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ORIGINAL ARTICLE *Reproductive endocrinology*

The post-operative decline in serum anti-Müllerian hormone correlates with the bilaterality and severity of endometriosis

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BACKGROUND: To assess the impact of ovarian cystectomy for endometriomas on the ovarian reserve, we evaluated the pre- and post-operative levels of serum anti-Müllerian hormone (AMH). We also analyzed the correlations between factors related to endometriosis and surgery for endometriomas and the serum AMH levels to investigate which factors affect ovarian reserve.

METHODS: Thirty-eight patients who were undergoing ovarian cystectomy for unilateral endometrioma ($n = 20$) and bilateral endometriomas ($n = 18$) participated. Preoperative and post-operative serum samples were collected and assayed for AMH levels, and changes between the two samples were analyzed in association with parameters of endometriosis and surgery for endometriomas.

RESULTS: The mean AMH level was 3.9 ng/ml prior to surgery, and was reduced to 2.1 ng/ml at 1 month post-surgery. The rate of decline of the serum AMH level was significantly higher in the bilateral group than the unilateral group (62.8 ± 29.6 versus $24.7 \pm 32.5\%$, $P < 0.001$). The rate of decline in the serum AMH levels showed a significant correlation to the revised American Society for Reproductive Medicine (rASRM) score ($P = 0.003$), but not age, cyst diameter, blood loss during the operation or the number of follicles removed in the specimens.

CONCLUSIONS: Our results suggest that the decrease in ovarian reserve should be taken into account in patients indicated for cystectomy for bilateral endometriomas or unilateral endometrioma with high rASRM scores.

Key words: anti-Müllerian hormone / cystectomy / endometrioma / ovarian reserve

Introduction

Endometriosis is a common but still enigmatic disease affecting women of reproductive age. The ovary is the organ most frequently affected by endometriosis, with ovarian endometriomas occurring in 17–44% of patients, in whom they cause pelvic pain and infertility (Jenkins *et al.*, 1986; Redwine, 1999). There has been a general consensus that a cystectomy should be considered the treatment of choice for endometriomas. However, the safety of this technique has been questioned with respect to the damage to the ovary that is occasionally caused by surgery. Regarding the number of oocytes obtained following ovarian stimulation during IVF cycles, several reports have demonstrated that fewer oocytes were obtained from ovaries which had undergone cystectomy (Nargund *et al.*, 1996; Geber *et al.*, 2002; Ho *et al.*, 2002; Somigliana *et al.*, 2003).

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 is well-correlated with the response to ovarian stimulation using exogenous gonadotrophin (Broekmans *et al.*, 2006). Over the years, various tests and markers of ovarian reserve have been reported. The static tests include serum markers, such as basal FSH, inhibin-B and anti-Müllerian hormone (AMH), and ultrasonographic markers, such as ovarian volume and antral follicle count (Broekmans *et al.*, 2006; Maheshwari *et al.*, 2006).

AMH belongs to the transforming growth factor-β family, and is produced by the granulosa cells of primary to small antral follicles to

prevent depletion of the primordial follicle pool (Durlinger *et al*., 1999, 2002). Recently, it has been shown that the serum AMH levels may be a valuable marker of the ovarian reserve (Seifer *et al*., 2002; Fanchin *et al*., 2003; McIlveen *et al*., 2007; Kwee *et al*., 2008). Moreover, AMH is the only marker of ovarian reserve, which is menstrual cycle-independent and is unaffected by the use of oral contraceptive pills or gonadotrophin-releasing hormone agonists (Seifer and Maclaughlin, 2007). Therefore, the serum AMH levels currently represent the most reliable and easily measurable maker of ovarian reserve.

In the current study, serum AMH concentrations were measured before and after surgery to assess the influence of cystectomy for endometriomas on the ovarian reserve. We also investigated what factors of endometriosis and surgery for endometriomas correlate with the post-operative decrease in serum AMH.

Materials and Methods

Patients

This study was conducted from January 2008 to May 2010 in the Department of Obstetrics and Gynecology of Nagoya University Hospital in Nagoya, Japan. 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: (i) 18–45-year-old females with regular menstrual cycles (25–35 days), and (ii) no evidence of any other endocrine disorders, including thyroid dysfunction, hyperprolactinemia or Cushing's syndrome. Exclusion criteria were as follows: (i) previous history of adnexal surgery, (ii) any suspicious findings of malignant ovarian diseases and (iii) oral contraceptive use within 3 months before surgery. The study was approved by the ethical committee of Nagoya University Graduate School of Medicine and informed consent was obtained from all patients. A total of 21 patients in the current study were also included in the previous preliminary study (Iwase *et al*., 2010).

