One-year follow-up of serum antimüllerian hormone levels in patients with cystectomy: are different sequential changes due to different mechanisms causing damage to the ovarian reserve?

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Objective: To investigate whether the serum antimüllerian hormone (AMH) levels recover within 1 year after cystectomy for endometriomas, and to analyze the pattern of sequential changes in the serum AMH levels.
Design: Prospective study.
Setting: University hospital.
Patient(s): Thirty-nine patients undergoing cystectomy for unilateral endometrioma (n = 22) and bilateral endometriomas (n = 17).
Intervention(s): Serum samples collected 2 weeks before, and 1 month and 1 year after surgery were assayed for AMH levels.
Main Outcome Measure(s): Assessment of the ovarian reserve damage based on alterations in the serum AMH levels and the association with parameters of endometriosis and surgery for endometriomas.
Result(s): The median AMH levels were 3.56, 1.90, and 2.10 ng/mL before, 1 month after, and 1 year after surgery, respectively. Twenty patients showed higher AMH levels 1 year after surgery than 1 month after surgery (increase group); 19 patients showed lower AMH levels (decrease group). We found a statistically significant difference in the number of follicles removed by surgery between the two groups.
Conclusion(s): The decrease in the serum AMH levels caused by cystectomy can recover. Our results suggest that removal of ovarian cortex might be involved in the decrease of the ovarian reserve just after surgery, and that a continuous decrease of the ovarian reserve after cystectomy might be attributed to other mechanisms. (Fertil Steril® 2013;100:516–22. ©2013 by American Society for Reproductive Medicine.)
Key Words: Antimüllerian hormone, cystectomy, endometriomas, ovarian reserve

Endometriosis is frequently associated with infertility, especially if one or both ovaries are involved (1–4). Ovarian endometriomas are found in 20% of patients with endometriosis (5), and they are often removed to improve spontaneous fertility or alleviate pelvic pain. Although the most effective treatment modality for endometrioma is controversial, cystectomy seems to have been the favored modality of many investigators, as it is associated with less recurrence of the disease (6). However, the safety of this technique has been questioned with respect to the damage to the ovary caused by

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surgery. Regarding the number of oocytes obtained after ovarian stimulation during IVF cycles, several reports have demonstrated that fewer oocytes were obtained from ovaries that had undergone cystectomy (7–10). Moreover, several independent researchers have demonstrated decreased ovarian reserve markers, such as the serum antimüllerian hormone (AMH) and inhibin B concentrations, after the surgical excision of ovarian endometriomas (11–16).

The ovarian reserve is defined as the functional potential of the ovary, which reflects the number and quality of the follicles left in the ovary, and it is well-correlated with the response to ovarian stimulation using exogenous gonadotropin (17). Antimüllerian hormone, a relatively new marker of the ovarian reserve, has gained widespread popularity because it offers several advantages over other tests; for example, it is very sensitive to changes in ovarian reserve with advancing age (18–20) and is menstrual cycle independent (21). Therefore, measurement of the serum AMH levels has been used to evaluate the ovarian reserve after treatments causing possible ovarian toxicity, such as chemotherapy (22, 23). Because AMH is produced by the granulosa cells of primary, preantral, and small antral follicles, but not primordial follicles, to prevent depletion of the primordial follicle pool (24, 25), the AMH level indirectly represents the total number of follicles estimated by the number of the early-growing-stage follicles. It has been demonstrated that the decrease in serum AMH levels just after an intervention causing ovarian damage could recover after several months to allow for the emergence of new growing and AMH-secreting follicles (26).

We previously measured the serum AMH levels before and 1 month after cystectomy for endometriomas and found that the serum AMH levels decreased postoperatively, especially in cases of bilateral cystectomy (16, 27). In the present study, we measured the serum AMH levels 1 month and 1 year after cystectomy to evaluate whether the ovarian reserve can recover after cystectomy for endometriomas and to identify the factors that affect the postoperative fluctuation of serum AMH levels.

