Chapter 3

Conservative Surgery and its Effect on Ovarian Reserve

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Ovarian endometrioma is one of the most common manifestations of endometriosis. Management of women with symptomatic endometrioma can be either medical or surgical therapy. However, medical treatment only relieves symptoms, but fails to completely eradicate the disease. It may also preclude or delay a definite histological diagnosis. Because of this limitation, the European Society of Human Reproduction and Embryology (ESHRE) has recommended a pathologically proven diagnosis of any endometriotic cyst larger than 3 cm.[1] The main indications for surgery are the following:

Pain relief

Dysmenorrhea, lower abdominal pain and chronic pelvic pain, caused by endometriosis, usually respond well to non-hormonal or hormonal treatment. Non-steroidal anti-inflammatory drugs [NSAIDs] are the first-line treatment for pain symptoms.[2] Patients with mild symptoms suggestive of endometriosis often respond well to this first line therapy. There are also a variety of hormonal therapies (e.g. estrogen-progestin contraceptives) that are highly effective in these cases. If such therapy is unsuccessful, a definitive diagnosis or surgical management may be preferred. Surgical treatment may also be required for patients who decline or have contraindications to medical therapy.

Malignant exclusion

There is a link between endometriosis and ovarian cancer, particularly the clear-cell and endometrioid types.[3] The important risk factors are bilaterality, and sizes in excess of 8 cm. Such cysts may have features suggestive of malignancy, and surgery is often required for both diagnosis and treatment.

Fertility enhancement

The prospects of surgery for improving fertility in endometrioma are very debatable. The response to gonadotropin therapy is poor in the presence of endometrioma, and reproductive age women with endometrioma often have higher rates of miscarriage. Nonetheless, a meta-analysis of surgical treatment for endometrioma demonstrated no improvement in IVF pregnancy rate.[4] One major concern is the negative impact on healthy ovarian follicles, as a decrease in ovarian reserve has been shown to occur in many studies. Busacca *et al*. reported a study on bilateral ovarian endometrioma excision, in which 2.38% of patients (3/126), with an average age 30.4 years, developed premature menopause immediately after surgery.[5, 6]

Laparoscopic ovarian cystectomy is now considered the procedure of choice in patients with endometrioma and benign ovarian cysts.[7] A systematic review, accompanied by meta-analysis, reported that excision of an ovarian endometrioma provides a better outcome than drainage and ablation in terms of recurrent ovarian endometrioma and pelvic pain.[8] This approach has gain popularity with increasing acceptance among gynecologic surgeons. However, in places where accessibility to laparoscopic surgery is limited, an open approach is still an option.

A negative consequence of ovarian cystectomy through either a laparoscopy or laparotomy is diminished ovarian reserve (DOR). Many studies, including systematic review and meta-analysis, uniformly demonstrated adverse effects of ovarian endometriotic cystectomy on ovarian reserve.

Ovarian reserve

Ovarian reserve is defined as reproductive potential in terms of the quality and quantity of oocytes, including the capacity to achieve a pregnancy.[9] A number of ovarian testing methods are in current use, including hormonal markers and sonographic evaluation. Serum markers include hormones, such as anti-Mullerian hormone (AMH), basal follicle stimulating hormone (FSH), estradiol and inhibin-B. Sonographic indicators consist of the antral follicle counts (AFCs) and ovarian volume measurement.[10] These screening tests have limitations in their reliability and accuracy, and also in their invasiveness and costs. Another factor to be considered is the convenience and availability of the tests. [11, 12] Commonly utilized tests are:

Day 3 FSH [13, 14]

Follicle stimulating hormone is produced by the anterior pituitary gland in a pulsatile fashion. Its main role is to stimulate folliculogenesis. A high basal level of FSH indicates a lower ovarian reserve. The cut-off value is in the range 10 – 25 mIU/ml, depending on individual laboratory, as different assay methodology can change the threshold value. A level below 10 mIU/ml is suggestive of good ovarian reserve. The advantages of this test are its low costs and ease of acquisition. The major drawback is the high individual variation and inconsistency between different menstrual cycles. Even in the same person, the level can fluctuate a lot during the proliferative phase of the cycle.

