The impact on ovarian reserve after laparoscopic ovarian cystectomy versus three-stage management in patients with endometriomas: a prospective randomized study

Dimitrios Tsolakidis, Ph.D.,[a] *George Pados, Ph.D.,*[a] *Dimitrios Vavilis, Ph.D.,*[a] *Dimitrios Athanatos, M.D.,*[a] *Tryfon Tsalikis, Ph.D.,*[a] *Anastasia Giannakou, M.D.,*[b] *and Basil C. Tarlatzis, Ph.D.*[a]

[a] "Papageorgiou Hospital," 1st Department of Obstetrics & Gynecology and [b] Laboratory of Immunology and Histocompatibility, Aristotle University of Thessaloniki, North Efkarpia, Greece

Objective: To investigate the effect of two different laparoscopic methods on ovarian reserve in patients with ovarian endometriomas.
Design: Prospective, randomized clinical trial.
Setting: Endoscopy unit of a university hospital.
Patient(s): Twenty women with endometriomas.
Intervention(s): Patients were randomly selected to undergo either laparoscopic cystectomy for endometrioma (group 1) or the "three-step procedure" (group 2). Before and 6 months after laparoscopy all patients were evaluated, and 12 months postoperatively they underwent ultrasound scan examination.
Main Outcome Measure(s): The primary end point was ovarian reserve damage based on the alterations of anti-Müllerian hormone (AMH). Secondary end points were the changes of antral follicle count and serum concentration of FSH, LH, E_2, and inhibin B.
Result(s): Mean serum AMH was reduced significantly from 3.9–2.9 ng/mL in group 1 compared with the reduction from 4.5–3.99 ng/mL in group 2.
Conclusion(s): Ovarian reserve determined by AMH is less diminished after the three-step procedure compared with cystectomy of endometriomas. (Fertil Steril® 2010;94:71–7. ©2010 by American Society for Reproductive Medicine.)

Key Words: Endometrioma, laporoscopic stripping, laparoscopic laser vaporization, ovarian reserve, anti-Müllerian hormone

Endometriosis is a common but still enigmatic disease affecting 3%–43% of reproductive-age women. The disease is usually manifested by pelvic pain and infertility in symptomatic patients. Endometrioma is defined as the formation of a cyst with ectopic endometriotic lining within the ovary. Endometriomas are the third most common manifestation of endometriosis after Douglas peritoneum and uterosacral ligament endometriosis, and represent 35% of benign ovarian cysts requiring surgery. They are associated with advanced stage of endometriosis and increased morbidity (1).

Although several theories and mechanisms have been proposed since the "retrograde transplantation theory" described by Sampson in 1927, the pathogenesis of endometriosis is still controversial (2). According to epidemiological, surgical, and pathological data, the most contemporary theory suggests that ovarian endometriosis, peritoneal endometriosis, and adenomyotic nodules of the rectovaginal septum are considered different entities of a single disease. Recently, it has been proposed that ovarian endometriomas, in most cases (90%), are formed by invagination of the ovarian cortex and metaplasia of the coelomic epithelium (3).

The complexity of the disease and the limited progress in identifying its exact cause explain the reason for existence of so many controversies in the literature regarding the most effective modality to treat endometriomas.

Operative laparoscopy compared with laparotomy has been established as the gold standard surgical approach in the treatment of endometriomas in terms of reduced postoperative pain, analgesic requirement, hospitalization, and lower incidence of de novo adhesion formation (4).

Despite the limited number of prospective trials and their drawbacks, excisional surgery for endometriomas seems to be more beneficial than drainage and ablative techniques, if the end points are recurrence of endometriomas and symptoms. To the best of our knowledge, no retrospective or prospective studies were found in the literature to address the issue of laparoscopic stripping versus drainage and ablation of endometriomas on ovarian function (5). Taking into consideration several pathology studies, stripping of the cyst

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Reprint requests: George Pados, M.D., Ph.D., 40 Mitropoleos str, 546 23 Thessaloniki, Greece (FAX: 30-2310-241133; E-mail: padosgyn@hol.gr).

wall may result in ovarian reserve damage due to the removal of healthy ovarian cortex and thermal destruction of ovarian follicles by excessive use of bipolar coagulation for hemostatic purposes (6, 7).

