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Removal of unilateral endometriomas is associated with immediate and sustained reduction in ovarian reserve

Bulent Urman ^{a,b,*}, Ebru Alper ^a, Kayhan Yakin ^a, Ozgur Oktem ^{a,b},
Senai Aksoy ^a, Cengiz Alatas ^a, Ramazan Mercan ^a, Baris Ata ^{a,c}

^a Department of Obstetrics and Gynecology and Assisted Reproduction Unit, American Hospital, Istanbul, Turkey;


^b Department of Obstetrics and Gynecology, Koc University School of Medicine, Istanbul, Turkey;

^c Department of Obstetrics and Gynecology, Uludag University Faculty of Medicine, Bursa, Turkey

* Corresponding author. E-mail address: burman@superonline.com (B Urman).



After his residency training in obstetrics and gynaecology in the University of Hacettepe, Ankara, Bulent Urman completed a 3-year fellowship programme in reproductive endocrinology and infertility in Vancouver, Canada. He returned to Hacettepe University in 1991 and participated in the foundation of one of the first IVF clinics in Turkey, where he worked as an associate professor until 1996. He founded the assisted reproduction unit of the American Hospital of Istanbul, one of the biggest IVF centres in the country. His major areas of interest are clinically assisted reproduction, laparoscopic and hysteroscopic surgery. Since 2011, he has been working as a professor and the head of the obstetrics and gynaecology department in the School of Medicine, Koc University.

Abstract Endometrioma surgery by stripping the cyst capsule has been associated with a reduction in ovarian reserve. It is still not clear whether the inflicted damage is immediate, sustained over time or associated with the use of electrocautery, nor which marker is more accurately reflects the post-operative reduction in ovarian reserve. This observational study assessed the damage inflicted by endometrioma removal with anti-Müllerian hormone (AMH) concentration and antral follicle count (AFC) pre and post-operatively. Twenty-five women with unilateral endometrioma underwent laparoscopic stripping of the endometrioma cyst capsule. There was a significant decrease both in AMH concentration (24%) and in AFC (11%) 1 month following surgery ($P < 0.01$). At 6 months post-operatively, the respective values were 24% and 15% less than preoperatively. AMH concentration and AFC showed no correlation with the use of bipolar electrocautery during surgery. Primordial follicles embedded adjacent to the cyst capsule were found in 61.5% of the specimens. Endometrioma surgery by stripping of the cyst capsule is associated with a significant reduction in ovarian reserve. The reduction is immediate and sustained over time. AMH appears to be a better indicator for post-operative quantification of the ovarian reserve. 

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KEYWORDS: anti-Müllerian hormone, antral follicle count, cyst stripping, endometrioma, laparoscopy, ovarian reserve

Introduction

Surgery has been the choice of treatment for alleviation of infertility in women with endometriomas (Busacca et al., 1999). It has been traditionally believed that the presence of endometriomas, as well as impeding natural conception, adversely affects the outcome of assisted reproduction treatment (Catenacci et al., 2009). However, this has been questioned and assisted reproduction outcomes have been reported to be similar in women with endometriomas compared with women with normal ovaries (Garcia-Velasco and Arici, 2004; Garcia-Velasco et al., 2004). These data changed the preferred treatment of endometriomas as physicians are moving away from surgery in favour of assisted reproduction treatment.

Another drawback of surgery that became evident recently is the adverse effect of endometrioma removal on ovarian reserve (Busacca and Vignali, 2009; Geber et al., 2002; Ho et al., 2002; Ragni et al., 2005; Somigliana et al., 2003; van der Weiden, 2006). Endometriomas result from the invagination of the ovarian cortex and hence present with a pseudocapsule that is often endowed with primordial follicles that are lost during stripping. Size of the endometrioma further contributes to the amount of ovarian parenchyma that is inadvertently removed during surgery (Roman et al., 2010). Ovarian reserve is of utmost importance in patients presenting with infertility and a diminished reserve is associated with decreased spontaneous and assisted-conception pregnancy rates (Dechaud et al., 2009). Thus, preoperative assessment of ovarian reserve is essential to guide the patient to the most appropriate treatment; that is surgery versus assisted reproduction treatment. Likewise post-operative assessment is also important to counsel the patient regarding the chances of spontaneous conception and conception via assisted reproduction treatment. This study assessed the ovarian reserve pre- and post-operatively by measuring anti-Müllerian hormone (AMH) concentrations and antral follicle counts (AFC) in women with endometriomas undergoing laparoscopic cystectomy. The presence or absence of primordial follicles in removed specimens was also assessed histologically.