Clomiphene citrate challenge test (CCCT) [12, 15]

This test comprises measurement of FSH before and after treatment with clomiphene citrate on cycle days 5-9. FSH is assessed on cycle day 3 and repeated on day 10. It has a higher sensitivity, but lower specificity, than basal FSH. The cut-off level is 10-22 mIU/ml on day 3 or day 10, or the sum of day 3 and day 10 FSH is higher than 22.5 mIU/ml. However, the benefits of using CCCT for the prediction of poor ovarian reserve and IVF outcomes are marginal and still unclear.

Inhibin B [12]

The serum level of inhibin B increases with FSH and gonadotropin–releasing hormone (GnRH) stimulation. The level varies widely between menstrual cycles. The use of this test is limited and not widely recommended.

AMH [11, 16]

AMH is a dimeric glycoprotein produced by granulosa cells of early follicles. Its main function is unclear, but it seems to play a role in selecting the dominant follicle from a group of preantral follicular pools. Serum level of AMH shows slight fluctuation during the menstrual cycle, making it a reliable serum marker of ovarian reserve that can be measured any day in the cycle. An AMH level < 1.0 ng/mL indicates a poor ovarian reserve with a high chance of retrieving few oocytes. An AMH level between 1.0 ng/mL - 3.5 ng/mL predicts an acceptable response to ovarian stimulation.[17]

Studies showed a correlation between low AMH and poor response to ovarian stimulation.[18, 19] Also, the embryo quality and IVF pregnancy outcomes are not good in women at high risk for diminished ovarian reserve (DOR), as predicted by a low AMH level.[20]

Antral follicle count (AFC) [12, 19]

The number of antral follicles during the early follicular phase is a good predictor of ovarian response and reserve. Antral follicles, with a mean diameter of 2 - 10 mm., can be visualized by two-dimensional transvaginal ultrasonography. The sum of these follicles in both ovaries is the antral follicle count (AFC). If this count is less than 3-6, the patient is considered to have a low AFC, indicating a high risk for DOR. This test is widely used because it is highly reliable and has a good specificity. Some important limitations are its low sensitivity, along with a wide inter- and intra-observer variability. AFC also has higher individual intra- and inter-cycle variation than serum AMH.

In summary, there are both advantages and limitations to each method of ovarian reserve tests. AMH level is a promising method, and is widely accepted as a screening test for ovarian reserve. This hormone represents the ovarian pool of preantral follicles, and may possibly serve as a predictor of quantitative and qualitative outcomes of assisted reproductive technology (ART) treatment. As a predictor, AMH is apparently superior to FSH, estradiol, CCTH and inhibin B in predicting ovarian response to a controlled ovarian stimulation.[18]

A reduction in ovarian reserve from surgery can be explained by one or more of the following factors: Firstly, the damage can occur prior to surgery, as the cyst itself can negatively affect the surrounding ovarian tissue. Secondly, during cystectomy some healthy follicles may be removed from stripping and excision of the cyst capsule. Thirdly, hemostasis by electrosurgical coagulation can play an important role in damaging ovarian stroma and vascularization. The detail of a standard operative procedure for laparoscopic ovarian endometriotic cystectomy is listed in Table 3-1.

Table 3-1 Standard procedures for a conservative surgery of endometrioma by laparoscopic cystectomy

- All patients receive general anesthesia
- A 5-mm umbilical incision is made
- A Verres needle is passed through the umbilical incision
- Pneumoperitoneum is created by CO_2 insufflation through the needle until the intra-abdominal pressure reaches 12 mmHg
- Entries of a 5-mm umbilical trocar and telescope
- Two to three 5-mm trocars are inserted into supra-inguinal or suprapubic area under direct laparoscopic observation
- Pelvic anatomy is surveyed to assess pelvic pathologies,
- Ovarian cyst is freed from adhesion and the underlying ovarian fossa
- Incise the ovarian cyst with monopolar scissors, identify the cyst wall, and remove it from the ovarian cortex by gentle traction with grasping forceps
- Try to excise the entire cyst without spilling its content, if possible
- If the cystic content leaks, wash the spilled content by copious suction and irrigation
- Apply bipolar forceps on the bleeding points in ovarian parenchyma to achieve hemostasis
- To reduce possible damage to normal ovarian tissues, hemostatic procedures are minimally performed
- If needed, suturing is made to re-approximate ovarian edges and control bleeding
- After the removal of ovarian tumor, specimens are visually assessed for any evidence of malignancy
- Specimens are subjected to histo-pathological examination
- Observe the patients for 24 to 48 hours after the operation

A number of studies used serum AMH to demonstrate the impact of laparoscopic cystectomy and its severity on ovarian reserve in patients with endometrioma. However, the results are conflicting and inconsistent, with no final conclusion.