Surgery

All women underwent either laparotomy or laparoscopic surgery under general anesthesia. A laparoscopic pneumoperitoneum was induced by CO_2 insufflation with an umbilical 12 mm trocar and was maintained at a pressure of 10 mmHg. 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 counter-traction after identification of the cleavage plane. When necessary, hemostasis was achieved with bipolar forceps, used as little as possible in order to avoid causing damage to normal tissues. Sutures were made for the closure of ovarian parenchyma. The cyst wall was stripped by hand and using atraumatic forceps, and hemostasis with bipolar forceps was performed at laparotomy, similarly to laparoscopic surgery. Endometriosis was classified according to the revised American Society for Reproductive Medicine (rASRM) classification (1985). A histological diagnosis was performed on the excised specimens. The patients were discharged on the 4th (laparoscopy) or 10th (laparotomy) post-operative day in the absence of adverse events. All laparoscopic procedures were performed by the same skilled surgical team.

Hormonal measurements

Blood samples were obtained from the patients 2 weeks before surgery and 1 month after surgery. The serum was separated from whole blood, transferred to sterile polypropylene tubes and stored at −80°C until being assayed. The serum AMH concentrations were measured by an enzyme immunoassay kit according to the manufacturer's instructions (EIA AMH/MIS, IMMUNOTECH, Marseille, France). The intra- and inter-assay coefficients of variation for the AMH assay were below 12.3 and 14.2%, respectively. The rate of decline of serum AMH levels was defined as follows: Rate of decline (%) = 100 × [preoperative AMH level − post-operative AMH level]/preoperative AMH level.

Histological analysis

Although the surgical technique employed is an ovarian tissue-sparing procedure, ovarian tissue is frequently inadvertently excised. In order to assess the removal of ovarian tissue, we counted the number of follicles, including primordial, primary, secondary and Graafian follicles, in three randomly selected specimens from each patient using an optical microscope (BX60, Olympus Corporation, Tokyo, Japan).

Statistical analysis

Data were analyzed using the SigmaPlot 11 software program (Systat Software Inc., San Jose, CA, USA). Simple linear regression analyses and the Pearson correlation were applied where appropriate. Multiple linear regression analyses were applied using the significant factors in the simple linear regression analyses. We used the Wilcoxon signed-rank test for comparing the serum AMH levels before and after surgery. We used Student's *t*-test and the Fisher exact test for comparing the patient characteristics and variables between unilateral and bilateral groups. The Mann–Whitney *U*-test was applied instead of the Student's *t*-test when the variables did not pass the normality test. A *P*-value of <0.05 was considered to be statistically significant.

Results

A total of 38 patients were recruited, of whom 20 had unilateral endometrioma and 18 had bilateral endometriomas. Table I presents their clinical characteristics, including data about the operation and serum AMH levels. There were significant post-operative decreases compared with the preoperative AMH levels in the overall ($P < 0.001$), the unilateral ($P < 0.001$) and the bilateral groups ($P < 0.001$). There were also significant differences in the blood loss during surgery and the rASRM scores between the unilateral and bilateral groups. The post-operative serum AMH levels were significantly lower in the bilateral endometrioma group. No other parameters differed significantly between the two groups.

The mean ± standard deviation (SD) of the rate of decline of the serum AMH level was 24.7 ± 32.5 and 62.8 ± 29.6% in the unilateral and bilateral groups, respectively. The rate of decline of the serum AMH level was significantly higher in the bilateral group (Fig. 1). We then analyzed the correlation between preoperative serum AMH levels and patient characteristics. The preoperative serum AMH level showed a negative correlation with patient age ($r = -0.392$, Fig. 2A). The preoperative serum AMH level did not show a significant correlation with cyst diameter ($r = -0.203$, Fig. 2B) or rASRM score ($r = -0.219$, Fig. 2C). A positive correlation was found between the preoperative serum AMH level and the number of follicles removed ($r = 0.488$, Fig. 2D).

We then analyzed what factors of endometriosis and surgery for endometriomas correlated with the post-operative decline in serum AMH. The rate of decline of the serum AMH level did not show a significant correlation with patient age ($r = -0.0122$, Fig. 3A), cyst

Table I Patient characteristics.