To investigate the extent of ovarian reserve damage, anti-Müllerian hormone (AMH) has been recently acknowledged as the most useful, reliable, and sensitive hormonal serum marker of the ovarian primordial follicle pool compared with other known serum markers (8). Furthermore, serum AMH levels are strongly correlated to early antral follicle count (AFC) measured by ultrasound (9).

This relationship was documented more reliable by AMH than those obtained with serum levels of inhibin B, E_2, FSH, and LH (10). In addition, the AMH level represents a stronger independent marker of ovarian reserve without significant fluctuation during the menstrual cycle, which progressively decreases with age (11, 12).

This prospective randomized study focused on the difference in ovarian reserve impairment between laparoscopic stripping of endometriomas and the "three-step procedure" based on AMH and AFC changes.

MATERIALS AND METHODS

This prospective study was conducted in "Papageorgiou" University Hospital of Thessaloniki in Greece between January 2005 and March 2007. Due to the lack of related published literature, a pilot study was conducted to define the sample size needed. It was estimated that inclusion of 10 patients in each group is sufficient to achieve statistical power of 80% with an $\alpha = 5\%$, considering a difference of 0.48 ng/mL for AMH. Thirty-seven consecutive women of reproductive age (22–40 years old) were examined in the outpatient department and a diagnosis of endometrioma with diameter of at least 3 cm was determined. These women were considered eligible for the study. The exclusion criteria were as follows: patients' refusal to participate, pregnancy, previous surgery for benign ovarian cysts, body mass index (BMI) more than 30 kg/m^2, history of cancer, suspected malignancy, presurgical evidence of premature ovarian failure (POF), and use of estrogen (E)-suppressive drugs, such as oral contraceptives, GnRH analogues, progestins, or danazol in the preceding 6 months. Finally, 20 of 37 patients accepted to participate in the study and gave written informed consent after being aware of the two methods of laparoscopic treatment. Randomization was performed by choosing 1 of the 20 files and allocating them in proportion 1:1 either to group 1 (one step—stripping procedure) or group 2 (three step—ablation procedure). In all cases, histologic examination confirmed the preoperative and intraoperative diagnosis of ovarian endometriotic cyst. No patient dropped out and all were adequately followed up.

Demographic data and symptoms, such as dysmenorrhea, dyschezia, chronic pelvic pain, dyspareunia, or presence of infertility, were documented in each patient. The primary outcome of our study was the impact on ovarian reserve determined by AMH after the application of the two laparoscopic techniques for the treatment of ovarian endometriomas. Secondary end points were the changes of AFC and serum concentration of LH, FSH, E_2, and inhibin B.

In all study patients, on days 3–6 during their spontaneous cycle preceding the operation and 6 months after the operation, AMH was assayed in duplicate using a commercial ELISA kit (The DSL ACTIVE MIS/AMH ELISA; Diagnostic System Laboratories, webster TX) according to the manufacturer's protocol. The detection limit of AMH was 0.006 ng/mL and the intra-assay and interassay coefficients of variation (CV) were less than 10% and 7%, respectively. Also, inhibin B was assayed using a commercial ELISA kit (DSL-ACTIVE Inhibin B ELISA, Diagnostic System Laboratories). The sensitivity of inhibin B assay was 7 pg/mL and the intra-assay and interassay CV were less than 8% and 11%, respectively.

In addition, concentrations of FSH, LH, and E_2 were measured by commercial solid-face, two-site chemiluminescent immunometric assay kits (AxSYM FSH Kit; Abbott Laboratories, Abbott Park, IL) and interassay CV were 0.1 mIU/mL and less than 3% and 5%, respectively, for FSH and LH. For E_2, functional sensitivity was 20 pg/mL and intra-assay and interassay CV were 7% and 9%, respectively.

Except for hormonal evaluation, all patients preoperatively and 6 months during their follow-up underwent transvaginal ultrasound examination (5–7.5 Mz transvaginal transducer) in the early proliferative phase of the cycle (days 3–6) to record the dimension of endometrioma AFC, ovarian volume, and to rule out functional or malignant suspected cysts. For cyst diameter, the mean diameter of the three perpendicular dimensions of the ovary was considered. Antral follicle count was estimated as the total number of follicles with a diameter less than 9 mm. Furthermore, ovarian and cyst volume were estimated using the formula $4/3 \times \pi \times (d/2)^3$ where d is the mean diameter. All ultrasound examinations were performed by the same investigator.

