

Effects of uterine artery occlusion during myomectomy on ovarian reserve: Serial follow-up of sex hormone levels, ultrasound parameters and Doppler characteristics

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Abstract

Aim: To evaluate the influence of uterine artery occlusion at myomectomy (UAO + M) on ovarian reserve based on serum sex hormone levels, ultrasound and color Doppler examinations.

Methods: In this cohort study, nine women with symptomatic uterine myomas underwent UAO + M were recruited. Each woman was assessed preoperatively and 3, 6 months postoperatively, through a serial of hormonal, ultrasound parameters and Doppler examination for ovarian stromal blood flow. The data were analyzed using generalized estimating equations.

Results: There was no significant difference in serum anti-Müllerian hormone (AMH) or follicle-stimulating hormone (FSH) levels before and 3, 6 months after UAO + M. The ovarian volume, antral follicle count (AFC) and ovarian stromal blood flow had significant changes in the right ovary. Ovarian volume and AFC significantly reduced at 3 months and recovered at 6 months postoperatively ($P = 0.046$, $P = 0.019$, respectively). Peak systolic velocity and end diastolic velocity significantly decreased at 3 months and leveled off at 6 months ($P < 0.001$, $P = 0.001$, respectively). Resistance index significantly increased at 3 months and decreased at 6 months ($P = 0.037$). A similar trend in ultrasound and Doppler findings was observed in the left ovary, but no statistical significance was found.

Conclusion: UAO + M had no detrimental effect on ovarian reserve 6 months postoperatively based on AMH and FSH levels. AFC, ovarian volume and stromal blood flow were transiently decreased in 3 months and recovered in 6 months.

Key words: anti-Müllerian hormone, myomectomy, ovarian reserve, ultrasound, uterine artery occlusion.

Introduction

Uterine myomas are the most common gynecological benign tumors; they have an incidence rate of about 70–80% before the age of 50.¹ Clinical symptoms are present in 20–50% of women with myomas; these include menorrhagia, chronic pelvic pressure/pain, obstructive symptoms and infertility issues.^{2,3} Myomectomy is the most straightforward treatment option when other medical treatments fail in women

with symptomatic fibroids who wish to preserve their uterus.⁴ However, peri-tumoral hypervascularization may lead to difficulties in performing myomectomy due to an increased risk of hemorrhage, either intraoperatively or postoperatively.

Several techniques have been developed to facilitate surgery and limit blood loss. Preventive uterine artery occlusion (UAO) during myomectomy is one option; various techniques have been described via a laparoscopic or open approach.⁵ Recent studies have

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reported the benefits of UAO, including reduced intraoperative blood loss and need for postoperative blood transfusion, fibroid-related symptoms and fibroid recurrence⁶ without affecting postoperative menstruation or uterine function.^{7,8} However, blockage of the uterine arteries, which are one of the dual blood supply to the ovaries, has been suspected to cause subsequent ovarian damage. The effects of UAO concomitant with myomectomy (UAO + M) on fertility are unclear.⁶ A previous study evaluated ovarian reserve after UAO + M using hormone markers and found no significant effect on subsequent ovarian function,⁹ while another study reported short-term alterations in ovarian reserve in patients undergoing internal iliac artery ligation (IIAL) for post-partum hemorrhage as assessed based on serum sex hormone levels and ultrasound parameters.¹⁰ To the best of our knowledge, few studies have evaluated the impact of UAO + M to the ovarian reserve, simultaneously using serology, ultrasound parameters and Doppler indices. This cohort study was aimed at comparing the baseline and subsequent changes in serum sex hormones levels and ultrasound Doppler parameters of ovaries after the UAO + M.

Methods

Patient population

This cohort study was conducted from February 2012 to August 2013 at the Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital. The study was approved by the Internal Review Board, and all patients provided informed consent. All patients were counseled on the potential benefits, risks, uncertain effects on fertility related to UAO + M and post-operative serial ovarian reserve examination. In total, 22 patients were assessed for eligibility. The inclusion criteria were: (i) women with symptomatic uterine fibroids who wanted to preserve their uterus; (ii) age less than 45 years with a regular menstrual cycle. The exclusion criteria were: (i) loss to follow-up during post-operative 6 months; (ii) association with adnexal tumors or previous adnexal surgery; (iii) previous treatment for fibroids before the study including oral contraceptive pill, GnRH analogues, hormone therapy, myomectomy or embolization; (iv) preoperative evidence of ovarian insufficiency; and (v) suspicion of gynecological malignancy. As for the cohort size estimation, one-way repeated-measures ANOVAS were conducted. Given the sex