Materials and methods

Twenty-five women with unilateral endometrioma were included in the study. All patients were counselled regarding the risks and benefits of surgery. All underwent a high-resolution transvaginal ultrasonography during the early follicular phase for assessment of the endometrioma size and AFC. All ultrasound examinations were carried out on the same day as the blood sample using the 9 MHz vaginal probe RIC6–12-D on a Voluson E8 (General Electric Company, USA). All 2–10 mm follicles in sight were counted in each ovary. The sum of counts in both ovaries produced the AFC. Bimanual and rectovaginal examinations were carried out to rule out deep infiltrating disease. Magnetic resonance imaging was performed in women with positive findings.

On the day of surgery, a serum sample was obtained for assessment of AMH concentration. AMH was measured in the same laboratory, using a commercial AMH Gen II ELISA assay

(Beckman Coulter, Ireland) and the lowest detectable concentration of AMH distinguishable from zero was 0.08 ng/ml.

After obtaining informed consent, laparoscopy was performed. Laparoscopic procedures were undertaken by three surgeons who had an experience in laparoscopic surgery over 10 years working as a team, all using the same surgical technique. At laparoscopy, the ovary harbouring the endometrioma was liberated from the pelvic sidewall and any adhesions when present were lysed. Stripping was initiated from the posterior aspect of the ovarian cortex where the cyst usually ruptured during adhesiolysis. Following identification of the cyst capsule, two atraumatic grasping forceps were used to gently strip the capsule from the ovary. The correct dissection plane was maintained at all times to avoid bleeding and damage to the underlying primordial follicles. Bleeders were cauterized using a bipolar forceps with a 40 W coagulation current. The ovarian cortex was left open and the pelvis was copiously irrigated at the end of the surgery. None of the patients received anti-adhesion adjuvants. Gonadotrophin-releasing hormone analogues were not used neither pre- nor post-operatively.

Removed cyst capsules were sent for histological examination. The presence or absence of primordial follicles was assessed in the removed specimens. Patients were discharged the day after surgery and asked to come for a follow-up visit 4 weeks later. During the follow-up visit, AFC was reassessed and serum samples were obtained for AMH measurements. Another follow-up visit was scheduled for 6 months after surgery for repeat AFC and AMH measurements.

Since the pre- and post-operative ovarian reserve tests and the histopathological examination of the surgically removed specimens are routinely performed as a part of the management of endometriotic cysts, no Ethics Committee approval was required.

Statistical analyses of the results were undertaken with a paired samples t-test. Bivariate correlation analyses were performed to determine if a relationship exists between the use of electrocautery and post-operative AFC and serum AMH concentration. A *P*-value of <0.05 was considered as significant.

Results

Twelve patients presented with pelvic pain, six with infertility and one with both pain and infertility. Six patients had no symptoms besides the presence of a large pelvic mass. Bimanual and rectovaginal examinations revealed nodular uterosacral ligaments in two patients. Both underwent pelvic magnetic resonance imaging with contrast that did not show any evidence of deep infiltrating lesions.

The characteristics of the study group are shown in **Table 1**. Patient age was 32.7 ± 6.1 years (range 23–46 years). Cyst diameter was 51.5 ± 14.5 mm (range 25–90 mm). Duration of surgery was 45 ± 15.5 min (range 20–96 min). In all patients, total stripping of the cyst capsule was achieved. Bipolar cauterization on the ovarian bed was used in 19 patients (76%). Cauterization was minimal (1–3 cauterized bleeders) in 13 patients and moderate (4–6 cauterized bleeders) in six patients. AMH concentration

Table 1 Patient characteristics and findings at surgery.

Characteristic	Patients (n = 25)
Symptoms	19
Pain	12
Infertility	6
Pain and infertility	1
Age (years)	32.7 ± 6.1 (23–46)
Cyst diameter (mm)	51.5 ± 14.5 (25–90)
Duration of surgery (min)	45 ± 15.5 (20–96)
Cauterization during surgery	
None	6 (24)
Minimal	13 (52)
Moderate	6 (24)
Primordial follicles in specimens	16/26 (61.5)

Values are *n*, *n* (%) or mean ± SD (range).

and AFC recorded post-operatively showed no correlation with the use of bipolar electrocautery during surgery.