Operative laparoscopy was performed during the late proliferative phase of the cycle through insertion of a 10-mm subumbilical trocar and three 5-mm trocars in the lower abdomen. In all patients the preoperative diagnosis of endometrioma was confirmed at laparoscopy All endoscopic procedures were performed by the same endoscopist (G.P.) and assistant (D.T.) and followed the same protocol during the diagnostic phase of laparoscopy. This included inspection of pelvic and peritoneal organs, peritoneal washings, staging of endometriosis, and adhesiolysis to fully release the adhesive ovaries from the surrounding structures. If the ovarian cyst remained unruptured despite the manipulations during adhesiolysis, it was punctured to drain and aspirate its chocolate content. Further extension of the incision into the antimesenteric edge facilitated meticulous inspection of the inner cyst's wall for exclusion of possible suspicious areas. Endometriosis was staged according to the revised American Society for Reproductive Medicine (ASRM) classification.

In group 1 patients after identification of the cleavage plane, the wall of the cyst was stripped from the healthy surrounding normal ovarian tissue with the use of two atraumatic grasping forceps by traction and countertraction, and sent for histologic examination. Finally, hemostasis was achieved with application of a 30-W current using bipolar forceps on the cyst bed. Peritoneal endometriotic implants were electrocoagulated as well with a power setting of 15 W.

Patients allocated to group 2 underwent the three-step technique, which was first described by Donnez et al. (12). During the first laparoscopy only drainage of the cyst content, irrigation, and inspection of its inner wall took place. Finally, a biopsy from the cyst's wall was sent for routine histologic examination or for frozen section if suspicious or atypical lesions were encountered to confirm the diagnosis of endometriosis. Then, GnRH agonists were administered for 3 months to reduce the cyst diameter, the stromal vascularization, and the rate of glandular mitotic activity of endometriosis. After 12 weeks, a second laparoscopy was carried out to vaporize the internal wall by using a CO_2 laser (Sharplan 1041S; Sharplan, Tel-Aviv, Israel) at a power density of 14,000 W/cm^2. The other areas of superficial active endometriosis involving of the other ovary or the pelvic peritoneum were also treated. No sutures were placed after ovarian cystectomy or vaporization. Reapproximation of the edges of the ovarian tissue was achieved by a low power density CO_2 laser in the de-focus mode (8,000 W/cm^2). All patients were discharged the following day. This study was approved by the Institutional Review Board (IRB) of our hospital.

Data analysis was performed with the software SPSS 15.0 (Chicago, IL). The χ^2 or Fisher's exact test was used for comparison of categorical variables. Student's *t*-test and the Wilcoxon-Mann-Whitney test were used for comparison of continuous variables. *P* values of $< .5$ were considered statistically significant.

RESULTS

The demographic data and baseline clinical characteristics of each group before operation, as shown in Table 1, were comparable in terms of age, parity, BMI, length of menstrual cycle, and presenting symptoms. The baseline ultrasonographic and operative findings of groups 1 and 2 are summarized in Table 2 and were, also, not statistically different.

Comparison of ultrasonographic findings and serum hormonal concentrations between the two groups before and 6 months after treatment are presented in Table 3. A significant difference ($P=.026$) regarding the decrease of mean AMH level was observed in group 1 (from 3.9–2.9 ng/mL) compared with group 2 patients (4.5–3.9 ng/mL). In addition, the AFC of the operated ovary increased significantly ($P=0.002$) in group 2 (from 1.27–4.36) in relation to group 1 patients (from 2–2.38).

Significant differences did not emerge from analysis of baseline and post-treatment mean ovarian volume, mean concentrations of inhibin B, LH, and E_2, which were measured during the early proliferative phase in the two groups, before and 6 months after laparoscopic treatment. Despite the observed difference in the increase of postoperative mean FSH concentrations between group 1 (from 7.2–19.3 mIU/mL) and group 2 (from 7.7–11.1mIU/mL), this finding was not significant, probably due to the small number of patients in each group.

