Observational Study

Medicine

OPEN

Serum anti-Müllerian hormone recovery after ovarian cystectomy for endometriosis

A retrospective study among Korean women

Juhun Lee, MD, PhD[a], Dae Gy Hong, MD, PhD[a,*]

Abstract

Serum anti-Müllerian hormone (sAMH) is a useful marker of ovarian reserve. In many patients, the sAMH levels gradually recover after falling to the lowest level after surgery (nadir phenomenon). This study aimed to analyze the factors related to sAMH recovery from the nadir after an ovarian cystectomy for endometriosis among Korean women. A total of 159 patients with ovarian endometriosis were included in the study. The sAMH levels were measured before surgery and at least twice within 12 months after the surgery. The patients were divided into two groups: those with recovery (nadir group) and those without recovery (reduction group). Postoperative recovery of the sAMH levels from the nadir was not related to the stage and bilaterality of the lesion, surgical methods, such as robot-assisted or laparoscopic surgery, or surgical time. In the nadir group, the level of preoperative cancer antigen 125 was significantly higher, and it decreased significantly after the surgery than in the reduction group ($P = .02$ and $P = .02$). Additionally, the postoperative C-reactive protein (CRP) level was significantly higher in the nadir group, and it increased significantly after the surgery than in the reduction group ($P = .03$ and $P = .04$). The increasing degree of perioperative CRP level showed a cutoff value on the receiver operating characteristic curve (0.735 mg/dL, area under curve = 0.604; $P = .04$). Increased serum CRP levels after surgery are significantly related to the recovery of sAMH levels from the nadir. Therefore, postoperative serum CRP level could be used as a marker to predict the sAMH nadir after surgery.

Abbreviations: AMH = anti-Müllerian hormone, CA-125 = cancer antigen 125, CRP = C-reactive protein, ESR = estimated sedimentation rate, FSH = follicle-stimulating hormone, GnRHa = gonadotropin-releasing hormone agonist, sAMH = serum anti-Müllerian hormone, WBC = white blood cell.

Keywords: anti-Müllerian hormone, inflammation, ovarian cystectomy, ovarian endometriosis, ovarian reserve

1. Introduction

Anti-Müllerian hormone (AMH) is a glycoprotein hormone that is synthesized by the granulosa cells of the ovarian cortex. This molecule is a useful marker of ovarian reserve. Thus, gynecologic endocrinologists often use this hormone as a clinical reproductive predictor.[1] The serum AMH (sAMH) levels slightly or dramatically decreased due to an ovarian cystic mass. Ovarian endometriosis typically occurs because of the progression of endometriosis in the ovary.[2] Most gynecologists treat this difficult disease with cystic mass lesion resection and frequent adhesiolysis to reduce pelvic pain or prepare for subsequent reproduction. However, according to meta-analyses, sAMH levels decrease by 54.2% after surgical resection of lesions.[3,4]

There are several methods for measuring ovarian reserve. The most widely used method is by measuring the levels of follicle-stimulating hormone (FSH). Although this method has an advantage of high specificity, its disadvantages include low sensitivity, severe variation according to the menstrual cycle, and low reproducibility between tests.[5–8] Estradiol has an advantage of being less affected by the menstrual cycle; however, it is not recommended to solely predict the ovarian reserve because of its low predictive power. It is more appropriate to interpret FSH levels.[8] Inhibin B is also not suitable for measuring the ovarian reserve because it varies with gonadotropin-releasing hormone agonist (GnRHa) and FSH levels.[5,9] sAMH is less affected by gonadotropin; therefore, it is less affected by the menstrual cycle. It also has the advantages of high sensitivity, specificity, and predictive power, making it a popular method for evaluating the ovarian reserve.[1] Although sAMH also has some limitations, it is a popular marker for evaluating ovarian reserve.[10]

Women are born with a certain number of follicles that produce AMH, and it is well known that surgery for ovarian lesions and endometriosis leads to a decrease in ovarian reserve. Decreased sAMH levels are due to destruction of follicles by surgical injury; therefore, sAMH levels remain reduced.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] *Department of Obstetrics and Gynecology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea.*

**Correspondence: Dae Gy Hong, Department of Obstetrics and Gynecology, School of Medicine, Kyungpook National University, 680 gukchaebosang-ro, Jung-gu, Daegu 41944, Republic of Korea (e-mail: dghong@knu.ac.kr).*

How to cite this article: Lee J, Hong DG. Serum anti-Müllerian hormone recovery after ovarian cystectomy for endometriosis: A retrospective study among Korean women. Medicine 2022;101:40(e30977).