hormone variables in Qu *et al.*'s study⁹ and the ultrasound and Doppler variables in Fu *et al.*'s study,⁸ with $\alpha = 0.05$, Power = 80% and expected correlation between measurements of 0.5, the sample size was calculated as 7 at least, by which the power could reach over 80%. All analyses were conducted using PASS version 11. Finally, nine patients were enrolled for this study, which was above the inferior limit to reach the power of 80%. All patients had symptomatic fibroids and underwent myomectomy associated with premyomectomy bilateral UAO through a laparoscopic or laparotomic approach. UAO was performed as follows.¹¹ First, an incision was made on the peritoneum to access the retroperitoneal area using a posterior or lateral approach. The ureter and uterine artery bifurcation were visualized, and the ureter was retracted to prevent injury. The adipose tissue around the artery was dissected to free the artery, and UAO was performed by ligation 2 cm from the bifurcation. Ligation was performed twice with 2-0 silk sutures, placed 0.5 cm apart. The same steps were performed on the other side. The ligation sutures were secured and left in situ at the end of the surgery. The operation was performed by the same surgical team, under the supervision of the senior surgeon (F. T. K) in each patient. None of the patient had experienced re-operation due to recurrence or for ligation removal.

Clinical follow-up

Hormone levels, including anti-Müllerian hormone (AMH) and follicle-stimulating hormone (FSH) were measured preoperatively, and at 3 and 6 months post-operatively for all of the patients. All the hormone levels, including AMH, FSH, were measured during the early follicular phase (days 3–7 of the menstrual cycle). Moreover, all patients underwent transvaginal ultrasonography to evaluate the features of the fibroids, ovarian volume, antral follicle count (AFC) and ovary stromal blood flow at the same time points. Bilateral ovaries were measured separately. The length and height of the ovaries were measured in the sagittal section, and the width was measured in the transverse section after 90° rotation of the transducer. Ovarian volumes (cm³) were calculated according to the prolate ellipse formula ($d1 \times d2 \times d3 \times \pi/6$) = transverse (cm) \times anteroposterior (cm) \times longitudinal (cm) \times 0.5233.⁸ The sum of the follicles (2–10 mm in size) in each ovary was defined as the AFC.¹² Ovary stromal blood flow was evaluated using the color Doppler mode. For each examination, the mean value of three consecutive waveforms was obtained.

Peak systolic velocity (PSV), end diastolic velocity (EDV), resistance index (RI), pulsatility index (PI) and systolic/diastolic (S/D) ratio were automatically calculated from three consecutive flow velocity waveforms.^{8,13} All the AFC, ovarian volume and Doppler parameters measurements were performed by two senior sonography technicians under the supervision of the senior surgeon (F. T. K) simultaneously through whole process, in order to correct the deviation immediately and to avoid the inner-observer variation.

Statistical analysis

Statistical analysis was performed using the STATISTICAL PACKAGE OF THE SOCIAL SCIENCES (SPSS) software (version 22.0). Due to the characteristics of repeated measurements, continuous variables in more than two groups, and a limited sample size, the data were analyzed using generalized estimating equations (GEEs). GEEs are popular for the analysis of longitudinal data; for instance, outcomes from the same subject followed over a time frame. A *P* value <0.05 was considered to be statistically significant.

Results

Patient characteristics

Table 1 shows the clinical characteristics of the nine patients. The mean age was 40 ± 2.9 years, with a mean parity of 1.9 ± 0.7 , gravidity 2 ± 0.8 and body mass index 22.2 ± 2.3 kg/m². With regards to the fibroid features, the mean number of myomas per patient was 1.6 ± 0.8 , and the largest myoma volume was 195.5 ± 182.9 cm³. The average operative time was 169.27 ± 38.16 (range, 103–217) min. The average blood loss during surgery was 134.54 ± 69.48 (range, 50–250) mL. The average postoperative hospital stay was 4 ± 0.8 (range 3–5) days. No blood transfusion was administered and no major complications occurred in any patient.

Ovarian reserve assessment

There were no significant differences in AMH and FSH levels at baseline, 3 and 6 months after UAO + M. However, there was an increasing trend in FSH at 3 months that decreased to baseline at 6 months. The changes in AMH and FSH levels are shown in Table 2.