Characteristics and variables	Overall (n = 38)	Unilateral (n = 20)	Bilateral (n = 18)	P-value
Age (years)	33.8 ± 4.7	34.0 ± 3.9	33.6 ± 5.4	0.830[a]
BMI (kg/m^2)	20.1 ± 2.3	20.4 ± 2.7	19.7 ± 1.7	0.781[b]
Preoperative				
Monocystic/Multicystic (%)	6 (16)/32 (84)	5 (25)/15 (75)	1 (6)/17 (94)	0.184[c]
Cyst size 1 (cm)	6.4 ± 2.2	6.1 ± 2.5	6.7 ± 1.8	0.125[b]
Cyst size 2 (cm)	3.9 ± 1.3	NA	3.9 ± 1.3	NA
Cyst size 1 + 2 (cm)	8.2 ± 3.4	6.1 ± 2.5	10.6 ± 2.5	<0.001[b]
Serum CA125 (IU/ml)	85.4 ± 84.8	99.7 ± 105.1	68.7 ± 46.3	0.915[b]
Surgery				
Laparoscopy/Laparotomy	33 (87)/5 (13)	18 (90)/2 (10)	15 (83)/3 (17)	0.653[c]
Blood loss (ml)	249 ± 305	152 ± 216	357 ± 350	0.005[b]
rASRM score	49.5 ± 28.3	36.7 ± 23.5	63.7 ± 26.3	<0.001[b]
Number of follicles in specimens	18.1 ± 19.8	16.9 ± 14.8	19.4 ± 24.2	0.763[b]
Serum AMH (ng/ml)				
Preoperative	3.9 ± 2.5	4.1 ± 2.3	3.6 ± 2.7	0.299[b]
Post-operative	2.1 ± 1.6	2.9 ± 1.6	1.2 ± 1.0	0.001[b]

Values are means ± SD. P-values in unilateral versus bilateral.
[a]Student's t-test.
[b]Mann–Whitney U-test.
[c]Fisher's exact test.

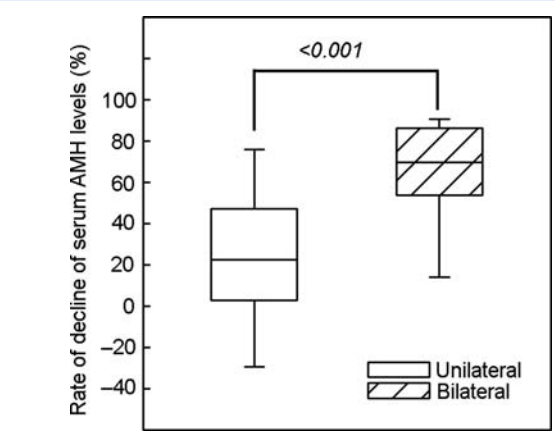

Figure 1 The rate of decline in serum AMH is defined as 100 × [preoperative AMH level − post-operative AMH level]/preoperative AMH level. Data are represented by box-and-whisker plots. The lines inside boxes indicate the median value, and the upper and lower limits of the boxes and whiskers indicate the interquartile and total ranges. The P-value is denoted with italicized numbers.

diameter (r = 0.259, Fig. 3B), preoperative CA125 levels (r = 0.00221, Fig. 3C) or preoperative AMH levels (r = 0.151, Fig. 3D). The rASRM scores showed a positive correlation with the rate of decline of the serum AMH level (r = 0.473, Fig. 3E). In the subgroup analysis of a unilateral cystectomy, a positive correlation was found between the rASRM scores and the rate of decline of serum AMH levels (r = 0.592, Fig. 3F). There was no significant correlation between the rate of decline of serum AMH levels and blood loss during surgery (r = 0.277, Fig. 3G) or the number of follicles removed (r = 0.215, Fig. 3H).

Finally, we performed multiple linear regression analyses using the two significant factors obtained from the simple linear regression analyses. The bilaterality of endometriomas still showed a significant correlation with the rate of post-operative decline of the AMH levels (Table II).

Discussion

The safety of cystectomy for endometriomas has been questioned with respect to damage to the affected ovary. Somigliana *et al.* (2006) reviewed a number of studies and suggested a possible reduction in the number of oocytes retrieved from the ovary subjected to surgery during IVF procedures, which indicates that cystectomy for endometriomas might affect the ovarian reserve. However, the patients who received surgery for endometriomas do not necessarily need to undergo IVF. Therefore, the results from the IVF outcomes might have been influenced by selection bias. The present study attempts to investigate the influence of ovarian cystectomy on the ovarian reserve by assessing the levels of serum AMH. We demonstrate that the post-operative serum AMH levels significantly decreased in comparison to the preoperative levels in patients with endometriomas, especially bilateral endometriomas. Our results suggest that the ovarian cystectomy for endometriomas affects the ovarian reserve, which correlates with the findings of previous reports (Chang *et al.*, 2010; Iwase *et al.*, 2010).