Received: 6 June 2022 / Received in final form: 2 September 2022 / Accepted: 6 September 2022

http://dx.doi.org/10.1097/MD.0000000000030977

However, sAMH levels gradually recover to an extent after falling to the lowest level after surgery. The "nadir," which looks like an impossible recovery, is shown in many patients treated with cystectomy.

This study aimed to analyze the factors related to sAMH recovery from the nadir after an ovarian cystectomy for endometriosis among Korean women.

2. Methods

A total of 182 patients with ovarian endometriosis who visited the Kyungpook National University Chilgok Hospital between April 2012 and February 2021 were reviewed. The stages of endometriosis (I–IV) in each patient were evaluated, according to the revised classification of endometriosis by the American Society for Reproductive Medicine. We excluded 15 patients who did not receive any drugs after the surgery. One patient was excluded due to unclear drug administration after the surgery, and seven patients were excluded because of insufficient sAMH measurements (Fig. 1). A total of 159 patients were reviewed and analyzed. The institutional review board of Kyungpook National University Chilgok Hospital approved this study (KNUMC2021-07-005).

All the participants underwent unilateral or bilateral ovarian cystectomy. All the surgeries were performed by four gynecologists using laparoscopic or robotic devices from a single institution. After introducing the laparoscopic or robotic device, the endometriosis lesion and its capsule in the ovary were completely resected, and adhesiolysis was performed around the pelvic cavity. Ovarian sutures and a hemostatic agent were used to control the hemorrhage. Bipolar cauterization was used to stop arterial bleeding, and a suture or hemostatic agent was used for uncontrolled bleeding.

A GnRHa was administered three times to many participants immediately after the surgery. Additionally, all the participants used dienogest or oral contraceptives to prevent postoperative recurrence.

All the participants were required to undergo sAMH measurement at least three times. These included sAMH measurement before the surgery (preoperative sAMH) and at least twice within 24 months after the surgery using the chemiluminescence immunoassay Unicel® DxI 800 (Beckman Coulter, Fullerton, CA), according to the manufacturer's instructions. This method had a detection threshold of 0.035 pmol/L (0.0049 ng/mL) and a variation coefficient of 10.0% or less for sAMH level of 0.16 ng/mL or more.

In most cases, a drastic reduction in the sAMH levels was observed at the first postoperative measurement. Some patients showed sAMH recovery at the next measurement during the follow-up period. The patients were classified into the nadir group. Others showed similar level of consecutive sAMH reduction and were classified into the reduction group.

The white blood cell (WBC) count, absolute neutrophil count, estimated sedimentation rate (ESR), C-reactive protein (CRP), and cancer antigen 125 (CA-125) were measured. Of the five inflammatory factors, WBC count, absolute neutrophil count, and CRP levels were measured on the day after surgery. The ESR and CA-125 levels were measured after 3 to 6 months.

The Student's *t* test or Mann–Whitney *U* test was used to compare the mean values of both groups. The chi-square test or Fisher's exact test was used to analyze the relationship between certain factors in both groups. The receiver operating