MATERIALS AND METHODS

Patients

This study was conducted from July 2008 to April 2012 in the Department of Obstetrics and Gynecology of Nagoya University Hospital in Nagoya, Japan. First, we focused on the comparison between unilateral and bilateral cystectomy. The total sample size and actual power were calculated to be 42 (21 vs. 21) and 0.80, respectively, when α err = 0.05, β err = 0.20, and effect size = 0.80, when taking the coeffcients of variation for the AMH assay into account. Before enrollment, every patient was diagnosed as having uni/bilateral endometrioma(s) by two or more transvaginal ultrasound examinations and by magnetic resonance imaging. The inclusion criteria were as follows: [1] women 20 to 42 years old with regular menstrual cycles (25 to 35 days), and [2] no evidence of any other endocrine disorders, including thyroid dysfunction, hyperprolactinemia, or Cushing syndrome. The exclusion criteria were as follows: [1] previous history of adnexal surgery or [2] any suspicious findings of malignant ovarian diseases. The study was approved by the ethics committee of Nagoya University Graduate School of Medicine, and informed consent was obtained from all patients. A total of 18 patients in the current study were also included in the previous preliminary study (27). We recruited patients undergoing laparoscopic myomectomy as controls to assess ovarian damage caused by cystectomy for endometriomas.

Image Diagnosis and Surgery

We performed transvaginal ultrasonography and magnetic resonance imaging in all eligible patients to diagnose endometriotic cysts. We evaluated cyst size laterality and whether the cysts were monocystic or multicystic before surgery using the latest transvaginal ultrasonography. We determined the mean diameter using the major axis and the minor axis of cross-section images of the cysts. In bilateral cases, the mean diameter of the larger cyst and the smaller cyst were defined as cyst sizes 1 and 2, respectively (Table 1).

All patients underwent either laparotomy or laparoscopic surgery under general anesthesia, as described previously elsewhere (27). Briefly, a laparoscopic pneumoperitoneum was induced by CO_2 insuffiation. The wall of the cysts was stripped from the healthy surrounding normal ovarian tissue with the use of two atraumatic grasping forceps by traction and countertraction after identification of the cleavage plane. When necessary, hemostasis was achieved with bipolar forceps, which were used as little as possible to avoid causing damage to normal tissues. Sutures were used for the closure of the ovarian parenchyma. The cyst wall was stripped by hand and using atraumatic forceps, and hemostasis with bipolar forceps was performed at laparotomy, similar to laparoscopic surgery.

Endometriosis was classified according to the revised American Society for Reproductive Medicine (rASRM) classification (28). Points were assigned for the severity of endometriosis based on the size and depth of the implant and the severity of adhesions by performing a thorough investigation during surgery. A histologic diagnosis was performed on the excised specimens. In laparoscopic myomectomy, enucleation of the uterine leiomyoma nodes was performed using grasping forceps, scissors, and monopolar electrosurgery. Sutures were used to close the myometrium of the uterus after achieving hemostasis with bipolar forceps. All laparoscopic procedures were performed by the same skilled surgical team.

Hormone Measurements

Blood samples were obtained from the patients 2 weeks before surgery and 1 and 12 months after surgery. The serum was separated from whole blood, transferred to sterile polypropylene tubes, and stored at −80°C until the assay. The serum AMH concentrations were measured by an enzyme immunoassay kit according to the manufacturer's instructions (EIA AMH/MIS; Immunotech). The intra-assay and interassay coefficients of variation for the AMH assay were below 12.3% and 14.2%, respectively. On the basis of the serum AMH levels, we defined two groups: the increase group showed

TABLE 1

Patient characteristics of the overall cohort and those who underwent unilateral and bilateral cystectomy.