The results of ultrasound parameters (ovarian volume, AFC, PSV, RI, PI and S/D of ovarian stromal

Table 1 Clinical characteristics of the patients

Characteristic	Mean \pm SD	Range
Age (years)	40 ± 2.77	35–44
Gravidity (no.)	2 ± 0.90	1–3
Parity (no.)	1.90 ± 0.80	1–3
Body mass index (kg/m ²)	22.90 ± 1.92	19.50–25.90
Number of myomas per patient	1.67 ± 0.87	1–3
Largest myoma volume (cm ³)	195.57 ± 182.93	11.30–571.19
Total myoma volume (cm ³)	207.75 ± 188.18	13.78–571.19
Estimated blood loss (mL)	134.54 ± 69.48	50–250
Operative time (min)	169.27 ± 38.16	103–217
Post operative hospital stay (days)	4 ± 0.80	3–5

Values are means \pm standard deviation (range).

blood flow on both sides) are shown in Table 3. There were significant differences in right ovarian volume and AFC, which were lower at 3 months after UAO + M and recovered at 6 months (*P* = 0.046 and *P* = 0.019); the same trend was found in left ovarian volume and AFC, but it was not reach statistical significance.

There were also significant differences in PSV and EDV of the right ovarian stromal blood flow, which decreased at 3 months and leveled off at 6 months (*P* < 0.001 and *P* = 0.001). The same trends were noted in the left ovarian stromal PSV and EDV, but without reaching statistical significance. There were significant differences in RI of the right ovarian stromal blood flow, with an increase at 3 months and decrease at 6 months after UAO + M (*P* = 0.037). Both PI and S/D of ovarian stromal blood flow showed no significant changes.

Discussion

In this cohort study, we found no significant changes in preoperative and postoperative serum sex hormone profiles, including AMH and FSH levels. Interestingly, subtle changes were observed in the ultrasound and Doppler parameters, with significant decreases in AFC, ovarian volume and ovarian stromal blood flow at 3 months, which then rebounded 6 months after UAO + M. The impacts on ovarian reserve were more

Table 2 Serum biochemical markers before and after surgery

	Baseline	3 months	6 months	P value	P*	P**	P***
FSH (mIU/mL)	7.32 ± 3.00	13.19 ± 15.94	9.22 ± 7.30	0.405	0.255	0.374	0.450
AMH (mIU/mL)	2.10 ± 2.47	1.86 ± 2.75	1.42 ± 1.34	0.144	0.198	0.151	0.394

*P value for the comparison between baseline and 3 months postoperatively. **P value for the comparison between baseline and 6 months postoperatively. ***P value for the comparison between 3 and 6 months postoperatively. P value <0.05 was considered statistically significant in generalized estimating equations. Values are means ± standard deviation (range).

prominent in the right ovary and were significant, while a similar trend was noted in the left ovary.

Previous studies have shown that serum hormone levels are predictive biomarkers of ovarian reserve,^{12,14} of which AMH and basal FSH are the most effective and commonly used. To the best of our knowledge, few studies have investigated serum AMH levels after UAO + M. Similar to our study, Kim *et al.*¹⁵ evaluated the effects of uterine artery embolization (UAE) for symptomatic uterine fibroids on ovarian reserve based on AMH, and reported significant decreases at 3 and 12 months postoperatively. The presumed cause of ovarian failure after UAE is that embolic material may reach the ovarian circulation and cause vascular occlusion, thereby resulting in hypoxic ovarian damage. However, this does not occur in UAO + M because no embolic materials are involved. In contrast, we found no significant differences in AMH levels before, 3 and 6 months after UAO + M. In addition, our results revealed no statistically significant differences in FSH levels before and after UAO + M, although an increasing trend at 3 months and recovery at 6 months postoperatively

were noted. The observations were consistent with the findings by Qu *et al.*,⁹ who reported a significant increase in FSH concentration 1 month after laparoscopic UAO + M, and recovery at 6 months postoperatively.