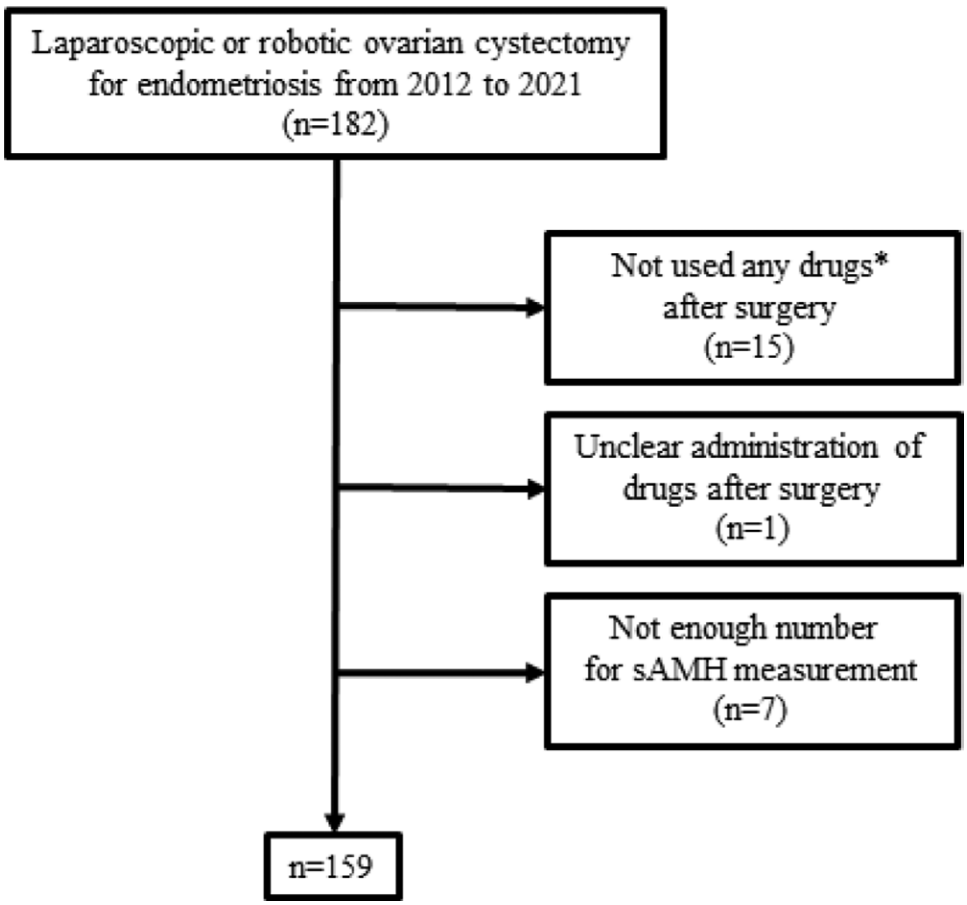

Figure 1. Flow diagram for patient selection (*Dienogest or ethinyl estradiol). sAMH = Serum anti-Müllerian hormone.

characteristic curve was used to evaluate the area under the curve, and the Youden's index was used to determine the cutoff value. Statistical analysis was carried out using SPSS software (v26; IBM Corp., Armonk, NY). Statistical significance was set at $P < .05$.

3. Results

Of the 159 patients, 106 (66.7%) were classified into the nadir group, and the rest were classified into the reduction group. No significant differences were found in the patient characteristics or clinical factors between the groups (Table 1).

There were 90.6% and 81.2% ($P = .23$) patients with stage III or IV endometriosis in the nadir and reduction groups, respectively. Bilateral ovarian endometriomas were observed in 47.2% and 45.3% ($P = .87$) of the patients in the nadir and reduction groups, respectively. The mean size of lesions was 7.12 ± 3.50 and 7.07 ± 3.17 cm in the nadir and reduction groups ($P = .95$), respectively. Robot-assisted cystectomy was performed in 59.4% and 52.8% ($P = .50$) of the patients in the nadir and reduction groups, respectively.

The postoperative recovery of sAMH level from the nadir after the surgery was not related to the stage and bilaterality of the lesion, surgical methods, such as robot-assisted or laparoscopic surgery, or surgical time.

In the nadir group, the level of preoperative CA-125 was significantly higher, and it decreased significantly after the surgery than in the reduction group ($P = .02$ and $P = .02$). The postoperative CRP level was significantly higher in the nadir group, and it increased significantly after the surgery than in the reduction group ($P = .03$ and $P = .04$). Other inflammatory factors were not significantly different between the groups before and after the surgery. These differences were not statistically significant (Table 2).

The four factors that showed significance were analyzed using the receiver operating characteristic curve, wherein, statistical significance was only observed for the change in serum CRP level ($P = .04$), with an area under the curve of 0.604. Additionally, the cutoff value of the change in serum CRP level for the sAMH nadir was 0.735 mg/dL, with 88.7% sensitivity, 31.4% specificity, 57.1% negative predictive value, 72.9% positive predictive value, and 70.1% accuracy (Fig. 2).

4. Discussion

This study presents a method to easily and objectively predict the postoperative nadir phenomenon in sAMH for ovarian endometriomas. This study deserves to be valued for presenting the relationship between the nadir phenomenon and postoperative sAMH levels using inflammatory factors, such as CA-125 and CRP, which can be easily identified in clinical practice.

The results of our study suggest that inflammation-related factors like CRP and CA-125 are associated with the nadir phenomenon for sAMH after surgery. This implies that sAMH recovery from postoperative nadir levels tends to develop under inflammatory conditions, and these findings are similar to those of a previous study.[11] In that study, an inverse correlation between sAMH levels and the activity index of Crohn's was revealed. Thus, researchers have found significantly lower levels of sAMH in the active disease group.