Characteristics and variables	Overall (n = 39)	Unilateral (n = 22)	Bilateral (n = 17)	*P* value
Age (y)	34.3 ± 5.0	34.0 ± 4.5	34.6 ± 5.5	.751[a]
BMI (kg/m^2)	20.1 ± 2.3	20.8 ± 2.4	19.2 ± 1.8	.069[b]
Preoperative factors				
Monocystic/multicystic, n (%)	16 (41)/23 (59)	13 (59)/9 (41)	3 (18)/14 (82)	.020[c]
Cyst size 1 (cm)	6.3 ± 1.6	5.6 ± 1.5	7.0 ± 1.5	.014[a]
Cyst size 2 (cm)	3.7 ± 1.9	NA	3.7 ± 1.9	NA
Cyst size 1 + 2 (cm)	7.8 ± 3.2	5.6 ± 1.5	10.7 ± 2.7	< .001[b]
Serum CA125 (IU/mL)	51.6 [27.2, 88.2]	44.4 [28.8, 136.2]	54.8 [24.3, 95.3]	.736[b]
Surgery				
Laparoscopy/laparotomy, n (%)	29 (74)/10 (26)	16 (73)/6 (27)	13 (76)/4 (24)	1.000[c]
Blood loss (mL)	112 [25, 306]	45 [10, 208]	273 [108, 416]	.003[b]
Revised ASRM score	53 [26, 84]	28 [22, 70]	77 [44, 96]	.007[b]
No. of follicles in specimens	4.0 [1.0, 12.3]	3.5 [0.8, 15.3]	5.0 [1.5, 15]	.608[b]
Serum AMH (ng/mL)				
Preoperative	3.56 [2.12, 6.67]	4.21 [2.15, 7.28]	3.49 [2.04, 6.66]	.944[b]
Postoperative 1 mo	1.90 [0.91, 4.01]	2.49 [1.19, 4.30]	1.04 [0.57, 2.78]	.030[b]
Postoperative 1 y	2.10 [0.85, 3.48]	2.72 [1.01, 5.15]	0.90 [0.52, 3.13]	.092[b]
Decrease/increase in serum AMH at 1 y, n (%)	19 (49)/20 (51)	12 (55)/10 (45)	7 (41)/10 (59)	.523[c]

Note: Cyst size 1 represents the mean diameter of the unilateral cyst or the larger cyst in patients with bilateral cysts. Cyst size 2 represents the mean diameter of the smaller cyst in patients with bilateral cysts. Cyst size 1 + 2 represents the sum of the diameters. The values are presented as the mean ± SD or median [25th, 75th percentile], with *P* values for the unilateral versus bilateral groups.
[a] Student's *t* test.
[b] Mann-Whitney *U* test.
[c] Fisher's exact test.

Sugita. Serial AMH levels after cystectomy. Fertil Steril 2013.

higher serum AMH levels 1 year after surgery compared with 1 month after surgery; the decrease group had decreased serum AMH levels 1 year after surgery.

Histologic Analysis

Although the surgical technique employed was an ovarian tissue-sparing procedure, ovarian tissue was frequently inadvertently excised. To assess the removal of ovarian tissue, the pathological slides were sliced out of paraffin blocks and selected at equal distances. We counted the number of follicles, including primordial, primary, secondary, and Graafian follicles, in four to five slides selected according to the size of the cyst wall from each patient using an optical microscope (BX60; Olympus Corporation).

Statistical Analysis

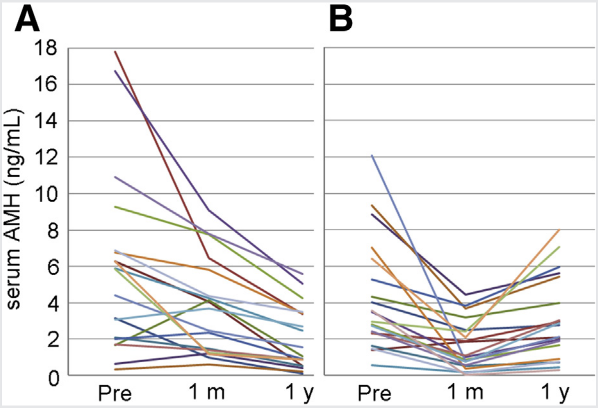
Data were analyzed using the SigmaPlot 11 software program (Systat Software Inc.). We used Student's *t* test and the Fisher exact test to compare the patient characteristics and variables between unilateral and bilateral groups, or between the increase and decrease groups. The Mann-Whitney *U* test was applied instead of Student's *t* test when the variables did not pass the normality test. $P < .05$ was considered statistically significant.

