Original Research

Association of Myomectomy With Anti-Müllerian Hormone Levels and Ovarian Reserve

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OBJECTIVE: To assess whether open and minimally invasive myomectomy are associated with changes in postoperative ovarian reserve as measured by serum anti-müllerian hormone (AMH) level.

METHODS: This prospective cohort study included patients who were undergoing open abdominal myomectomy that used a tourniquet or minimally invasive (robot-assisted or laparoscopic) myomectomy that used vasopressin. Serum AMH levels were collected before the procedure and at 2 weeks, 3 months, and 6 months after surgery. The mean change in AMH level at each postsurgery timepoint was compared with baseline. The effect of surgical route on the change in AMH level at each timepoint was assessed by using multivariable linear regression. A subanalysis evaluated postoperative changes in AMH levels among the open myomectomy and minimally invasive myomectomy groups individually.

RESULTS: The study included 111 patients (mean age 37.9±4.7 years), of whom 65 underwent open myomectomy and 46 underwent minimally invasive myomectomy. Eighty-seven patients contributed follow-up data. Serum AMH levels declined significantly at 2 weeks postsurgery (mean change −0.30 ng/mL, 95% CI −0.48 to −0.120 ng/mL, P=.002). No difference was observed at 3 months or 6 months postsurgery. On multiple linear regression, open myomectomy was significantly associated with a decline in AMH level at 2 weeks postsurgery (open myomectomy vs minimally invasive myomectomy: $\beta=-0.63\pm0.22$ ng/mL, P=.007) but not at 3 months or 6 months. Subanalysis revealed a significant decline in mean serum AMH levels in the open myomectomy group at 2 weeks (mean change −0.46 ng/mL, 95% CI −0.69 to −0.25 ng/mL, P<.001) postsurgery but not at three or 6 months. In the minimally invasive myomectomy group, no significant differences in mean AMH levels were detected between baseline and any postoperative timepoint.

CONCLUSION: Myomectomy is associated with a transient decline in AMH levels in the immediate postoperative period, particularly after open surgery in which a tourniquet is used. Anti-müllerian hormone levels returned to baseline by 3 months after surgery, indicating that myomectomy is not associated with a long-term effect on ovarian reserve, even with the use of a tourniquet to decrease blood loss.

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Uterine leiomyomas affect up to 80% of reproductive aged people with a uterus and can cause significant morbidity and quality-of-life issues.[1–3]

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Leiomyomas may negatively affect fertility and pregnancy, particularly when located in the submucosal or intramuscular layers.[4–7] Treatment options for leiomyomas include medical suppressive therapies such as oral contraceptive pills, progesterone receptor modulators, and leuprolide acetate; reductive procedures that include uterine artery embolization and radiofrequency ablation; and surgical removal via myomectomy or hysterectomy.[3,8] In patients who desire to conceive, myomectomy is the standard treatment because medical and other procedural options have a contraceptive or an undetermined effect on fertility.[3,8,9] Data on pregnancy rates and outcomes after myomectomy are reassuring.[8,10–12] However, the effect of myomectomy on ovarian function is largely unknown.

Other invasive and minimally invasive treatments for leiomyomas, including uterine artery embolization and hysterectomy, may decrease ovarian reserve, and it is possible that myomectomy may affect ovarian reserve through similar mechanisms, such as interrupting the collateral vasculature that supplies the ovaries through cautery, sutures, or temporary occlusion.[13–18] The use of a tourniquet to minimize blood loss during myomectomy transiently decreases blood supply to the ovaries and could potentially harm ovarian reserve.[19–22] The few studies that have assessed a possible effect of myomectomy on ovarian reserve are limited by small sample sizes, short-term follow-up, or unspecified surgical route and details.[16,17,23,24]

Data on the association of myomectomy with ovarian reserve are useful to patients who desire to conceive, especially those pursuing treatment with assisted reproductive technologies. Information regarding the short-term and long-term effects on ovarian reserve would assist in planning the timing of surgery and ovarian stimulation to optimize oocyte yield and in vitro fertilization outcomes. Assessing the effect of open compared with minimally invasive myomectomy on postoperative ovarian reserve will also be informative as patients and clinicians consider surgical approach.

The objective of this study is to determine whether patients who undergo myomectomy experience a change in ovarian reserve postoperatively, as assessed by serum anti-müllerian hormone (AMH) level, and to evaluate the association of change in AMH with open myomectomy, in which a tourniquet is used compared with minimally invasive myomectomy in which no tourniquet is used.