Table 1

Patient characteristics and clinical factors between the serum anti-Müllerian hormone nadir and reduction groups.

	Nadir group	Reduction group	*P* value
Total patients (n)	106	53	
Age (yr)	29.86 ± 6.20	29.57 ± 6.82	.79*
Obstetric history			
Gravida (n)	0.41 ± 0.95	0.43 ± 1.01	.62*
Parity (n)	0.26 ± 0.68	0.25 ± 0.59	.86*
Abortion (n)	0.14 ± 0.45	0.25 ± 0.83	.40*
Menarche (yr)	13.23 ± 1.31	13.38 ± 1.43	.51*
Dysmenorrhoea‡	4.92 ± 2.66	5.19 ± 2.68	.55*
rASRM stage (n)			
I	4 (3.8%)	3 (5.7%)	.23†
II	6 (5.7%)	7 (13.2%)	
III	13 (12.3%)	9 (17.0%)	
IV	83 (78.3%)	34 (64.2%)	
Bilaterality of lesion (n)			
Unilateral endometrioma	56 (52.8%)	29 (54.7%)	.87†
Bilateral endometrioma	50 (47.2%)	24 (45.3%)	
Total size of lesion (cm)	7.12 ± 3.50	7.07 ± 3.17	.95 *
Method of surgery (n)			
Robot-assisted cystectomy	63 (59.4%)	28 (52.8%)	.50†
Laparoscopy-assisted cystectomy	43 (40.6%)	25 (47.2%)	
Time of surgery (min)	114.52 ± 48.37	122.49 ± 64.65	.31*
Method of bleeding control (n)			
Suture and hemostatic agent	100 (94.3%)	49 (92.5%)	.73†
Hemostatic agent alone	6 (5.7%)	4 (7.5%)	
Administration of GnRHa after surgery (n)	75 (70.8%)	36 (67.9%)	.86†
Medication after surgery			
Dienogest (n)	96 (90.6%)	45 (84.9%)	.43†
Medication period (m)	19.18 ± 11.30	21.04 ± 11.35	.36*
Drospireonone/ethinyl estradiol (n)	10 (9.4%)	8 (15.1%)	.43†
Period of medication (m)	26.60 ± 26.14	28.63 ± 24.39	.87*

Data are presented as means ± SDs or numbers.

rASRM = revised American Society for Reproductive Medicine, GnRHa = Gonadotropin-releasing hormone agonist.

*Evaluated with Student *t* test or Mann–Whitney *U* test.

†Evaluated with chi-square test or Fisher's exact test.

‡Evaluated with visual analogue scale (VAS) score.

Table 2

Comparison of inflammatory factors before and after the surgery, and the difference between the serum anti-Müllerian hormone nadir and reduction groups.

	Nadir group	Reduction group	*P* value
WBC count (n)			
Preoperative	6233.21 ± 1625.26	6565.28 ± 1674.57	.237*
Postoperative	9250.38 ± 2690.38	8961.89 ± 2644.84	.521*
Difference	3017.17 ± 2495.01	2396.60 ± 2481.45	.141*
ANC (n)			
Preoperative	3978.32 ± 1474.48	3994.90 ± 1403.89	.946*
Postoperative	7268.09 ± 2707.97	6879.39 ± 2553.16	.404*
Difference	3372.64 ± 2585.94	3067.02 ± 2368.79	.492*
ESR (mm/h)			
Preoperative	17.05 ± 15.23	19.37 ± 15.83	.386*
Postoperative	3.48 ± 4.66	2.29 ± 0.83	.776†
Difference	–9.74 ± 9.73	–8.07 ± 9.49	.454†
CRP (mg/dL)			
Preoperative	0.15 ± 0.30	0.24 ± 0.96	.378*
Postoperative	3.22 ± 3.21	2.32 ± 2.05	.033*
Difference	3.07 ± 3.20	2.05 ± 2.18	.040*
CA-125 (U/dL)			
Preoperative	78.86 ± 99.78	52.93 ± 36.80	.022*
Postoperative	16.78 ± 13.67	23.88 ± 37.52	.300*
Difference	–61.33 ± 109.03	–25.77 ± 40.91	.024*

Data are presented as means ± SDs or numbers.

ANC = absolute neutrophil count, CA-125= cancer antigen 125, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, WBC = white blood cell.