RESULTS

A total of 42 patients were recruited, of whom 22 had unilateral endometrioma and 20 had bilateral endometriomas. We lost 1 year of follow-up for three patients in the bilateral group. Therefore, we analyzed a total of 39 patients, of whom 22 had unilateral endometriomas and 17 had bilateral endometriomas. Table 1 presents their clinical characteristics, including data about the operation and their serum AMH levels. There were statistically significant differences in the ratio of monocystic/multicystic lesions, the cyst size, the blood loss during surgery, and the revised ASRM scores between the unilateral and bilateral groups. The serum AMH levels 1 month after surgery were statistically significantly lower in the bilateral group than in the unilateral group. The 1-year postoperative serum AMH levels were similar to those 1 month after surgery in both the unilateral and bilateral groups, and no statistically significant difference in the serum AMH level was found 1 year after surgery between the unilateral and bilateral groups. The preoperative, 1-month, and 1-year postoperative AMH levels in the laparotomy group were 5.02 ± 4.42/3.59 (mean ± SD/median), 2.96 ± 2.56/2.23, and 2.40 ± 2.38/1.37, respectively, whereas those in the laparoscopy group were 5.06 ± 3.92/3.56, 2.52 ± 2.15/1.85, and 2.57 ± 1.91/2.12, respectively. There were no statistically significant differences at any time point between the laparotomy and laparoscopy groups.

We recorded the sequential changes in the serum AMH levels and patient characteristics in the increase and decrease groups (Fig. 1 and Table 2), and found that the patients were divided almost equally into the two groups (n = 19 in the decrease group, and n = 20 in the increase group). There were no statistically significant differences in the patient characteristics, such as age, laterality of endometriomas, or cyst size, between the increase and the decrease groups. We also found no statistically significant differences in the blood loss during surgery or the revised ASRM scores. On the other hand, our results showed that statistically significantly more follicles were removed during surgery in the increase group compared with the decrease group ($P = .035$).

FIGURE 1



The serial changes in the serum AMH levels in each case in the decrease group (A) and the increase group (B) before surgery, 1 month after surgery, and 1 year after surgery.

Sugita. Serial AMH levels after cystectomy. Fertil Steril 2013.

Therefore, we analyzed the sequential changes in the serum AMH levels according to the number of removed follicles (Supplemental Fig. 1, available online). The serum AMH levels 1 month after surgery were relatively lower in the group with $\geq$10 follicles removed (n = 28) than in the group with $<$10 follicles removed (n = 11), although no statistically significant differences were found (median 1.10 vs. 2.46 ng/mL, P=.089). The preoperative and 1-year postoperative serum AMH levels in the group with $\geq$10 follicles removed were comparable with those observed in the group with $<$10 follicles removed (preoperative median 3.79 vs. 3.49 ng/mL, and 1-year postoperative median 2.07 vs. 2.10 ng/mL).

The laparoscopic myomectomy group, as a control, included 13 patients with a mean age of 35.0 $\pm$ 2.8 (mean $\pm$ SD). No statistically significant differences were found between the preoperative level (2.38 $\pm$ 1.73 ng/mL, mean $\pm$ SD), 1 month after surgery (1.88 $\pm$ 1.25), and 1 year after surgery (1.83 $\pm$ 1.03) serum AMH levels. The sequential changes in the serum AMH levels in the myomectomy group are shown in Supplemental Figure 2 (available online).

DISCUSSION

We previously reported that the serum AMH levels decline 1 month after cystectomy for endometriomas, especially for bilateral endometriomas, in comparison with the preoperative levels (16, 27). The present study investigated the medium-term influence of ovarian cystectomy on the ovarian reserve by assessing the levels of serum AMH 1 month and 1 year after surgery. Until now, four previous reports had evaluated the serum AMH levels multiple times after cystectomy for endometriomas (11, 14, 29, 30). However, ours is the first report to evaluate the serum AMH levels 1 year after surgery. We found that the serum AMH levels 1 year after surgery were similar to those 1 month after surgery, and there was a tendency for bilateral cystectomy to cause more damage to the ovarian reserve. However, the significance of the differences between the unilateral and bilateral groups disappeared according to the 1-year postoperative serum AMH levels. However, the small sample size may be one reason for this observation.

When we compared the AMH levels 1 month and 1 year after surgery, the serum AMH levels at 1 year had increased in approximately half of the cases. As shown in Table 2, 10 (59%) of the 17 patients in the bilateral group exhibited increased AMH levels, and 10 (45%) of 22 patients in the

TABLE 2

Comparison between the decreased and increased AMH groups at the 1-year follow-up evaluation versus 1 month after surgery.