METHODS

This prospective cohort study included patients at one academic site who were undergoing myomectomy by a single supervising attending surgeon from May 2018 through March 2020. Patients who were scheduled for open abdominal myomectomy, robot-assisted laparoscopic surgery, or conventional laparoscopic surgery during the study period were included. Patients who underwent robot-assisted and conventional laparoscopic surgeries were grouped together as the minimally invasive myomectomy group and were compared with the open myomectomy group. Surgical route was decided by the surgeon and patient based on size, location, and number of leiomyomas. Minimally invasive myomectomy was typically chosen if all leiomyomas were determined by the surgeon to be accessible laparoscopically. Postmenopausal patients were excluded.

Serum AMH level was collected before the procedure, either at the patient's preoperative visit 1 week before surgery or on the day of surgery. The surgeons were not aware of the preoperative AMH level. Follow-up AMH levels were drawn 2 weeks after surgery, 3 months after surgery, and 6 months after surgery. Patients were contacted by phone before each follow-up timepoint and were scheduled to return for blood work. Patients were contacted a minimum of three times at each timepoint. Patients who missed one follow-up were not excluded and were contacted again at each follow-up timepoint.

Samples were analyzed using the AMH electrochemiluminescence assay (Elecsys AMH assay), performed on Cobas e601. The assay has a detection range of 0.03–23 ng/mL, with a low-level (mean AMH 0.9 ng/mL) intra-assay coefficient of variation of 1.6% and a high-level (mean AMH 5.0 ng/mL) coefficient of variation of 0.9%.

All surgeries were performed using a standard surgical procedure. Open myomectomies were performed using a three-quarter inch Penrose drain tourniquet. The uterus was exteriorized through the abdominal incision and the drain was tied at the base of the uterus around the uterine and ovarian vessels, incorporating the ovaries and fallopian tubes within the tourniquet. Vasopressin was not routinely used during abdominal myomectomies but may have been used in rare circumstances. The uterus was incised, and all palpable leiomyomas were removed. In the patients who were undergoing open myomectomy, the tourniquet remained in place throughout the procedure without intermittent release. For minimally invasive myomectomies, vasopressin was injected into the uterine serosa before incising the uterus over the leiomyomas to be removed. A tourniquet was not used during minimally invasive myomectomy. For both routes, leiomyomas were removed through one-to-two large incisions with additional superficial incisions for subserosal leiomyomas. The myometrium and serosa were closed in two-to-three layers. Data were collected regarding length of procedure, estimated blood loss, leiomyoma weight, and concomitant procedures such as lysis of adhesions or adnexal surgery.

Baseline demographics, surgical characteristics, and serum AMH levels were entered into a deidentified database by study investigators and reviewed to ensure accuracy of the data. The study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai. Written informed consent was signed.

The primary outcome was the mean change in AMH level at 2 weeks, 3 months, and 6 months after the procedure, respectively, compared with baseline. The secondary outcome was the association of open myomectomy compared with minimally invasive myomectomy with the change in AMH level at each timepoint compared with baseline. A subanalysis was performed assessing the mean change in AMH level 2 weeks, 3 months, and 6 months postoperatively for the two groups.

An a priori power analysis revealed that for the main analysis, a sample size of 43 patients was needed to detect a 15% difference in mean AMH level with 80% power and an alpha of 0.05. Effect size was determined based on prior studies.[15,16] Baseline variables and surgical characteristics were compared using χ^2 test and t test, with Wilcoxon rank sum used for nonparametric variables. Anti-müllerian hormone levels at each postoperative timepoint were compared with baseline using paired t tests. Multiple linear regression was used to assess the association of open myomectomy compared with minimally invasive myomectomy with change in AMH level at each timepoint, adjusting for confounding variables. All P values were two-sided, with a significance level of 0.05. SAS 9.4 and SAS Studio were used for analysis.

RESULTS

A total of 111 patients with scheduled open abdominal myomectomy or minimally invasive myomectomy were recruited for the study and had baseline serum AMH levels collected before myomectomy, including 65 patients who were undergoing open myomectomy and 46 patients undergoing minimally invasive myomectomy (Fig. 1). Twenty-four patients voluntarily withdrew from the study or were unable to be reached at the contact information provided despite multiple attempts; 87 patients presented at one or more follow-up timepoints. A total of 62 patients had serum AMH levels collected at their 2-week postoperative visits, 47 returned for the 3-month postoperative visit, and 41 returned for the 6-month visit.