It is important to mention that none of the patients included in the study required conversion of the laparoscopic procedure to laparotomy. No intraoperative or postoperative complications occurred in either group. No recurrence of endometrioma was noted in group 1, whereas two recurrences were noted in group 2 on ultrasound examination 12 months later.

DISCUSSION

The best and most effective conservative laparoscopic technique for the management of endometriomas remains a controversial issue in the literature (14–21). The debate between excision and ablation exists, because the exact cause has not been found and several hypotheses have been proposed to explain the pathogenesis of ovarian endometriosis. Despite the differences between the recently proposed metaplasia theory and the implantation theory, both reached the conclusion that endometriomas are pseudocysts formed by inversion and invagination of the ovarian cortex, which contains the primordial follicles (22).

According to the recently published Cochrane review (4), only three randomized controlled trials have been conducted comparing cystectomy to drainage with ablation by electrosurgery (23–25). These studies provided evidence that excisional surgery for endometriomas resulted in a more favorable outcome than the combination of drainage with electrocoagulation regarding the cyst recurrence or symptoms, as well as the response to ovarian stimulation and subsequent pregnancy rates (PR) in infertile women. Weak points of these randomized controlled trials were the use of bipolar electrocoagulation instead of CO_2 laser as the source of energy in cases of ablation and the absence of preoperative power calculation to determine whether the number of studied patients were sufficient to detect a difference. On the contrary, there were few published retrospective and comparative studies in favor of drainage and ablation or with similar cumulative clinical PRs compared with those observed after cystectomy, but without mentioning in detail the methods or the medication used for the infertility treatment (26–29). Also, the discrepancy in the reported recurrence rates could be attributed to several factors, such as the nonuniform number of patients included in each group, the different follow-up interval of the series, the heterogenic criteria used to define recurrence, and of course the skill level, training and experience of the gynecologist to perform complete ablation of the cyst wall lining without leaving untreated areas. However, all review and meta-analysis articles emphasize the lack of studies comparing the two laparoscopic approaches of endometriomas regarding their effect on ovarian function after surgery.

TABLE 1

Baseline demographic and clinical characteristics of the two groups of patients with ovarian endometriomas.

Variable	Group 1 one-step stripping (n = 10)	Group 2 three-step laser vaporization (n = 10)	*P* value
Mean (±SE) age (y)	32.8 ± 1.7	29.9 ± 1.8	NS
Mean (±SE) cycle length (d)	29.4 ± 0.6	27.6 ± 0.4	NS
BMI (kg/m^2)	22.9 ± 1.5	22.9 ± 1.9	NS
No. of nulliparous patients (%)	5 (50)	6 (60)	NS
No. of patients with infertility (%)	1 (10)	3 (30)	NS
No. of patients with dysmenorrhea (%)	8 (80)	7 (70)	NS
No. of patients with dyspareunia (%)	3 (30)	1 (10)	NS
No. of patients with chronic pelvic pain (%)	5 (50)	4 (40)	NS
No. of patients with dyschezia (%)	1 (10)	3 (30)	NS

Note: Values are mean ± SE. NS = not significant.

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The present study is the first prospective randomized trial that compares cystectomy to laser CO_2 vaporization–ablation of the inner lining according to the three-step procedure for the management of endometriomas and assesses the impact of each technique on ovarian reserve.

The introduction of CO_2 laser in the laparoscopic management of endometriomas has been well established as an alternative, safe, and effective modality (29–33). We have also adopted in our institution the use of CO_2 laser as a modality for ablation because it provides precise tissue dissection and ablation, controlled penetration, and tissue thermal damage. These advantages justify the reason why lasers may be potentially more tissue sparing than other sources of energy. Twelve years have passed since Donnez et al. (13) published the largest series of treated endometriomas with the spectacular postoperative cumulative PR of 51% and the recurrence rate of 8% for a follow-up of 2–11 years with the application of the three-step procedure in 814 women. Also, Brosens et al. (34) confirmed that destruction of the filmy superficial internal lining of endometriomas was a safe and effective approach for the treatment of endometriotic cysts without sacrificing the adjacent healthy ovarian cortex.