*Evaluated with Student *t* test.

†Evaluated with Mann–Whitney *U* test.

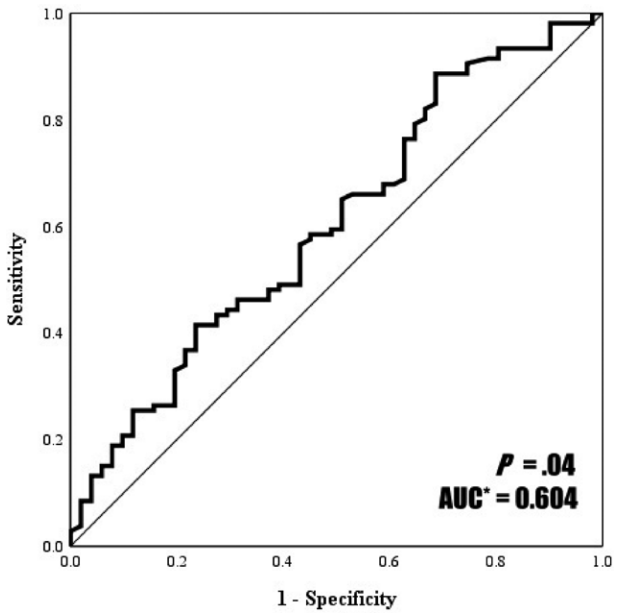

Figure 2. Receiver operating characteristic curve for increased serum CRP and its cutoff value, which showed the nadir of serum AMH after ovarian cystectomy due to ovarian endometriosis (*Determined by the Youden's index). AMH = anti-Müllerian hormone, CRP = C-reactive protein.

We conducted a subgroup analysis to determine whether sAMH increased significantly compared to the lowest level in the nadir group. The mean latest sAMH level of the nadir group was not significantly higher than the lowest. Additionally, it remained at a significantly lower level than the preoperative level. Furthermore, we could not find any patient who recovered above the preoperative level.

We found a previous study that may explain the insufficient recovery of sAMH levels. Postoperative ovarian inflammation can either decrease AMH secretion by the granulosa cells or modify follicle development with a transitory decrease in the activity of several primary, preantral, and small antral follicles.[12] As reported by the authors, the sAMH in this study might have been transiently suppressed by a certain level of inflammation above the threshold. Another recent study examined the correlation between inflammatory response and ovarian reserve after surgery for ovarian endometriosis.[13] These authors showed that serum interleukin-6 related to the inflammatory response was lower in a dinogest group than in a GnRHa group before surgery, although they could not explain the reason. The relationship between ovarian follicles and systemic inflammation has not been proven by meta-analyses or by large randomized controlled studies.

Previous studies have reported a relationship between certain drugs or surgical methods and recovery from sAMH. According to Kitajima et al, the preoperative use of dinogest suppresses lesion progression, which is effective for sAMH recovery after ovarian endometriosis treatment.[14] These authors explained that the ovarian tissue is protected from severe surgical injury using the dinogest, which suppresses endometriosis preoperatively. In our study, all the participants used dinogest or ethinylestradiol for an average of 19 to 29 months postoperatively. The drugs used and duration of usage did not correlate with sAMH recovery from the nadir. Tsolakidis et al reported laser CO_2 vaporization ablation as an effective treatment for ovarian function preservation under GnRH suppression in endometriosis.[15]

According to another recent study, sAMH levels show variability during the menstrual cycle (intra-cycle), between the menstrual cycles (inter-cycle), and between women (inter-participant). There are conflicting reports in the literature regarding the degree of inter-cycle and intra-cycle variability of sAMH levels. Less variability was suggested for 26 to 40 years age group than for 18 to 25 years age group.[16] Another study reported that a higher circulating sAMH level was observed during the luteal phase, although the reason for this is still unclear. It has been postulated that the measured sAMH levels reflect the recruited follicle pool rather than the overall number of primordial follicles residing in both ovaries.[17] Considering these and previous studies, sAMH does not appear to reflect the overall

number of primary follicles. This suggests that sAMH may not be a precise marker for predicting successful reproduction.

This study had some limitations. First, this was a retrospective study with data from a single institution. Second, we could not exclude bias due to inter-cycle variability of sAMH. Third, some postoperative inflammatory factors, such as CA-125 or ESR were not measured on the planned date. Fourth, we could not exclude participants older than 40 years, although they generally showed lower levels of sAMH than women in their 20s or 30s. In this study, nine (5.7%) patients in the total group were 41 to 45 years old.