Baseline demographics and surgical characteristics in the group overall and among individuals in the open myomectomy and minimally invasive myomectomy groups are shown in Table 1. The two groups were similar in terms of age, gravidity, parity, and prior surgical history. Median baseline serum AMH level was 1.59 ng/mL (interquartile range 1.81 ng/mL) in the cohort overall and was similar between the open and minimally invasive groups (median [interquartile range] 1.56 ng/mL [2.36 ng/mL] vs 1.61 ng/mL [1.52] ng/mL, P=.81). Individuals in the open myomectomy group had higher body mass indexes (BMIs, calculated as weight in kilograms divided by height in meters squared) compared with those in the minimally invasive group (median [interquartile range] 29.7 [7.6] vs 25.2 [5.9], P<.001). Individuals in the open

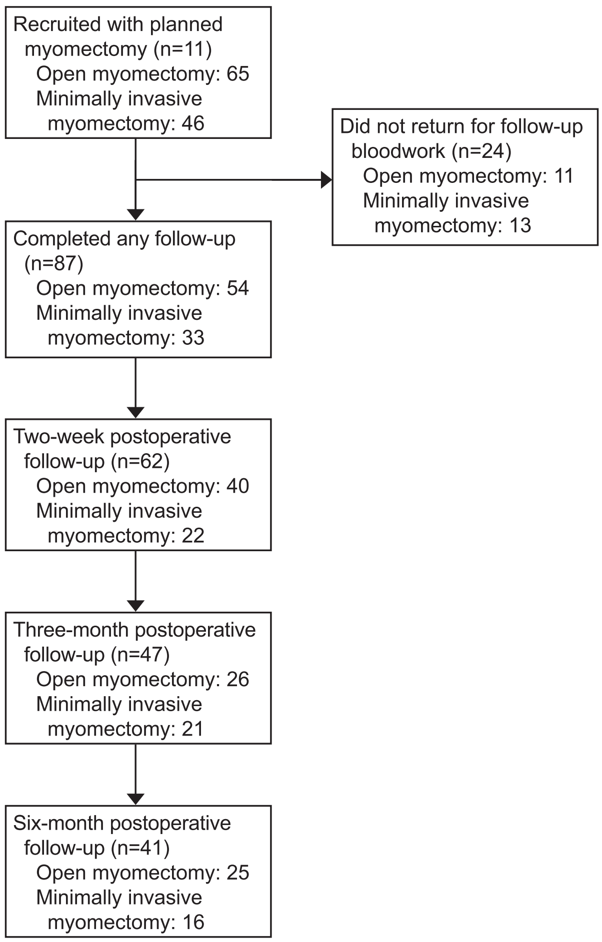

Fig. 1. Patient recruitment and follow-up.

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Table 1. Baseline Demographics and Surgical Characteristics

Variable	All Patients (N=111)	OM (n=65)	MIM (n=46)	*P* (OM vs MIM)
Age (y)	37.9±4.7	37.7±5.0	38.3±4.3	.54
BMI (kg/m²)	26.7 (7.9)	29.7 (7.6)	25.2 (5.9)	<.001
Gravidity	0 (1)	0 (1)	0 (1)	.32
Parity	0 (0)	0 (0)	0 (0)	.44
Baseline AMH level (ng/mL)	1.59 (1.81)	1.56 (2.36)	1.61 (1.52)	.81
Prior surgical history	33.3	40.0	23.9	.08
Length of surgery (min)	119 (61)	109 (46)	134 (56)	.001
Estimated blood loss (mL)	200 (200)	200 (200)	100 (150)	.006
Leiomyoma weight (g)	449 (583)	640 (778)	296 (363)	<.001
Additional surgical procedures	19.8	13.9	28.3	.06
Blood transfusion	4.5	6.2	2.2	.32

Data are mean±SD, median (IQR), or % unless stated otherwise.
OM, open myomectomy; MIM, minimally invasive myomectomy; BMI, body mass index; AMH, anti-müllerian hormone.

myomectomy group had shorter operating times (median [interquartile range] 109 minutes [46 minutes] vs 134 minutes [56 minutes], *P*=.001), higher estimated blood loss (median [interquartile range] 200 mL [200 mL] vs 100 mL [150 mL], *P*=.006), and larger weight of leiomyomas removed (median [interquartile range] 640 g [778 g] vs 296 g [363 g, *P*<.001) compared with those in the minimally invasive group. A trend toward a higher proportion of patients with concomitant adnexal procedures or lysis of adhesions was seen in the minimally invasive myomectomy group compared with the open myomectomy group, though this difference did not reach statistical significance (28.3% vs 13.9%, *P*=.06). Five patients (4.5%) received a blood transfusion, of whom four underwent open myomectomy (6.2%) and one underwent minimally invasive myomectomy (2.2%, *P*=.32).