Unfortunately neither Donnez nor other investigators have conducted a prospective randomized study to compare this type of ablative treatment of endometriomas with the stripping technique. We strongly believe that the two operations instead of one is not a disadvantage of this ablative technique, because the administration of GnRH analogues between the two operations was found to reduce the endometrioma's size up to 50%, the mitotic glandular activity, the stroma

TABLE 2

Ultrasonographic and operative findings.

Variable	Group 1 one-step stripping (n = 10)	Group 2 three-step laser vaporization (n = 10)	*P* value
			NS
Mean (±SE) diameter of the cyst (mm)	37.9 ± 4.8	36.8 ± 5,5	NS
Mean revised AFS score	43 ± 5.5	38 ± 3.8	NS
No. of patients with stage III (%)	5 (50)	6 (60)	NS
No. of patients with stage IV (%)	5 (50)	4 (40)	NS
No. of endometriomas in right ovary (%)	6 (46.2)	7 (58.3)	NS
No. of endometriomas in left ovary (%)	7 (53.8)	5 (41.7)	NS
Percentage of red color peritoneal lesions	80	82	NS
Percentage of black color peritoneal lesions	5	1	NS
Percentage of white color peritoneal lesions	15	17	NS

Note: Values are mean ± SE. NS = not significant.

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TABLE 3

Comparison of the sonographic and serum indicators of ovarian reserve of groups 1 and 2 patients before and 6 months after laparoscopy.

	Group 1 one-step stripping (n = 10)			Group 2 three-step laser vaporization (n = 10)		
Variable	**Baseline**	**Follow-up**	***P* value**	**Baseline**	**Follow-up**	***P* value**
AFC	2.0 ± 1	2.4 ± 0.8	NS	1.3 ± 0.5	4.36 ± 0.8	.02
Mean (±SE) ovarian volume (mL)	89.7 ± 29.63	11.5 ± 4.8	NS	77.7 ± 23.6	11.0 ± 2.9	NS
FSH (mIU/mL)	7.2 ± 0.8	16.3 ± 3.8	NS	7.7 ± 0.8	11.1 ± 3.8	NS
LH (mIU/mL)	4.45 ± 0.8	6.5 ± 0.9	NS	5.7 ± 0.8	6.6 ± 0.9	NS
E_2 (pg/mL)	97.8 ± 25.9	74.9 ± 22.5	NS	48.7 ± 25.9	48.9 ± 22.5	NS
Inhibin B (pg/mL)	107.5 ± 13.9	122.5 ± 22	NS	103 ± 10.6	93.1 ± 12.6	NS
AMH (ng/mL)	3.9 ± 0.4	2.9 ± 0.2	.026	4.5 ± 0.4	3.99 ± 0.6	NS

Note: Values are mean ± SE. NS = not significant; AFC = antral follicle count; AMH = anti-Müllerian hormone.

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vascularization, the presence of functional cysts, such as corpus luteum (CL), and enhance the apoptosis of endometriotic cells (35). All of these effects may result in facilitation of the laparoscopic approach, thus minimizing the surgical trauma, subsequent follicle loss, and the risk of POF. We have adopted the proposed technique by Donnez because the adequate depth of vaporization and the surrounding thermal damage was shallow and controlled with the use of the CO_2 laser in contrast to the uncontrolled destruction after the use of bipolar electrocoagulation. It was suggested that only the internal lining with a thickness not exceeding 1.0–1.5 mm should be vaporized and there was no need to destroy the entire fibrotic capsule surrounding the endometrioma (36).

Another strong argument against cystectomy as an ovarian tissue-sparing procedure is the absence of a cleavage plane due to endometriosis-induced fibrosis. This often leads to inadvertent removal of an amount of the adjacent ovarian cortex and serious bleeding at the ovarian hilus requiring extensive application of bipolar electrocoagulation and hence, adverse changes in ovarian blood supply, as well as a functional loss in the ovarian reserve (37, 38). The damage of ovarian tissue was also confirmed by several pathological studies of the cyst capsule after the application of different laparoscopic stripping techniques of endometriomas. These analyses reached the conclusion that stripping was inadvertently associated with excision of normal functioning ovarian tissue, especially close to the ovarian hilus (39, 40). Other studies correlated the severity of ovarian reserve depletion to the ease of capsule removal (6).