Regarding ovarian reserve, several reports have suggested that vaporization or fenestration is favorable compared with cystectomy

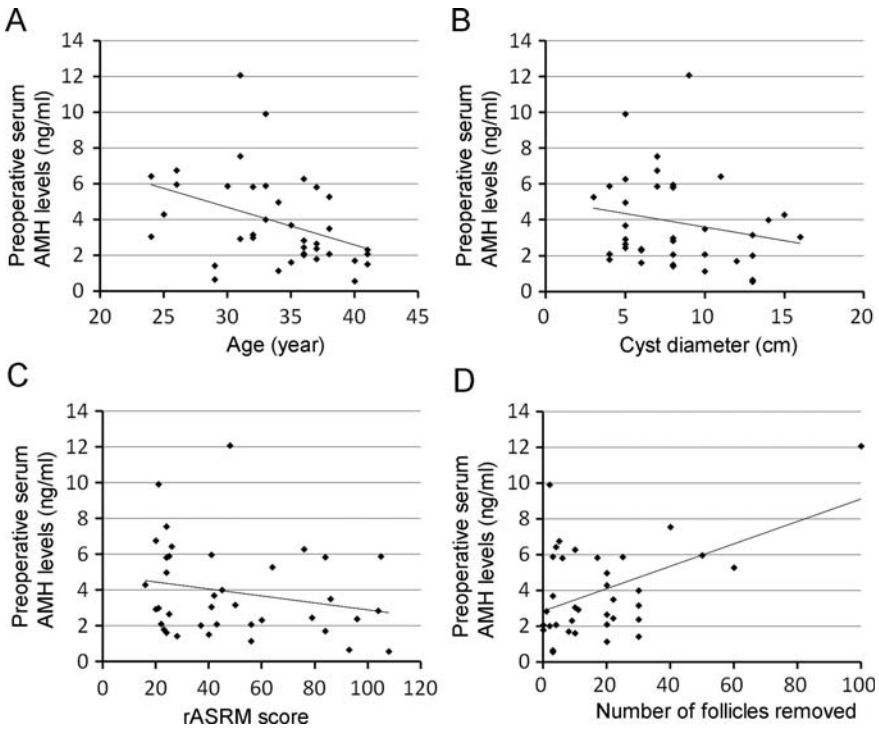

Figure 2 Correlation of the preoperative serum AMH level with (**A**) age ($r = -0.392$, $P = 0.0149$), (**B**) cyst diameter ($r = -0.203$, $P = 0.22$), (**C**) rASRM score ($r = -0.219$, $P = 0.187$) and (**D**) the number of follicles removed ($r = 0.488$, $P = 0.00255$). The r is the Pearson correlation coefficient.

for endometriomas (Donnez *et al*., 2001; Tsolakidis *et al*., 2010). However, Alborzi *et al.* (2004) demonstrated that laparoscopic cystectomy results in a lower recurrence rate and a higher cumulative pregnancy rate than fenestration, and therefore concluded that laparoscopic cystectomy is a better choice than fenestration. Moreover, decreased AMH levels in patients with mild/minimal endometriosis (Lemos *et al*., 2008) and negative effects of endometriotic cysts on the rate of spontaneous ovulation (Benaglia *et al*., 2009) have been reported. All things considered, although removal of endometriotic lesions of the ovary using a surgical approach is recommended, it will be necessary to determine what type of surgery should be selected each for different types of endometriosis and for individual patients.

Precisely which parameters regarding endometriosis and surgery for endometriomas affect the decrease in ovarian reserve could not be elucidated; however, such information might be helpful for the optimization and individualization of treatment options for patients with endometriomas. In the current study, we found that the rate of decline of the serum AMH level showed a significant difference between unilateral and bilateral endometriomas and a significant correlation to the severity of endometriosis, but not with patient age, cyst diameter, blood loss during surgery or the number of follicles removed in specimens. Several mechanisms underlying the post-operative reduction of ovarian reserve have been proposed. First, the damage may precede surgery, i.e. the cyst itself may cause negative effects on the surrounding tissue (Maneschi *et al*., 1993). Therefore, it may be possible that the endometriomas themselves reduce serum AMH levels. However, in the present study, the preoperative serum AMH levels did not show a significant correlation with cyst diameter, severity of endometriosis or a significant difference between unilateral and bilateral endometriomas (data not shown).