Characteristics and variables	Decrease (n = 19)	Increase (n = 20)	*P* value
Age (y)	33.9 ± 5.4	34.6 ± 4.5	.690[a]
BMI (kg/m^2)	20.6 ± 2.3	19.7 ± 2.2	.228[a]
Preoperative factors			
Unilateral/bilateral	12 (63)/7 (37)	10 (50)/10 (50)	.523[b]
Monocystic/multicystic, n (%)	10 (53)/9 (47)	6 (30)/14 (70)	.200[b]
Cyst size 1 (cm)	6.4 ± 2.0	6.1 ± 1.2	.767[c]
Cyst size 2 (cm)	3.7 ± 1.3	3.7 ± 2.2	.973[a]
Cyst size 1 + 2 (cm)	7.7 ± 3.1	7.9 ± 3.3	.978[c]
Serum CA125 (IU/mL)	51.7 [25.8, 108.7]	47.4 [27.9, 83.7]	.759[c]
Surgery			
Laparoscopy/laparotomy, n (%)	12 (63)/7 (37)	17 (85)/3 (15)	.155[b]
Blood loss (mL)	77 [26, 259]	175 [20, 377]	.715[c]
Revised ASRM score	45 [22, 79]	62 [28, 91]	.327[c]
No. of follicles in specimens	3.0 [0.0, 7.0]	5.5 [1.5, 27.3]	.035[c]
Serum AMH (ng/mL)			
Preoperative	5.87 [2.01, 6.89]	3.23 [2.32, 6.13]	.407[c]
Postoperative 1 mo	3.66 [1.24, 5.81]	1.07 [0.55, 2.50]	.004[c]
Postoperative 1 y	1.07 [0.52, 3.42]	2.44 [1.09, 5.07]	.156[c]

Note: The values are presented as the mean ± SD or median [25th, 75th percentile], with *P* values for the decrease versus increase groups.
[a] Student's *t* test.
[b] Fisher's exact test.
[c] Mann-Whitney *U* test.

Sugita. Serial AMH levels after cystectomy. Fertil Steril 2013.

unilateral group exhibited increased AMH levels, although the difference was not statistically significant. This may be another reason why the significance of the differences between the unilateral and bilateral groups disappeared in the 1-year postoperative serum AMH levels. We performed standardized surgery using a fixed team, so we do not believe that surgeon-dependent variations affected the study results; however, it is known that bilateral cystectomy can cause severe decreases in the AMH levels immediately after surgery, so there is a possibility that we performed cystectomy of bilateral cysts more carefully than with unilateral cysts.

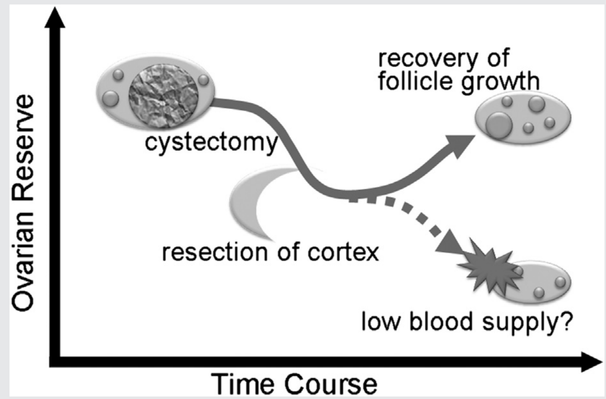
Rearrangements of follicle cohorts might make it possible to recover the serum AMH levels (Supplemental Fig. 3, available online). Because AMH is produced by primary, preantral, and small antral follicles but not primordial follicles, growing follicles, including AMH-producing follicles, are damaged by cystectomy, resulting in a decrease in the serum AMH levels. However, as long as normal, healthy primordial follicles exist beyond a certain quantity, the recruitment and growth of primordial follicles results in rearrangements of the follicle cohort, in which AMH-producing follicles are included.

On the other hand, several cases failed to recover the serum AMH levels. In those cases, a continuous decrease in the ovarian reserve might have occurred after surgery. Folliculogenesis from primordial follicles to preovulatory follicles is considered to take approximately 180 days. Therefore, taken together, our data showing a decrease in the serum AMH levels 1 year after surgery in comparison with 1 month after surgery might be due to a disturbed rearrangement of follicle cohorts derived from residual primordial follicles.