The preoperative and post-operative (1 and 6 months) AMH concentration and AFC are shown in **Figure 1**. There was a 24% decrease in AMH concentration and a 11% decrease in AFC 1 month following surgery compared with the preoperative values ($P < 0.01$ and $P = 0.01$, respectively). The values did not change further for 6 months after surgery; at 6 months post-operatively, the respective values were 24% and 15% less than the values recorded preoperatively.

Of the 26 specimens removed from 25 patients, 16 (61.5%) showed the presence of primordial follicles embedded in the cortical tissue adjacent to the cyst capsule.

Of the seven patients who presented with infertility, two conceived spontaneously (5 and 9 months after surgery). Two patients underwent assisted reproduction treatment 6 months after surgery. The procedure was successful in one and failed in the other. There was no case of endometrioma recurrence in the study group for 6 months.

Discussion

The optimal treatment of endometriomas is currently unknown. Surgical treatment is usually preferred in the symptomatic patient, particularly when the patient presents with pelvic pain. It is yet to be defined whether surgery is beneficial or harmful in the asymptomatic patient or when the patient presents with infertility. When surgery is instituted, most physicians tend to remove the cyst capsule with a technique so-called stripping, also known as excision of the endometrioma. Stripping is associated with lower incidence of recurrence and a higher pregnancy rate compared with coagulation or vapourization. However, given the possible mechanism of cortical invagination leading to endometrioma formation, stripping of the cyst capsule may result in inadvertent removal of primordial, preantral and antral follicles from the healthy cortical tissue. This in turn may lead to iatrogenic depletion of ovarian follicles resulting in a diminished ovarian reserve and subsequently poor follicular response to controlled ovarian stimulation (Busacca and Vignali, 2009; van der Weiden, 2006;

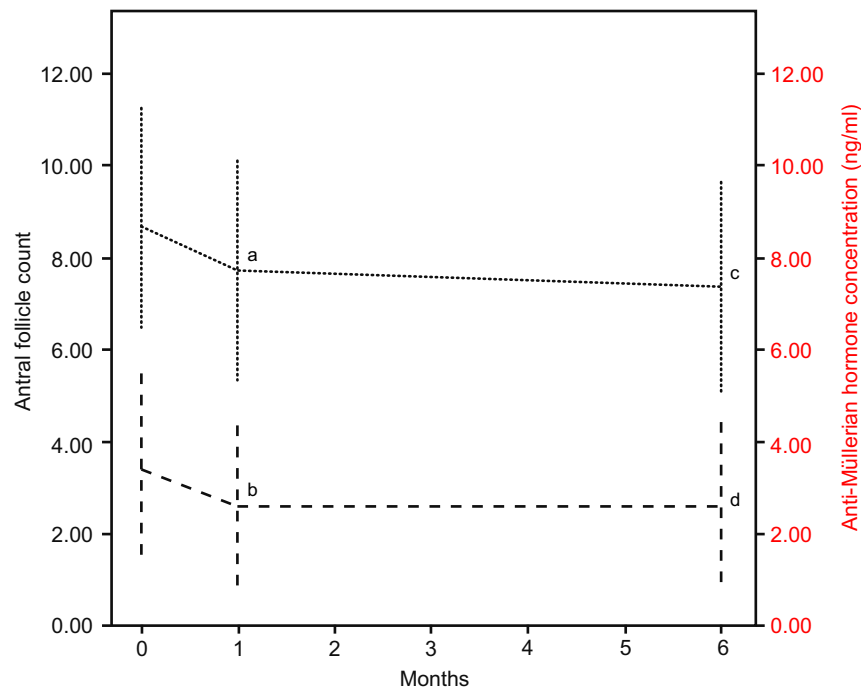


Figure 1 Preoperative and post-operative anti-Müllerian hormone concentration (dashed line) and antral follicle count (dotted line). Error bars indicate standard deviation. Letters indicate mean difference from preoperative value by paired-samples t-test: a = -0.96 (95% CI -1.67 to -0.25), $P = 0.01$; b = -0.81 (95% CI -1.21 to -0.42), $P < 0.01$; c = -1.32 (95% CI -1.99 to -0.65), $P < 0.01$; d = -0.82 (95% CI -1.07 to -0.56), $P < 0.01$. No significant difference exists between 1-month and 6-month values.

Ragni, 2005). Removal of healthy ovarian tissue appears to be proportional to the size of the endometrioma (Roman et al., 2010). In the current study, 61.5% of the removed specimens contained primordial follicles embedded in the cortical tissue adjacent to the cyst capsule, indicating that this is a common consequence of the stripping technique.