Baseline demographics among the 87 patients who presented for any follow-up and for the 62 patients who presented at 2 weeks, the 47 patients who presented at 3 months, and the 41 patients who presented at 6 months are shown in Appendix 1, available online at http://links.lww.com/AOG/C908. In each of these subgroups, baseline AMH level was similar among individuals in the open and minimally invasive myomectomy groups, and other baseline characteristics followed similar trends compared with the full group of recruited patients.

Mean serum AMH level at each timepoint in the overall group, the open myomectomy cohort, and the minimally invasive myomectomy cohort are shown in Table 2. Mean differences were calculated based on paired analysis of each follow-up timepoint compared with preoperative baseline levels. Serum AMH levels declined significantly at 2 weeks postsurgery in the overall group, with a mean change of −0.30 ng/mL (95% CI −0.48 to −0.12 ng/mL, *P*=.002). No significant change from baseline was observed at 3 months or 6 months postsurgery (3 months: mean change 0.15 ng/mL, 95% CI −0.11 to 0.40 ng/mL, *P*=.25; 6 months: mean change 0.12 ng/mL, 95% CI −0.18 to 0.42 ng/mL, *P*=.42).

Linear regression controlling for age, BMI, history of prior surgery, length of surgery, estimated blood loss, leiomyoma weight, and additional operative procedures demonstrated that route of surgery was significantly associated with the change in AMH level from the preoperative baseline value to 2 weeks postsurgery. Open myomectomy compared with minimally invasive myomectomy accounted for a significant decline in AMH level at 2 weeks postoperatively: $\beta=-0.63\pm0.22$ ng/mL, *P*=.007. No significant association of open myomectomy compared with minimally invasive myomectomy with change in AMH level was seen at 3 months or 6 months postsurgery (3 months: $\beta=0.07\pm0.36$ ng/mL, *P*=.84; 6 months: $\beta=0.08\pm0.43$ ng/mL, *P*=.85) (Table 3).

When assessing paired mean changes in AMH level among the open and minimally invasive groups, a significant decline in mean serum AMH level was detected in patients who underwent open myomectomy after 2 weeks (mean change −0.46 ng/mL, 95% CI −0.69 to −0.25 ng/mL, *P*<.001) but not after 3 months (mean change 0.25 ng/mL, 95% CI −0.17 to 0.67 ng/mL, *P*=.24) or 6 months (mean change 0.15 ng/mL, 95% CI 0.75–1.34 ng/mL, *P*=.44). In the minimally invasive group, in contrast, no significant differences in mean AMH level were detected at any postoperative timepoint (2 weeks: mean change 0.01 ng/mL, 95% CI −0.29 to 0.31 ng/mL, *P*=.96; 3 months: mean change 0.02 ng/mL, 95% CI −0.23 to 0.28 ng/mL, *P*=.87; 6 months: mean change 0.07 ng/mL, 95% CI −0.45 to 0.60 ng/mL, *P*=.75) (Table 2). Figure 2 shows mean serum AMH levels among all patients who presented

Table 2. Mean Change in Serum Anti-Müllerian Hormone Levels (ng/mL) at 2 Weeks, 3 Months, and 6 Months Postsurgery Compared With Baseline

Patient Group	Baseline (N=111)	2 wk (n=62)	2 wk vs Baseline: Mean Difference*	2 wk vs Baseline: P	3 mo (n=47)	3 mo vs Baseline: Mean Difference*	3 mo vs Baseline: P	6 mo (n=41)	6 mo vs Baseline: Mean Difference*	6 mo vs Baseline: P
All patients	1.95 (1.64–2.26)	1.62 (1.28–1.97)	−0.30 (−0.48 to −0.12)	.002	1.96 (1.44–2.47)	0.15 (−0.11 to 0.40)	.25	2.15 (1.55–2.76)	0.12 (−0.18 to 0.42)	.42
OM	2.05 (1.60–2.49)	1.51 (1.05–1.97)	−0.46 (−0.69 to −.25)	<.001	2.11 (1.32–2.89)	0.25 (−0.17 to 0.67)	.24	2.30 (1.39–3.22)	0.15 (0.75–1.34)	.44
MIM	1.81 (1.38–2.24)	1.82 (1.29–2.37)	0.01 (−0.29 to 0.31)	.96	1.77 (1.06–2.47)	0.02 (−0.23 to 0.28)	.87	1.92 (1.18–2.66)	0.07 (−0.45 to 0.60)	.75