In 2010 Chang *et al.* [21] measured serial changes in AMH levels in a prospective cohort study. Twenty participants with benign ovarian masses were recruited, of whom 13 had endometrioma. The AMH levels decreased after the first week following the operation, and persisted at low levels for three months before returning to 65% of the preoperative levels. The serum AMH levels significantly decreased in patients with endometrioma compared with those without endometrioma. Also, the level decreased more in the bilateral group compared with the unilateral group. The results were consistent with a Thai study by Suksompong *et al.* [22]. However, these adverse effects were not compatible with the results reported by Ercan *et* *al.* [23]. In the later study, the AMH reduction was not statistically significant, and the presence of the endometrioma did not impair the AMH levels.

Lee *et al.* [24]and Iwase *et al.* [25] showed that there was a significant decrease in the mean levels of serum AMH immediately following surgery in both cystectomy and oophorectomy groups, and these levels persisted for as long as three months.

In a retrospective study in 1,642 infertile women by Hwu *et al.* (2011) [26] , they found that the mean level of serum AMH in women without endometrioma (n= 1,323) was significantly higher than those with endometrioma (n= 141) or those with previous cystectomy (n= 178). The mean serum AMH level was significantly lower in women with bilateral endometrioma than those with unilateral endometrioma. Women who previously underwent bilateral cystectomy also had significantly lower mean AMH level than those with unilateral cystectomy. This study suggested a significant reduction in ovarian reserve in cases with ovarian endometrioma, and in those with previous cystectomy.

Recent studies by Alborzi *et al.* [27]and Kwon *et al.* [28] supported the negative effect of laparoscopic ovarian cystectomy on AMH and FSH levels. Their data pointed out bilaterality of the ovarian cyst as the most important risk factor for diminished ovarian reserve after surgery. Evidence from a systematic review with meta-analysis, which included 21 analytical studies, confirmed a significant fall in serum AMH following endometriotic cystectomy.[29]

In a one-year follow-up study, the serum AMH level in 41% of cases did not increase when compared with the level at the first month following surgery.[30] Surprisingly, more follicles were removed during surgery in the increased group than the other group whose AMH level showed a continuous decline without recovery one year after surgery, in spite of fewer follicles being removed. The authors suggested that the removal of healthy follicles during ovarian cystectomy might be involved in the short-term decrease in AMH levels. However, the long-term influence might be determined by other factors, such as vascular compromise and/or inflammation in the ovaries due to the surgeries.

Our study[31] focused on the mechanism of diminished ovarian reserve following conservative surgery. In this study, the changes in AMH levels were selected to represent the decline in ovarian reserve. The impact of laparoscopic ovarian cystectomy (LOC) for endometrioma was compared to non-ovarian pelvic surgery (NOS), and patients were followed up to six months after surgery. Both groups had decreased levels of AMH 1 month after surgery, as shown in figure 3-1. However, at sixth months after surgery, the AMH level in the NOS group had significantly recovered while that in the LOC group remained at low level. Our data implied that the initial negative impact on ovarian reserve was not only related to ovarian damage, but could also be due to anesthetic effects, blood loss during surgery, or other physiologic changes, and deserve further investigation.