Damage to the ovarian reserve may not be immediate, as the 33% reduction in the volume of an operated ovary that was not evident in the early post-operative period was recorded in a subsequent ultrasound assessment (Candiani et al., 2005). In line with this observation, Ercan et al. (2010) failed to show a significant drop in AMH concentration when measured shortly after surgery. On the contrary, Chang et al. (2009) suggested that the trauma inflicted upon the ovary was immediate and a certain degree of recovery is possible in the post-operative period; the serum AMH concentration recovered to about 65% of early post-operative value (3 months after surgery).

Benaglia et al. (2010) showed a severely compromised ovarian reserve in 13% of the patients as evident by a complete lack of response in the operated ovary. In patients operated for bilateral endometriomas, premature ovarian failure is a real threat, albeit in a small percentage of subjects (Busacca and Vignali, 2009). In patients operated for a unilateral endometrioma, the normal contralateral ovary may compensate for the diminished ovarian reserve in the operated ovary. Pregnancy rates in patients operated for a unilateral endometrioma are similar to patients who had not undergone surgery, indicating that the contralateral ovary may compensate for the diminution of ovarian reserve due to the surgical trauma inflicted by surgery (Esinler et al., 2006; Kahyaoglu et al., 2008; Ragni et al., 2005; Shimizu et al., 2010). This, however, may not be the case in women who have undergone surgery for bilateral endometriomas (Busacca and Vignali, 2009; Matalliotakis et al., 2007). Hirokawa et al. (2011) showed that AMH concentration declined significantly more when bilateral endometriomas were removed; The decline rate of 63% showed a significant correlation with the severity of the disease as assessed by the revised American Fertility Society classification, but not with the cyst diameter, the patient's age nor the amount of blood lost during the operation.

Donnez et al. (2001) showed in 85 patients that ablation of the cyst capsule by laser did not adversely affect ovarian response to gonadotrophins in subsequent IVF cycles performed in women who failed to conceive spontaneously following surgery. The same study group suggested a more physiological treatment scheme in women with endometriomas that resulted in no or minimal ovarian damage (Donnez et al., 2002; Donnez et al., 2003a,b). In line with the observations, recent data also suggest that drainage and coagulation of the cyst capsule may result in less follicle loss than stripping of the cyst capsule (Shimizu et al., 2010; Tsolakidis et al., 2009). A combined approach of partial excision of the cyst capsule with ablation of the remaining 10–20% close to ovarian hilus resulted in no diminution of the ovarian volume and similar AFC to their preoperative numbers (Donnez et al., 2010). In a more recent randomized study, Var et al. (2011) compared the post-operative AFC, ovarian volume and response to ovulation stimulation in patients with bilateral endometriomas treated either by cystectomy or coagulation of cyst capsule with bipolar energy; they found that

cystectomy was associated with more damage to the ovaries when assessed for these variables.

It appears extremely important to quantify the extent of damage that is inflicted on the ovary following excision of endometriomas. This information will undoubtedly aid the clinician in deciding whether to proceed with or avoid surgical treatment. In women with a normal ovarian reserve, the impact of surgery especially performed for a unilateral endometrioma on future fertility may be minimal. However, the reserve is still adversely affected, as evident from the results of this study. There was approximately a 24% reduction in AMH concentration and an 11% reduction in AFC 1 month after surgery. The discordance between reduction in AMH concentration and AFC may be attributed to the inadequacy of ultrasound in accurately determining the latter in the ovary occupied by an endometrioma. AMH may be a better predictor of ovarian reserve under these circumstances.

A recent meta-analysis conducted from the studies in the literature that assessed the ovarian reserve following endometrioma surgery showed a significant post-operative drop in AMH concentration (Raffi et al., 2012). In this study, AMH concentration and AFC recorded post-operatively showed no correlation with the use of bipolar electrocautery during surgery. This does not mean that bipolar electrocautery has no adverse effect but may simply be due to the lesser impact of electrocautery above and over that inflicted by surgery that did not reach significance due to small numbers of patients included.

The major limitations of this study were its observational design, lack of a control group and the limited number of patients.

In conclusion, this study shows that laparoscopic excisional surgery in women with unilateral endometriomas results in decreased AFC and AMH concentration compared with their preoperative values. The decreased AFC and AMH concentration at 1 month post-operatively persisted for 6 months. The reduction of AMH concentration was greater compared with AFC. AMH compared with AFC may be a better predictor of the ovarian damage inflicted by surgery.

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