Several studies have reported that both AFC and ovarian volume are reliable non-invasive markers for ovarian reserve.^{12,14,16,17} While AFC represents follicular quantity, ovarian volume is correlated with AFC and implies the growth and regression of follicles.¹² Our study showed statistically significant trends of a decrease at 3 months but recovery at 6 months after UAO + M in both AFC and ovarian volume, and these trends were more prominent in the right ovary. Similarly, Kim *et al.*¹⁵ evaluated the effects of UAE for symptomatic uterine fibroids on ovarian reserve, and found a significant decrease in AFC at 3 months, which then rebounded at 12 months after UAE. Although different blockage methods were used, we observed a transient reduction in ovarian reserve at 3 months which then recovered at 6 months after UAO + M. A previous study investigating the biochemical and histologic effects of adnexal torsion on

Table 3 Ultrasound parameters and spectral Doppler analysis before and after surgery

		Baseline	3 months	6 months	P value	P*	P**	P***
Uterus volume (cm ³)		368.70 ± 177.68	168.27 ± 38.25	165.87 ± 54.52	<0.001	<0.001	<0.001	0.865
Ovary volume (cm ³)	R't	6.28 ± 3.95	4.03 ± 1.87	5.10 ± 3.09	0.046	0.013	0.106	0.113
	L't	4.67 ± 3.19	4.3 ± 2.04	5.84 ± 3.75	0.392	0.764	0.499	0.188
AFC (no.)	R't	4.57 ± 1.62	3.29 ± 1.98	4.33 ± 1.80	0.019	0.022	0.596	0.007
	L't	4.11 ± 1.83	3.44 ± 2.24	4.56 ± 2.40	0.109	0.303	0.416	0.037
PSV (cm/s)	R't	19.76 ± 6.05	12.30 ± 5.00	10.77 ± 3.16	<0.001	0.014	<0.001	0.384
	L't	28.44 ± 19.58	17.81 ± 14.98	17.39 ± 6.34	0.200	0.192	0.074	0.935
EDV (cm/s)	R't	5.63 ± 2.94	3.68 ± 2.87	2.04 ± 1.88	0.001	0.003	0.002	0.165
	L't	6.13 ± 2.93	3.62 ± 1.74	3.76 ± 1.02	0.440	0.204	0.289	0.927
RI	R't	0.89 ± 0.15	0.98 ± 0.51	0.78 ± 0.15	0.037	0.605	0.044	0.199
	L't	1.02 ± 0.48	0.71 ± 0.19	0.80 ± 0.18	0.118	0.062	0.224	0.273
PI	R't	1.92 ± 0.90	1.85 ± 1.93	1.44 ± 0.81	0.372	0.915	0.160	0.616
	L't	3.00 ± 2.29	2.78 ± 2.58	1.73 ± 0.51	0.349	0.789	0.167	0.240
S/D	R't	4.39 ± 3.76	3.20 ± 1.03	4.95 ± 4.36	0.219	0.360	0.800	0.238
	L't	8.80 ± 9.70	4.03 ± 4.84	7.93 ± 11.39	0.715	0.413	0.659	0.440

*P value for the comparison between baseline and 3 months postoperatively. **P value for the comparison between baseline and 6 months postoperatively. ***P value for the comparison between 3 and 6 months postoperatively. P value <0.05 was considered statistically significant in generalized estimating equations. Values are means ± standard deviation (range). AFC, antral follicle count; EDV, end diastolic velocity; PI, pulsatility index; PSV, peak systolic velocity; RI, resistance index; S/D, systolic/diastolic ratio.

Table 4 Summary of published studies of ovarian reserve assessments before and after uterine artery occlusion during myomectomy (UAO + M)

Study	N. of UAO+M	Outcome measures	Timing	Results
Jin <i>et al.</i> ²⁶	67	AMH (ng/mL)	Preoperative baseline Postoperative 2 days 3 months 6 months 12 months	Statistically significant drop in AMH levels from baseline to 2 days postoperatively AMH levels returned to baseline values by 3 months postoperatively
Ji <i>et al.</i> ²⁷	33	AMH (μ L/L) FSH (U/L) LH (U/L)	Preoperative baseline Postoperative 2 days 3 months 6 months 12 months	Statistically significant drop in AMH levels from baseline to 2 days postoperatively AMH levels returned to baseline values by 3 months postoperatively
Qu <i>et al.</i> ⁹	30	FSH (IU/L) LH (U/L) Estradiol (pg/mL) Inhibin B (pg/mL)	Preoperative baseline Postoperative 1 month 3 months 6 months	No difference in values at any time point
Fu <i>et al.</i> ⁸	31	Ovarian stromal blood flow PSV (m/s) EDV (m/s) PI RI	Preoperative baseline Postoperative 1 day 1 month 10 months	No difference in values at any time point
Chen <i>et al.</i> (current study)	9	AMH (mIU/mL) FSH (mIU/mL) AFC (no.) Ovarian volume (cm ³) Ovarian stromal blood flow PSV (cm/s) EDV (cm/s) PI RI S/D	Preoperative baseline Postoperative 3 months 6 months	No difference in AMH and FSH levels at any time point Right ovary: Ovarian volume and AFC significantly reduced at 3 months and recovered at 6 months postoperatively. PSV, EDV significantly decreased at 3 months and leveled off at 6 months. RI significantly increased at 3 months and decreased at 6 months Left ovary: similar trend in ultrasound and Doppler finding, without statistical significance