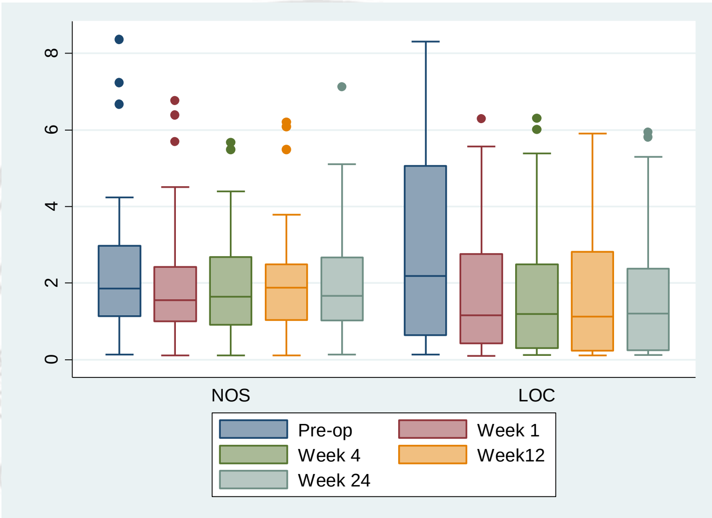

Figure 3-1 The changes in the serum AMH level at preoperative, and first week, one, three and six months post-operative in the LOC and NOS groups (AMH: antimullerian hormone, LOC: laparoscopic ovarian cystectomy, and NOS: nonovarian laparoscopic pelvic surgery).

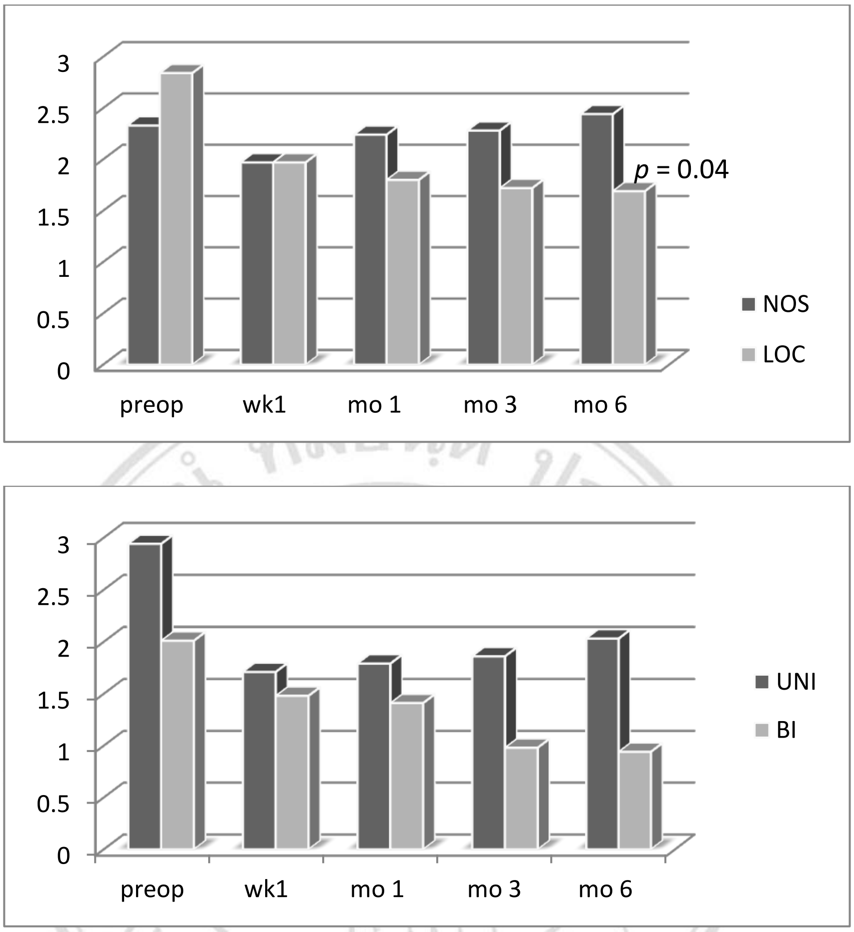

Figure 3-2 The changes in serum AMH level in NOS versus LOC group (above), and unilateral versus bilateral endometrioma in LOC group (below) from preoperative up to 6 months after operation (AMH: antimullerian hormone, LOC: laparoscopic ovarian cystectomy, NOS: non-ovarian laparoscopic pelvic surgery, UNI: unilateral ,BI: bilateral).