According to the recent Cochrane review (5) there was insufficient evidence to favor one approach against the other concerning the subsequent PRs in women who underwent ovarian stimulation after laparoscopic excisional or ablative surgery for endometrioma. Furthermore, there have been published retrospective, not randomized, clinical trials with conflicting results concerning the assessment of the remaining ovarian reserve, which were conducted only in infertile women after cystectomy or ablation of their endometriomas (7, 25, 41, 42). In the majority of these studies, the ovarian reserve was assessed by measuring the early follicular phase serum AMH level, the follicular response of ovaries, and the number of retrieved oocytes, after controlled ovarian hyperstimulation (COH) with clomiphene (CC) or gonadotropins. In our opinion, in these studies there were severe biases and definite conclusions cannot be drawn for the following reasons. First, the determination of ovarian reserve was limited only to the patients with infertility because ovarian stimulation is ethically unacceptable in fertile patients suffering only from pelvic pain. Second, the use of drugs or protocols for COH could result in different numbers of oocytes retrieval or PRs, leading to false impressions. Third, these studies included patients who were carefully selected and might have other co-existing infertility factors. These reasons could influence not only the follicular response, but also the PR, which was the desired result of infertility treatment leading to false conclusions. Finally, the impact of each method on ovarian reserve interests all women with treated endometriomas in terms of early menopause due to the damage of ovarian tissue (37).

In this prospective study, the ovarian reserve was evaluated in an unselected population with endometriomas suffering mainly from pelvic pain and less from infertility, without using any type of ovarian hyperstimulation. Among the contemporary serum markers for ovarian reserve, AMH, which is produced by granulosa cells (GC), is considered the most reliable indicator of the nongrowing primordial follicles, because its serum levels fluctuate slightly within the menstrual cycle. This marker is not influenced by the developing FSH-dependent follicle and by the hypothalamic-pituitary axis, therefore it reliably reflects the size of the primordial follicle pool (8, 43–45).

In addition it was found that the recruited number of growing follicles, known as AFC, was strongly correlated to the size of the primordial follicle stock and could be used as an indirect quantitative indicator of ovarian reserve (46).

Our results showed that the ovarian follicle pool was significantly damaged after excision of endometriomas compared with the CO_2 laser vaporization by the three-step procedure, as reflected by the degree of decrease in serum AMH in the cystectomy group (P=.026). On the other hand, the three-step procedure slightly altered the levels of AMH and a significant improvement (P=.02) in the AFC was observed after laser vaporization. These favorable results of our study group of patients treated with the three-step procedure could be explained—normal ovarian tissue removal was avoided and the excessive thermal damage was eliminated by the use of laser vaporization. This minimal loss of ovarian cortex by the technique of vaporization was also confirmed in the literature by similar PRs in patients undergoing laser vaporization of endometriomas compared with women with unexplained or tubal infertility (47).

However, our study demonstrated that excision of endometriomas was not associated either with a reasonable decrease in E_2 and inhibin B levels or an increase of FSH level, as was expected in the cystectomy group, despite the greater observed damage of ovarian reserve. This is because traditional tests, such as for early follicular phase FSH, E_2, and inhibin B levels, suffer from low sensitivity in the early stages of diminished ovarian reserve and become significantly abnormal once this decrease is critical and chances of pregnancy are significantly compromised (48).

The advantage of our study is that the ovarian reserve was assessed in our unselected population without postoperative stimulation of ovaries for determination of follicular response. Despite the small number of patients included in each group, both groups were comparable and homogenic in terms of age, mean size of ovaries and endometriomas, revised ASRM score, color distribution of lesions, and with no differences in baseline values of measured hormones, symptoms, and ultrasound scan findings.

In conclusion, this study clearly demonstrated that ovarian cystectomy was associated with diminished ovarian reserve in women of reproductive age, and follicular recruitment of the treated ovary was improved after laser vaporization of the endometriomas' internal wall. In addition, it was confirmed that AMH and AFC can be used as sensitive and reliable indicators to evaluate the impact of each technique on ovarian reserve. Given the frequency of ovarian endometriomas, the heterogenicity and the limitations of the few available studies, additional well-designed trials are needed to address this complicated issue, of the most effective treatment of ovarian endometriomas taking into consideration not only the relief of symptoms, the cyst recurrence, and PR, but also the ovarian function and reserve after surgery.

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