Secondly, it has been proposed that a consistent amount of ovarian tissue containing follicles is unintentionally removed during cystectomy (Hachisuga and Kawarabayashi, 2002; Muzii *et al*., 2002), which leads to the decrease in ovarian reserve. We found a significant correlation between the number of follicles removed in the specimens and the preoperative serum AMH level, but not with the rate of decline of serum AMH levels. This result might suggest that patients who have more follicles tend to lose more follicles during the removal of ovarian endometriotic tissue. While a direct proportional relationship between endometrioma size and the amount of ovarian parenchyma removed during cystectomy has been reported (Roman *et al*., 2010), Somigliana *et al.* (2003) reported that the diameter of the cyst did not appear to play a relevant role in determining the number of follicles in IVF procedures following ovarian cystectomy. Our results also indicated no significant correlation between the cyst diameters and the rates of decline of serum AMH levels. Taken together, although the accidental removal of ovarian tissue may affect the ovarian reserve following cystectomy for endometriomas, the cyst diameter or the number of follicles removed in the specimens is not useful for predicting the severity of the decrease of ovarian reserve when the procedure is performed by a sufficiently skilled surgeon.

Another possible reason for the post-surgical reduction of ovarian reserve is the damage inflicted on the vascularization due to

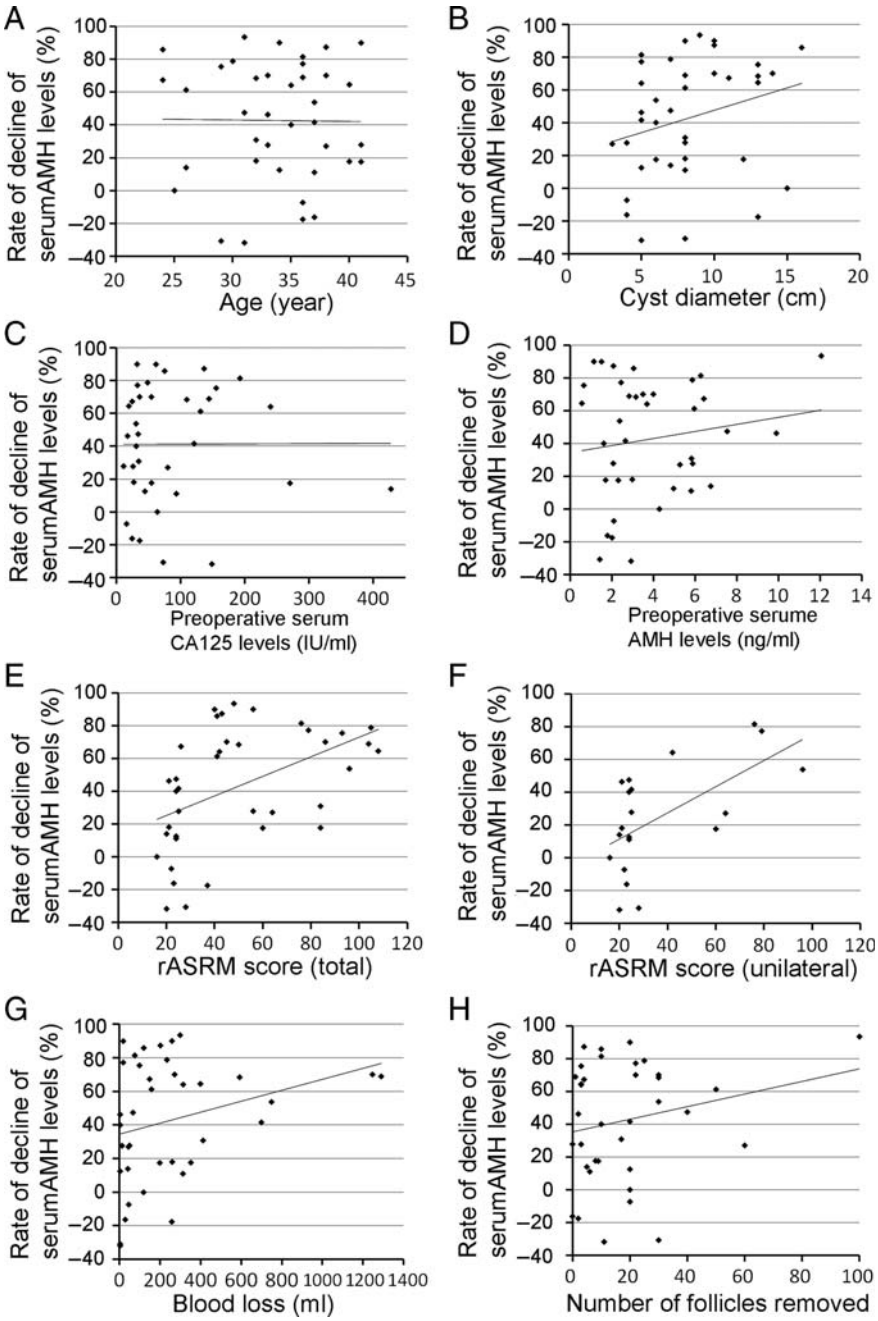

Figure 3 Correlation of rate of decline in the serum AMH level with (**A**) age ($r = -0.0122$, $P = 0.942$), (**B**) cyst diameter ($r = 0.259$, $P = 0.117$), (**C**) preoperative CA125 level ($r = 0.00221$, $P = 0.99$), (**D**) preoperative serum AMH level ($r = 0.151$, $P = 0.365$), (**E**) rASRM score in all patients ($r = 0.473$, $P = 0.00273$), (**F**) rASRM score in the unilateral patients ($r = 0.592$, $P = 0.00594$), (**G**) blood loss during operation ($r = 0.277$, $P = 0.0927$) and (**H**) the number of follicles removed ($r = 0.215$, $P = 0.208$). The r is the Pearson correlation coefficient.

surgery-related local inflammation and electrosurgical coagulation (Li *et al.*, 2009). We demonstrated a significant correlation between rASRM scores and the rate of decline of the serum AMH level in the all patients, as well as in the subgroup analysis of unilateral patients. Dense and wide adhesions surrounding adnexal lesions increase rASRM scores. Therefore, it is necessary to perform sufficient adhesiolysis surrounding the adnexal lesions to complete cystectomy for endometriomas. The vascular system of the ovary might also be injured during adhesiolysis, thus possibly resulting in poor blood supply to the post-surgical ovary. In fact, Li *et al.* (2009) demonstrated lower peak systolic velocity in the ovary subjected to laparoscopic surgery.