In the LOC group, the level of AMH decreased immediately one week after surgery, and continued to decline continuously over the next 6 months post-operatively. However, the difference from the preoperative level was significant only at 6 months after surgery. In contrast, the decline in AMH level in the NOS group occurred one week immediately after surgery, but AMH began to rebound thereafter, and reached the preoperative level within few months after surgery, as shown in Figure 3-2. In the LOC group, the AMH level in a subgroup of women with bilateral endometrioma dropped immediately after the operation and continued to decline up to sixth months after surgery. In the group with unilateral endometrioma, the level of AMH began to rebound one month after surgery and reached the preoperative level by 6 months after surgery. Our study suggested that bilaterality might be an important risk factor for poor ovarian reserve after surgery. However, this suggestion was only hypothetical, as the number of patients in each subgroup was too small, and the study was not adequately powered to analyze risk factors, as it is not the main objective of the study.

Hemostatic Technique

The hemostatic technique during a laparoscopic excision of ovarian cysts is another important variable that deserves attention. It is questionable whether it plays an important role in compromising ovarian reserve. After laparoscopic excision of ovarian cysts, it is a traditional practice to suture ovarian tissues or apply bipolar electrocoagulation to secure bleeding, as summarized in the table 3-2. It is still debatable whether one method is more preferable to the other in terms of preventing ovarian reserve impairment.

Table 3-2 Different hemostatic techniques during laparoscopic excision of ovarian cysts

Bipolar coagulation method	Suturing method
Bipolar forceps with a current set at 25–30 W is applied to the bleeding points on ovarian parenchymal tissues. Bipolar coagulation must be applied very carefully and used as minimal as possible. Try to avoid unnecessary damage to normal ovarian parenchyma .	The hemorrhagic ovarian tissue is sutured for bleeding control, using a single polydioxanone suture (2-0 Vicryl) on a CT curved needle holders. The edges of operated ovary are re-approximated to achieve good hemostasis. The suture is performed with intra-ovarian knots to hide the knots inside ovarian surface, if possible. Bleeding from ovarian hilus can be resolved by careful suturing as well.

Few studies have addressed the issue of hemostatic methods during laparoscopic endometriotic cystectomy on ovarian reserve, and the available data are still conflicting and inconclusive. One early study by Fedele *et al.* in 2004 compared bipolar coagulation with ovarian suturing, using basal serum FSH as a marker for ovarian reserve.[(32)] At 12 months of follow up, a high basal FSH level along with menstrual cycle change from normal to oligo-amenorrhea was found twice as often in the bipolar coagulation group compared with the suturing group. They concluded that bipolar electrocoagulation to stop the bleeding during laparoscopic stripping of an endometriotic cyst could adversely affected subsequent ovarian function. The findings were supported by a number of later studies, such as Li *et al.* in 2009[33], Coric *et al.* and Var *et al.* in 2011[34, 35], which employed AFC and ovarian volume as markers for ovarian reserve.

Low AFC count was found in both the laparoscopic cystectomy and fenestration and coagulation group, but the occurrence was statistically more frequent in the first than that in the second group. Perhaps cystectomy by stripping, excision and coagulation of bleeding points could be more destructive to the ovary than an incomplete treatment by fenestration and coagulation. At least one study showed that patients achieved a pregnancy in a shorter time (1.4 years) after laparoscopic fenestration and coagulation than those who underwent laparoscopic cystectomy (2.2 years) [36]. This potential advantage should be weighed against the risk of endometrioma recurrence, which is known to be higher after laparoscopic fenestration and coagulation than after laparoscopic cystectomy.

Hemostatic techniques had an immediate and long-term negative effect on ovarian reserve. However, a randomized controlled trial of bilateral endometrioma cystectomy did not find a statistically difference in basal FSH between bipolar coagulation and suture groups at one-year after the surgery.[37] Also, a recent meta-analysis showed that the adverse effects of different hemostatic methods were evident only shortly after surgery, and the difference began to disappear within only three months after the operation.[38] There is still limited evidence to make a conclusion regarding the long-term adverse effects of different hemostatic methods on ovarian reserve.