OM, open myomectomy; MIM, minimally invasive myomectomy.
Data are mean (95% CI).
* Calculated based on paired analysis.

at each timepoint among the group overall, and among the open and minimally invasive groups.

DISCUSSION

Myomectomy was associated with an immediate decline in serum AMH level at 2 weeks postsurgery, compared with preoperative baseline levels. This appeared to be a transient effect, because AMH levels recovered within 3 months of undergoing the procedure. Surgical route was associated with change in postoperative ovarian reserve, with open myomectomy being associated with a significant decline in AMH level at 2 weeks postsurgery compared with minimally invasive myomectomy. The effect of open myomectomy on ovarian reserve likely accounts for the difference in AMH level in the study group overall, because this difference was not seen when assessing minimally invasive myomectomy alone.

Anti-müllerian hormone is produced by the granulosa cells of growing follicles within the ovaries.[25] Although AMH level is generally a stable marker of ovarian reserve, it may decline and recover in certain circumstances, such as after gonadotoxic treatments or prolonged oral contraceptive use.[26–28] An insult to or suppression of growing follicles will manifest as a decrease in AMH level; however, as primordial follicles are recruited and grow into preantral and small antral follicles, higher serum AMH levels may be detected. Interruption in distal blood supply to the ovaries is associated with a decline in AMH levels, as evidenced from studies of internal iliac artery ligation.[29] It is possible that transient ischemia during myomectomy affects growing follicles, leading to a temporary decline in AMH level until new follicles are recruited.

Our findings are consistent with a prior study that compared serum AMH levels after hysterectomy and myomectomy and found that both groups had lower AMH levels 2 days after the procedure, but only the hysterectomy group had lower AMH levels after 3 months.[16] However, that study did not analyze changes in AMH level according to the route of myomectomy. One study that assessed seven patients who were undergoing abdominal myomectomy found no difference in follicle-stimulating hormone levels up to 6 months from the procedure.[24] Two studies of laparoscopic myomectomy found no long-term effect on ovarian reserve, as assessed by AMH level, follicle-stimulating hormone levels, or antral follicle counts. One of these studies included five patients with follow-up data; the other included 48 patients but did not specify how many completed follow-ups.[17,23] These studies may have been underpowered to detect differences in markers of ovarian reserve.

In this study, open myomectomy was associated with a decline in AMH levels assessed 2 weeks postoperatively, even after adjusting for leiomyoma size, blood loss, and length of procedure; however, it is difficult to completely control for the baseline differences in patients who were undergoing open myomectomy compared with those undergoing minimally invasive myomectomy, because patients in the open group had significantly more leiomyomas by number and mass. It is possible that the surgical procedure of incising the uterus and removing leiomyoma tissue decreases blood flow to the ovaries, leading to a transient decline in AMH level, and the larger leiomyoma bulk in abdominal myomectomies accounts for the difference in outcome between the two groups. The use of the tourniquet, which transiently decreases

Table 3. Effect of Open Myomectomy Compared With Minimally Invasive Myomectomy on Change in Anti-Müllerian Hormone Compared With Baseline on Adjusted Analysis

Timepoint (No. of Patients)	Parameter Estimate	Standard Error	*P*
2 wk (N=62)	−0.63	0.22	.007
3 mo (N=47)	0.07	0.36	.84
6 mo (N=41)	0.08	0.43	.85

ovarian blood supply, may also account for the short-term decline in AMH level in the open group but not in the minimally invasive group. Our findings are consistent with a prior study that found no significant decline in AMH level 6 weeks after myomectomy with single or triple tourniquet use.[21] A meta-analysis found no differences in clinical pregnancy or live birth rates after uterine artery occlusion during myomectomy, though data on ovarian reserve were heterogeneous and insufficient for metaanalysis.[20]

This study provides additional evidence supporting the safety of tourniquet use in myomectomies. The most common complication in myomectomies is excessive blood loss and need for blood transfusion.[30,31] Tourniquets used throughout the procedure without intermittent release have been shown to significantly decrease the risk of blood loss and need for blood transfusion.[19,32] However, concerns exist regarding injury to the ovaries secondary to hypoperfusion, and data on long-term ovarian reserve after tourniquet use are limited.[20–22] This study provides evidence that, although there may be a short-term decline in AMH level after tourniquet use, the ovaries recover without any evidence of injury by 3 months after surgery.