In conclusion, ovarian cystectomy for endometriomas is associated with a decreased ovarian reserve as assessed by the levels of serum AMH. Furthermore, the bilaterality of endometriomas and the severity of endometriosis are significantly related to the rate of decline of the

Table II Multiple linear regression analysis of predictive factors of rate of decline of serum AMH levels.

Variables	Coefficient (β)	SE	*P*-value
Bilateral/unilateral	0.417	0.112	0.015
rASRM score	0.193	0.002	0.077

$n = 38$. Adjusted $R^2 = 0.308$.

serum AMH level. Our results suggest that the decrease in ovarian reserve should be taken into account when performing a cystectomy for bilateral endometriomas and even for unilateral endometrioma with severe adhesion surrounding the ovary. In fact, post-surgical ovarian failure was reported in three cases out of 126 patients operated on for bilateral endometriomas in a previous study, corresponding to a rate of 2.4% (Busacca *et al.*, 2006). Another study of patients operated on for unilateral endometrioma showed the absence of follicular growth in the affected ovary in 12 out of 93 patients (Benaglia *et al.*, 2010). However, the serum AMH level at 3 months post-operatively, which was still significantly lower than the preoperative AMH level, has been reported to partially recover in comparison to the AMH level at 1 week post-operation (Chang *et al.*, 2010). Therefore, further study using a time-course observation for a longer period of time and in a larger number of patients will be needed to definitively determine the post-operative changes in the ovarian reserve.

It has also recently been reported that prior to chemotherapy, the AMH level may be predictive of chemotherapy-related amenorrhea among premenopausal patients of early stage breast cancers (Anders *et al.*, 2008). Taken together, these results indicate that further studies will be required to determine the optimal fertility-preserving surgical approach for endometriomas in patients who show low preoperative serum AMH levels, bilaterality of endometriomas, and/or who are expected to have severe endometriosis.

Authors' roles

W.H., M.G., S.T., T.N.: Collection of clinical data with involvement in the conception of the project. Y.N., B.B., T.N.: Sample preparation and assay for AMH. S.M.: Surgery for endometrioma. A.I.: Chief organizer of the study, surgery for endometrioma. F.K.: Organize the department and laboratory and supervise the study.

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