Although most studies demonstrated negative effects of cystectomy on ovarian reserve in cases of endometrioma, the underlying mechanisms of the adverse effect were not clearly explained. It is not known why ovarian reserve can rebound or becomes normal during the follow-up time after surgery in some but not in other patients. Also, we do not have conclusive results regarding the impact of different hemostatic techniques on ovarian reserve in cases of laparoscopic ovarian endometriotic cystectomy. These unresolved problems led us to conduct our own study to explore and shed more light on this controversial topic.

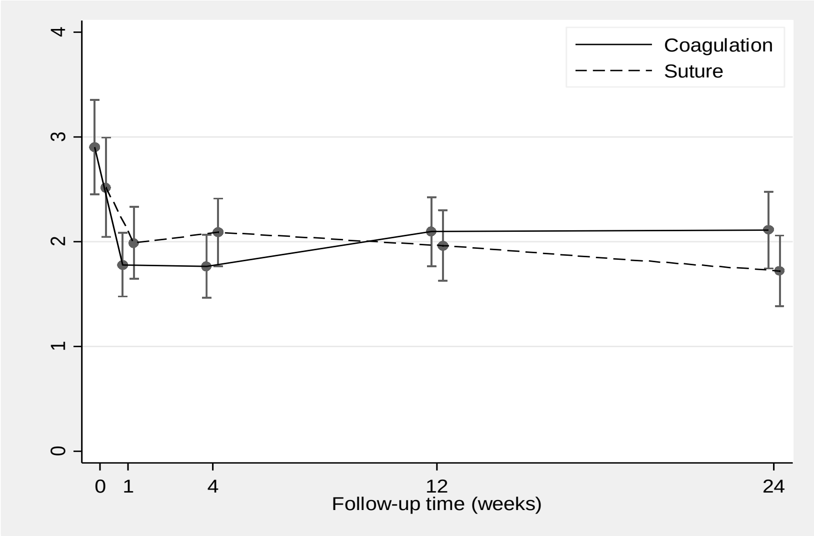

Figure 3-3 The changes of serum AMH level at preoperative, one week, one, three and six months after surgery in the coagulation and the suturing group.[39]

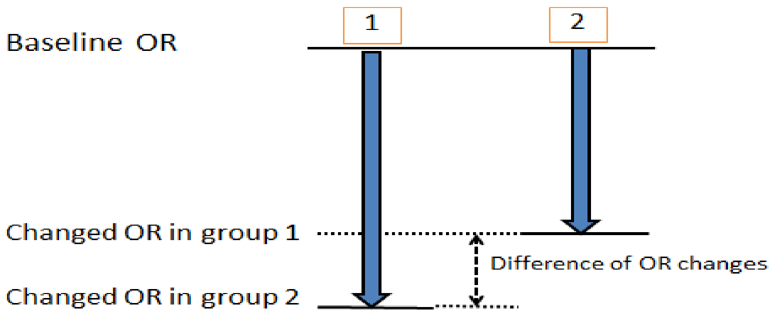

Figure 3-4 A diagram to demonstrate the difference in ovarian reserve between two different techniques of hemostasis (OR; ovarian reserve)

In our randomized controlled trial[39], the AMH levels in the bipolar coagulation and suturing groups were compared. The decrease in AMH levels in both groups showed no significant difference. There was no recovery of AMH level throughout the six month of follow-up, as shown in figure 3-3. The immediate drop in AMH level 1 week after surgery was probably related mostly to the removal or destruction of preantral/antral follicles. Other factors, such as general anesthesia, blood loss, and body reaction to surgery might play a minor role. The level of AMH continued to decrease 3-6 months after surgery only in the suturing group, but not in the coagulation group. Statistically, there was no significant difference due to a small size of only 25 subjects in each study group. With such a limited sample size, random chance could occur and it would be too premature to make any definite conclusion (figure 3-4). However, we could not rule out the possibility that the remaining suturing materials inside the ovary in the suturing group could elicit further inflammatory response, and, thus, resulting in further damage to ovarian follicles. Secondly, we measured AMH level by a manual 2nd generation ELISA method, which is less robust in terms of repeatability and precision than the present-day methods, such as the Elecsys AMH® assay (Roche) and the Access AMH assay® (Beckman Coulter), which were not available at the time of our study. In the future, other novel ovarian reserve markers that have a higher sensitivity than AMH may be available, and provide more conclusive evidence than the use of AMH.

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