AMH level 1 month after laparoscopic myomectomy in 15 patients. Use of anesthesic drugs and hypotension due to blood loss may affect the small follicles which secretes AMH. Fluid replacement during the operation may also affect the measurement of serum AMH level on the second day after operation.

Our result indicated the adverse effect of myomectomy on the ovarian reserve is only short term and disappear 3 months after the operation. In another study, Cela (16)

also found no statistically significant differences between mean pre-operative AMH and that detected at 6 months of follow-up in robot-assisted laparoscopic myomectomy. However, the adverse effect of hysterectomy on the ovarian reserve last up to 3 months after the operation. This may be related to ligation or clamping of uterine vessels during hysterectomy. It would be of interest to follow up these patients for a longer period of time so that the adverse effects of hysterectomy can be better understood.

A similar pattern of the change in serum AMH level was shown in another study (17). In that study, changes in serum AMH level in 30 patients who underwent the uterine artery embolization and in 33 patients who underwent hysterectomy were compared. AMH levels were decreased in both groups until the 6^{th} week after the operation. Serum AMH level later increased and was similar to the "expected" level between the 12^{th} and 24^{th} months in the hysterectomy group. The author found the AMH level return to preoperative level 12 month after hysterectomy. But no control group was employed and changes were evaluated using an "expected model" according to a previous report (18).

In a recent study (19), serum AMH levels were measured at baseline and 4 months after total abdominal hysterectomy in 22 women and 20 age-matched healthy women and no significant difference was found following hysterectomy compared with age-matched controls. In another study (20), no significant change was detected in either AMH or ovarian arterial blood flow indices after hysterectomy 3 months. But

In those studies, the age of the subjects was under 50 years old whereas in our study, the patients were younger than 45 years old. As we know, women older than 45 years might suffer from significant decline in ovarian function and this may be a confounding factor in evaluating the impact of hysterectomy on ovarian reserve.

Serum basal FSH level has been widely accepted and used as an ovarian reserve marker. However, the clinical value of basal FSH is limited (21). Our results indicate that FSH and LH levels in these patients did not change after operation. These finding coincide with previous studies (6-7). Iwase (15) demonstrated that postoperative serum AMH levels significantly decreased compared with preoperative levels in patients with endometriomas whereas postoperative basal FSH levels did not significantly change in comparison with preoperative levels. Taken together, it seems that serum AMH level is superior to FSH in evaluating the changing of ovarian reverse.

One of the limitations of this study includes different operations for myomectomy and hysterectomy including laparoscopic and laparotomy approach, although it is not anticipated the different approaches will have significant difference on the impact of ovarian reserve. Another limitation is the lack of a control group at similar ages but without operations done. A 3 month follow up period is not long enough to evaluate the long term implication of myomectomy and hysterectomy on ovarian reserve. Therefore, a long term study is needed.

In conclusion, serum AMH level was significantly reduced 2 days after

myomectomy and hysterectomy. It remained low 3 months after hysterectomy but was back to the pre-operative level 3 months after myomectomy.

Table 1: Demographic characteristics of patients

	Hysterectomy group (n=35)	Myomectomy group (n=35)	P value
Age(yr)	41±2.10	40±2.17	0.054
Parity	1.63±1.06	0.89±0.80	0.001*
Weight(kg)	56±6.4	55±5.4	0.72
Cycle length (days)	27.6±2.2	28.5±2.4	0.11
Blood loss (ml)	170±150	170±112	0.993

Comparison by the t-test

Table 2: Serum AMH, FSH and LH levels prior to the operation (T1), 2 days (T2) and 3 months (T3) following the operation

	T1		T2		T3	
	Hyst.	**Myom.**	**Hyst.**	**Myom.**	**Hyst.**	**Myom.**
AMH(ng/ml)*	1.08±0.77	1.54±0.95	0.78±0.58	1.18±0.77	0.81±0.58	1.50±0.58
FSH(IU/L)	9.30±5.03	8.30±3.06	-	-	9.37±4.70	9.60±4.20
LH (IU/L)	7.15±5.78	8.39±7.96	-	-	5.86±3.84	7.90±5.84

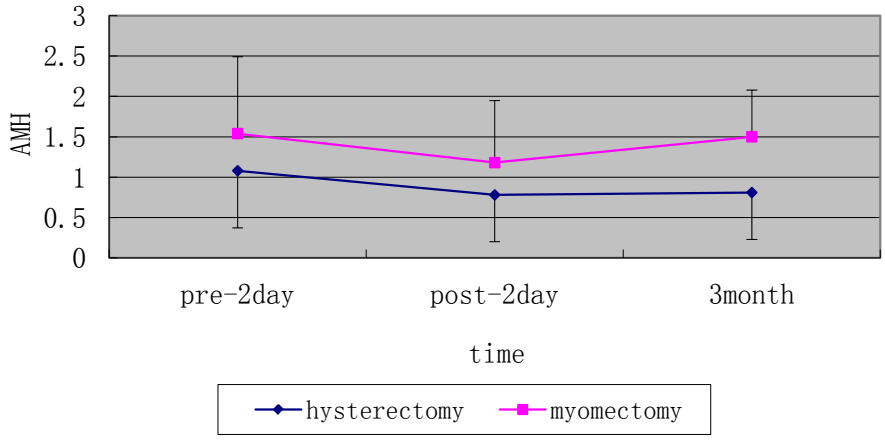
Data are presented as the mean±standard deviation

Hyst. Hysterectomy group ; Myom. Myomectomy group

Statistical differences in AMH *serial change by repeated measures ANOVA($p<0.01$)

No Statistical differences in FSH or LH serial change by repeated measures ANOVA($p>0.05$)

Figure 1: Serial changes of serum AMH levels after hysterectomy and myomectomy



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