5. Conclusions

Increased serum CRP levels after surgery are significantly related to the recovery of sAMH from the nadir. Postoperative serum CRP level could be used as a marker to predict the sAMH nadir after surgery.

Acknowledgments

We appreciate our colleagues Nan Young Lee, Yoon Soon Lee, Yoon Hee Lee, Gun Oh Chong who provided excellent insight and advice that greatly assisted the research.

Author contributions

Conceptualization: Dae Gy Hong.
Data curation: Juhun Lee.
Formal analysis: Juhun Lee.
Investigation: Juhun Lee.
Methodology: Juhun Lee.
Project administration: Juhun Lee.
Resources: Juhun Lee.
Software: Juhun Lee.
Supervision: Dae Gy Hong.
Validation: Juhun Lee.
Visualization: Juhun Lee.
Writing – original draft: Juhun Lee, Dae Gy Hong.
Writing – review & editing: Juhun Lee, Dae Gy Hong.

References

[1] La Marca A, Sighinolfi G, Radi D, et al. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update. 2010;16:113–30.
[2] Yılmaz HB, Güler CS, Ata B. Endometrioma and ovarian reserve: effects of endometriomata per se and its surgical treatment on the ovarian reserve. Facts Views Vis Obgyn. 2019;11:151–7.
[3] Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2012;97:3146–54.
[4] Younis J, Shapso N, Ben-Sira Y, et al. Endometrioma surgery-a systematic review and meta-analysis of the effect on antral follicle count and anti-Müllerian hormone. Am J Obstet Gynecol. 2022;226:33–51.e7.
[5] Broekmans FJ, Kwee J, Hendriks DJ, et al. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update. 2006;12:685–718.
[6] Silberstein T, MacLaughlin DT, Shai I, et al. Mullerian inhibiting substance levels at the time of HCG administration in IVF cycles predict both ovarian reserve and embryo morphology. Hum Reprod. 2006;21:159–63.
[7] Jayaprakasan K, Campbell B, Hopkisson J, et al. Establishing the inter-cycle variability of three-dimensional ultrasonographic predictors of ovarian reserve. Fertil Steril. 2008;290:2126–32.
[8] Ramalho de CB, Gomes Sobrinho DB, Vieira AD, et al. Ovarian reserve assessment for infertility investigation. ISRN Obstet Gynecol. 2012;2012:576385.
[9] McIlveen M, Skull JD, Ledger WL. Evaluation of the utility of multiple endocrine and ultrasound measures of ovarian reserve in the prediction of cycle cancellation in a high-risk IVF population. Hum Reprod. 2007;22:778–85.
[10] Rustamov O, Smith A, Roberts SA, et al. .The measurement of anti-Müllerian hormone: a critical appraisal. J Clin Endocrinol Metab. 2014;99:723–32.
[11] Şenateş E, Çolak Y, Erdem E, et al. Serum anti-Müllerian hormone levels are lower in reproductive-age women with Crohn's disease compared to healthy control women. J Crohns Colitis. 2013;7:e29–34.
[12] Roman H, Bubenheim M, Auber M, et al. Antimullerian hormone level and endometrioma ablation using plasma energy. JSLS. 2014;18:e2014.
[13] Muraoka A, Osuka S, Yabuki A, et al. Impact of perioperative use of GnRH agonist or dienogest on ovarian reserve after cystectomy for endometriomas: a randomized controlled trial. Reprod Biol Endocrinol. 2021;19:179.
[14] Kitajima M, Matsumoto K, Murakami N, et al. Ovarian reserve after three-step laparoscopic surgery for endometriomas utilizing dienogest: a pilot study. Reprod Med Biol. 2020;19:425–31.
[15] Tsolakidis D, Pados G, Vavilis D, et al. The impact on ovarian reserve after laparoscopic ovarian cystectomy versus three-stage management in patients with endometriomas: a prospective randomized study. Fertil Steril. 2010;94:71–7.
[16] Biniasch M, Laubender RP, Hund M, et al. Intra- and inter-cycle variability of anti-Müllerian hormone (AMH) levels in healthy women during non-consecutive menstrual cycles: the BICYCLE study. Clin Chem Lab Med. 2021;60:597–605.
[17] Kelsey TW, Wright P, Nelson SM, et al. A validated model of serum anti-müllerian hormone from conception to menopause. PLoS One. 2011;6:e22024.