A nonsignificant trend towards an increase in mean AMH level was observed from preoperative baseline to three and 6 months in the overall group and in the open and minimally invasive myomectomy cohorts individually, and at 2 weeks in the MIM group. It is possible that beyond the immediate decline seen in AMH levels after open myomectomy, myomectomy could have a long-term positive effect on ovarian function by removing leiomyomas, which may be structural impediments to optimal blood flow or may divert vascular flow from the adnexa to themselves. Our study was not powered for this outcome, and further studies will help assess whether myomectomy may have a beneficial effect on ovarian function and whether leiomyoma size and location modify this effect.

Strengths of this study include the prospective design, with a larger sample size compared with prior studies. We were able to assess both short-term and long-term effects of myomectomy on ovarian reserve, as well as to assess the association of surgical route with postoperative ovarian reserve. Limitations of the study include loss of patient participation at follow-up, which may introduce bias and leads to a decreased ability to detect a significant difference in outcome at 6 months. Additionally, data on medication such as oral contraceptives were not consistently available, because many patients returned to their primary gynecologist for long-term management. We are limited in our ability to determine the specific mechanism underlying the decline in AMH level at 2 weeks in the open myomectomy group. It is possible that differences in indication for treatment could be related to postoperative AMH levels, because the

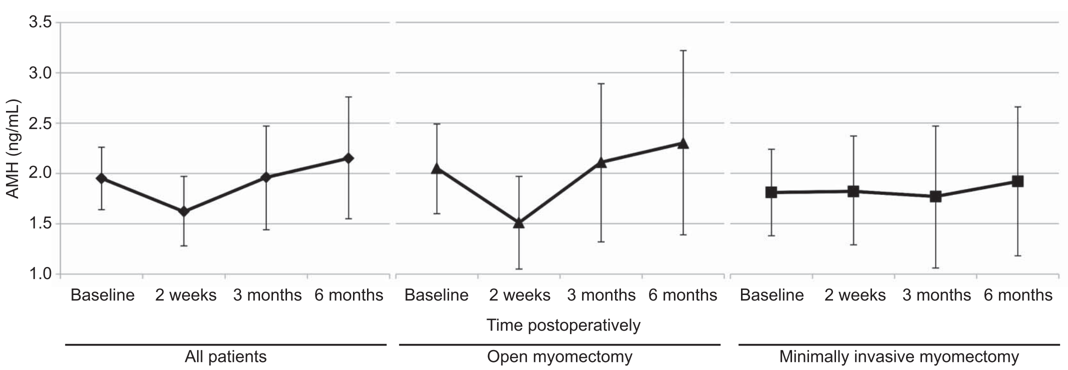

Fig. 2. Mean serum anti-müllerian hormone (AMH) levels at baseline, 2 weeks postoperatively, 3 months postoperatively, and 6 months postoperatively in all patients, the open myomectomy group, and the minimally invasive myomectomy group. *Error bars* represent 95% CIs.

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route of surgery was determined based on size, location, and number of leiomyomas, which differed among the open myomectomy and minimally invasive myomectomy groups and might potentially affect AMH levels. We controlled for baseline differences in our analysis in attempt to isolate the effect of surgical technique. Open surgery, itself, could theoretically account for the differences in postoperative AMH levels, and further study comparing different types of abdominal surgery would help to assess this factor.

Patients who undergo myomectomy may experience a short-term decline in serum AMH level that subsequently recovers in the months after surgery. This effect is more pronounced in patients who undergo an open myomectomy in which a tourniquet is used to reduce blood flow to the uterus and ovaries, compared with minimally invasive myomectomy. Patients who are trying to conceive or planning ovarian stimulation can anticipate that postoperative decline in AMH level is transient, with expected recovery to baseline levels by three to 6 months postsurgery. Our findings provide reassurance that myomectomy, regardless of route and even with temporary uterine artery occlusion, does not appear to have a sustained effect on ovarian reserve.

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