One of the main reasons for the damage to the ovarian reserve is the unintentional removal of normal ovarian cortex during cystectomy for endometriomas. Roman et al. (31) demonstrated that normal ovarian tissue was found in 97% of the specimens of surgically removed endometriomas. Moreover, several other possible mechanisms affecting the ovarian reserve have been proposed. For example, vascular compromise from excessive electrosurgical coagulation and/or excessive adhesiolysis may also cause ovarian damage. Postsurgical inflammation could be another reason for the damage (32, 33). It is interesting that Celik et al. (30) reported that they did not find any correlation between the results of the histopathologic analysis of the removed ovarian tissue and the reduction in the AMH levels, similar to our previously reported data that showed no correlation between the number of follicles removed in the specimen and the rate of decline in the serum AMH levels (27). In our present study, the serum AMH levels measured 1 month after surgery, not those measured 1 year after surgery, were relatively lower in the group with $\geq$10 follicles removed than in the group with $<$10 follicles removed, although the difference was not statistically significant.

In addition, we found that more follicles were removed in the increase group, who recovered their serum AMH level during the year after surgery. In contrast, the decrease group showed a continuous decrease of the serum AMH levels, in spite of fewer follicles being removed during surgery. These results suggest that removal of ovarian cortex by cystectomy might be implicated in the short-term decrease of the ovarian reserve, and that the medium-term influence of cystectomy on the ovarian reserve might be attributed to vascular compromise and/or inflammation due to the surgeries (Fig. 2). We performed electrosurgery and closure of the ovaries in most cases of cystectomy as a standardized protocol. It is difficult to assess the variables of the surgical procedure, such as the time and strength of electrosurgery and the tightness of closure, retrospectively. In a future prospective study, we must evaluate such surgery-related variables as well as the ovarian blood flow measured on ultrasonography.

FIGURE 2



Schematic illustrations of the hypothesis regarding the postoperative changes in the ovarian reserve after cystectomy for endometriomas.
Sugita. Serial AMH levels after cystectomy. Fertil Steril 2013.

The recovery of the ovarian reserve damaged by cystectomy has been assessed in previous studies by the serial evaluation of the serum AMH levels. Lee et al. (14) investigated the serum AMH levels at baseline, 1 week, 1 month, and 3 months after surgery in 27 patients with endometriomas. They showed that there was an approximately 18% increase in the serum AMH levels 3 months after surgery in comparison with those 1 month after surgery. Chang et al. (11) reported that the mean serum AMH level, which was 2.23 ng/mL preoperatively, was reduced to 0.67 ng/mL at 1 week after surgery, followed by an increase to 1.5 ng/mL at 3 months after surgery. Biacchiardi et al. (29) reported the serum AMH levels observed after laparoscopic stripping were significantly decreased and that the mean of the serum AMH levels measured at 3 and 9 months after surgery were similar. On the other hand, Celik et al. (30) reported that most of the patients who had undergone cystectomy for endometriomas showed a significant and progressive decline in serum AMH levels (1.78 ± 1.71 ng/mL, preoperative; 1.32 ± 1.29 ng/mL, 6 weeks after surgery; and 0.72 ± 0.79 ng/mL, 6 months after surgery). However, they included only 39 patients in the evaluation for 6 months after surgery, although 64 patients had been included in the 6-week evaluation. In addition, 10 patients were excluded from their study due to pregnancy within 6 months. In addition to ovarian surgery, the decrease in the serum AMH levels induced by chemotherapy has been reported to increase from the third month after the end of chemotherapy, returning to the pretreatment value 12 months after the end of chemotherapy (26). Therefore, based on our present and previous findings, the decrease in the ovarian reserve induced by surgery, in which no remarkable changes or continuous decreases were found in the serial measurements, may be capable of recovering after a sufficient period for the rearrangement of follicle cohorts.

Our present study found that there are two possible patterns of sequential changes in the serum AMH levels after cystectomy for endometriomas, which might be related to different mechanisms causing ovarian damage. A decrease of the ovarian reserve in the short term after cystectomy appears to occur, as indicated by measuring the serum AMH levels. Further studies that include prospective evaluations of the surgical techniques, such as electrosurgery and adhesiolysis, will be required to assess the medium- and long-term influence of cystectomy on the ovarian reserve in association with pregnancy rates and the endometrioma recurrence rates after surgery. Such studies would help to reveal the mechanism leading to the decrease in ovarian reserve after cystectomy, which would be helpful for optimizing the surgical modalities for endometriomas.