AFC, antral follicle count; AMH, anti-Müllerian hormone; EDV, end diastolic velocity; FSH, follicle stimulating hormone; LH, luteinizing hormone; N, case numbers; PI, pulsatility index; PSV, peak systolic velocity; RI, resistance index; S/D, systolic/diastolic ratio; UAO + M, uterine artery occlusion and myomectomy.

ovarian activity reported a reduced number of growing follicles after torsion, mainly due to tissue ischemic injury.¹⁸ Thus, we presumed that the reduction of AFC and ovarian volume may be due to a transient slight ischemic injury of the ovaries at 3 months after UAO + M, with subsequent compensation at 6 months.

The results we obtained were consistent with those obtained from spectral Doppler examinations of ovarian stromal blood flow. Adequate vascularization of ovaries is essential for the growth and regression of ovarian follicles. Therefore, Doppler measurements

of ovarian stromal blood flow are another popular indicator of ovarian reserve.¹⁹ Previous studies have reported that increases in vascular PSV and EDV or a decrease in RI suggest increased blood flow in the ovaries.^{20,21} We observed significant reductions in PSV and EDV, and an increase in RI at 3 months after UAO + M, implying decreased intraovarian blood flow. However, we observed a significant decrease in RI with constant PSV and EDV at 6 months after UAO + M, implying a subsequent increase in ovarian stromal blood flow. Ovaries have a dual blood supply

system, with the ovarian arteries being the major supply, and collateral circulation from the uterine arteries being additional sources. UAO blocks one of these dual supplies, which causes a reduction in ovarian stromal blood flow. Raba *et al.*²² reported dilatation of the ovarian arteries as seen on computed tomography angiography 6 months after bilateral IIAL, suggesting an increase in blood flow from the ovarian arteries after bilateral IIAL. Increased blood flow from the ovarian arteries may therefore compensate for post-UAO shortage.

Even though the right and left ovaries are histologically similar, there are differences between them, such as venous drainage and follicular development.²³ Several studies^{24,25} have shown that the right ovary has more antral follicles than the left ovary, but the cause of lateralization is unknown. We observed that the temporary change in ovarian reserve is more prominent in the right ovary on ultrasound parameters. It is possible that the right ovary requires more blood supply to support more follicles, hence it is susceptible to the blood flow changes after the UAO. Further studies would be needed to investigate the underlying mechanism. Serum ovarian hormone changes are related to central endocrine control and the activity of both ovaries. While there were temporary changes in the ultrasound measures, the hormone levels were unaffected.

A major strength of this cohort study is that it is a comprehensive and integrated evaluation of ovarian reserve and stromal blood flow after UAO + M assessed on the basis of sex hormone levels, ultrasound parameters and color Doppler characteristics. To our knowledge, most of the published studies contributed to the analysis of sex hormone levels, but might omit the significance of ultrasound and Doppler assessments (Table 4). Furthermore, this is a longitudinal comparison of ovarian function preoperatively, and at 3 and 6 months after UAO + M in the same group of patients, who served as their own controls. This diminished the bias between different surgical groups. However, this study has several limitations that need to be considered. First, it was conducted at a single institution. Second, due to comprehensive yet cumbersome follow-ups on multiple clinical parameters, the high dropout rate that led to the small sample size of this study was inevitable. To overcome the limitation, we used GEE as the method for data analysis. GEE have been confirmed appropriate and widely used when the sample size is limited and to improve power in small longitudinal studies. Third, the same surgical team reduced inter-operator errors, but this inevitably

resulted in intra-operator bias. Last, the long-term fertility potential was unknown.

In conclusion, this study shows that ovarian function, assessed using levels of AMH and FSH were not affected at 6 months after UAO + M. Subtle changes in ovarian reserve and stromal blood flow were observed in AFC, ovarian volume and color Doppler parameters, with a transient decrease at 3 months and recovery at 6 months after UAO + M.

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Disclosure

The authors have no conflicts of interest to declare.

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