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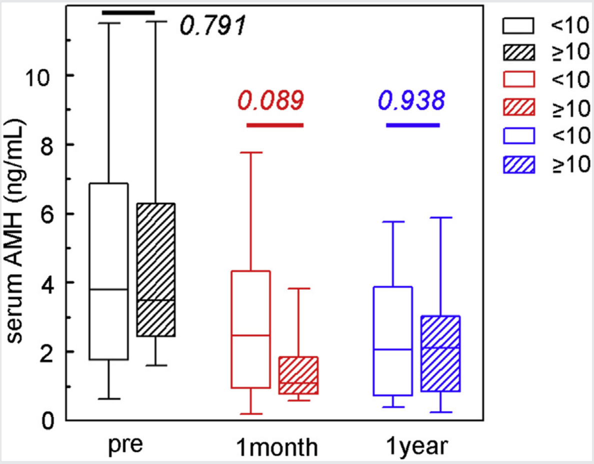
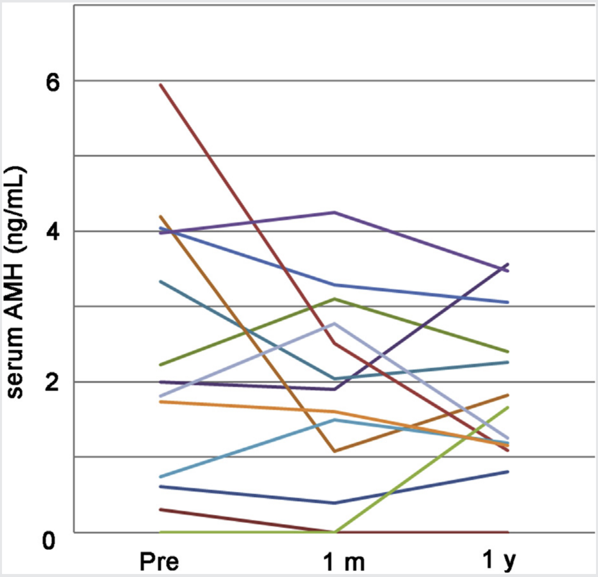
SUPPLEMENTAL FIGURE 1



The preoperative, 1-month, and 1-year postoperative serum AMH levels according to the number of removed follicles in the specimen. The *open box* and *shaded box* in each color show the serum AMH levels in the patients with <10 and ≥10 follicles in the specimens, respectively. The data are represented by *box*-and-*whisker plots*. The *lines* inside the *boxes* represent the median values, and the *upper* and *lower* limits of the *boxes* and *whiskers* indicate the interquartile and total ranges. The *P* values are represented by the italicized numbers.

Sugita. Serial AMH levels after cystectomy. Fertil Steril 2013.

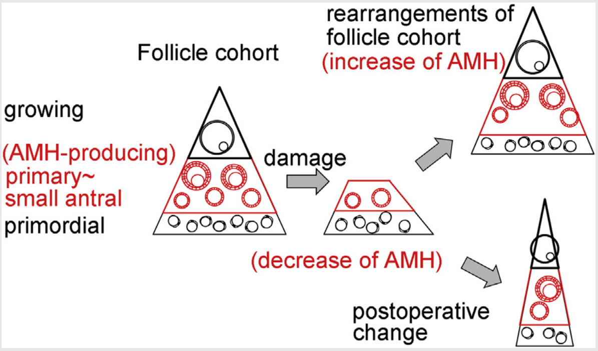
SUPPLEMENTAL FIGURE 2



The serial changes in the serum AMH levels in each case of laparoscopic myomectomy before surgery, 1 month after surgery, and 1 year after surgery.

Sugita. Serial AMH levels after cystectomy. Fertil Steril 2013.

SUPPLEMENTAL FIGURE 3



Schematic illustrations of the rearrangements of the follicle cohort. Ovarian cystectomy possibly causes decreases in the number of AMH-producing follicles. Recruitment of primordial follicles to primary and small antral follicles may result in recovery of the serum AMH levels. Postoperative changes after cystectomy may cause decreases in the follicle cohort and thus a continuous decline of the serum AMH levels.

Sugita. Serial AMH levels after cystectomy. Fertil Steril 2013.