Special Report

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Women's Health

Pearls and pitfalls in surgery for endometrioma

Endometrioma surgery should be planned and executed very carefully as it is associated with risks that may hamper future reproductive potential. Symptoms, age, risk of malignancy, bilaterality, ovarian reserve, and desire to have children should all be taken into account prior to surgical intervention. Cyclic and noncyclic severe pain may be an indicator or deep infiltrating diseases. Laparoscopic surgery is the gold standard, however, the issue of resection versus ablation should be further studied.

Keywords: endometrioma • endometriosis • cyst capsule stripping • cyst recurrence • deep infiltrating endometriosis • laparoscopy • oral contraceptives • ovarian cyst

Bulent Urman
Obstetrics & Gynecology & Assisted Reproduction Unit, American Hospital, Istanbul, Department of Obstetrics & Gynecology, Koc University, Faculty of Medicine, Guzelbahce sokak No:20, Nisantasi, Istanbul, Turkey
burman@superonline.com

Endometriosis is one of the most common pathologies affecting women of reproductive age. Manifestations of the disease include superficial peritoneal or deep infiltrating lesions and cyst formation commonly referred to as endometrioma. Although extrapelvic localization has been frequently encountered [1,2], endometriomas are most commonly located in the ovaries and there is predilection for the left side with two-third of the endometriomas located in the left ovary. Endometriomas present with pelvic pain or are detected in an otherwise asymptomatic patient during pelvic examination. The association of endometriomas with infertility is dubious and a cause-and-effect relationship has not been proven beyond doubt.

Indications for surgery

Treatment of endometriomas may be indicated for several reasons. It is debatable whether endometriomas should be removed in the asymptomatic patient. Expectant management is acceptable in circumstances where malignancy can be excluded. Ultrasound is a relatively reliable tool in differentiating endometriomas from malignant adnexal masses especially when benign sonographic characteristics are present [3,4]. However, atypical ultrasound appearances are common; at times making the diagnosis difficult. Serum markers such as CA125 are not helpful in such cases as they may be elevated in patients with endometrioma as well as malignant ovarian cysts. Laparoscopy is inevitable when ultrasound findings are controversial and CA125 levels are elevated. Otherwise a conservative approach may be adopted with frequent ultrasound examinations and administration of birth control pills. This is particularly important in the adolescent and younger women where early surgery may be associated with recurrences that may necessitate further interventions during the childbearing years thus resulting in severe pelvic adhesions and furthermore depleting the ovarian reserve.

More recently the origins of ovarian cancer are being debated and no longer the ovarian surface epithelium (OSE) is considered the sole origin of this deadly disease [5,6]. Endometrioid and clear cell cancers of the ovary most likely originate in foci of endometriosis and if this theory holds then one should consider removing endometriotic cysts once the woman completes her family, however, more research needs to be done before this approach can be recommended routinely.

Pain is the main indication for endometriosis surgery. Different mechanisms have

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been proposed to explain the relationship that exists between endometriosis and pelvic pain such as tissue inflammatory reaction, production of prostaglandins (PGs) with consequent uterine contraction and nerve entrapment within lesions [7]. Whether ovarian endometriomas are the source of severe pelvic pain is debatable. Pain associated with ovarian endometriomas may be due to the cyst itself, or to coexisting pathology such as adhesions of deep infiltrating lesions [8]. The density of nerve fibers was higher in deep infiltrating lesions compared with peritoneal and ovarian lesions. Among deep infiltrating lesions involvement of the distal colon was associated with most severe pain and showed the highest density of nerve fibers in histological sections of the removed specimens [9]. Ovarian endometriosis may be a sign of more extensive pelvic disease [10,11] and deep infiltrating lesions of the uterosacral ligaments, rectovaginal septum, bowel and the bladder should be carefully sought out prior to embarking upon surgery. A rectovaginal pelvic examination should be an integral part of patient evaluation as deep infiltrating lesions involving the uterosacral ligaments, rectovaginal septum and the lower rectum are within the reach of the examining finger. For the lesions listed above, rectovaginal examination is almost as sensitive as an MRI.

It is debatable whether or not size constitutes an indication for surgical removal. There are no data in the literature suggesting an increased risk for malignancy for cysts measuring more than 4 cm that is commonly accepted as upper limit after which expectant management is not advised. In asymptomatic adolescents and young women not contemplating pregnancy watchful waiting with frequent ultrasound assessments will prove to be of more benefit to the patient as opposed to early intervention with long-term consequences of diminished ovarian reserve, postsurgical pelvic adhesions and the need for reoperation in case of cyst recurrence. We advise these patients to use birth control pills with the intention to reduce the chances of cyst expansion as rapid growth of endometriomas is commonly due to the rupture of the dominant follicle into the cyst cavity. One should particularly be wary of operating on asymptomatic bilateral endometriomas in women without children as the operation carries with it a significant risk of adversely affecting the ovarian reserve.

Endometrioma and infertility commonly coexist; however, whether endometrioma is the cause of infertility is controversial. Infertility results from the consequences of endometriosis on the pelvic cavity, the ovary and the endometrium. As it would be naive to assume that the pelvis is compartmentalized the effect of endometriosis on fertility likely results from a combination of the factors listed above. Retrospective case series indicate that endometrioma removal is associated with a 40–50% spontaneous pregnancy rate [12] lending credit to the notion to the association between endometrioma and infertility. Endometriomas are commonly associated with anatomical distortion of the tubal anatomy and adhesions. However, there are no studies performed up to date that randomized patients to surgery versus expectant management. Ovarian reserve may be assessed by antral follicle counts or AMH measurements. AMH may be more reliable in the setting of an endometrioma as the latter may obscure the visibility of antral follicles giving a false impression of diminished ovarian reserve [13].

Endometrioma & ovarian reserve: a paradox for the reproductive surgeon

In women who have not completed their family and present with endometrioma/s, the reproductive surgeon is faced with the dilemma of relieving symptoms and improving fertility versus diminution or loss of ovarian function. It has been long debated whether endometriomas by mass or other unidentified effects cause a decrease in ovarian reserve.

Although it is now commonly accepted that endometrioma removal results in decreased ovarian reserve the effect of the presence of endometriomas *per se* on ovarian function is controversial. In a few studies performed in infertile women lower AMH levels were detected in women with advanced stages of endometriomas including ovarian involvement [14,15]. However, the presence of endometriomas was not surgically confirmed in most subjects. More recently Kitajima *et al.* compared cortical biopsy specimens from ovaries containing small endometriomas (<4 cm) to contralateral normal ovaries. Follicular density was significantly lower (6.3 ± 4.1/mm^3 versus 25.1 ± 15.0/mm^3; p <0.0002) in cortical specimens obtained from ovaries with endometriomas [16]. However, in a more recent cross sectional study involving 1262 women Streuli *et al.* were unable to demonstrate a significant difference in AMH levels in women with a visually or histologically confirmed endometrioma compared with women with normal ovaries. In all subjects AMH measurements were obtained prior to surgical intervention [17]. Almog *et al.* compared the number of oocytes retrieved from the normal and the affected ovary with endometrioma in 81 women undergoing *in vitro* fertilization treatment. The presence of ovarian endometrioma in a controlled ovarian hyperstimulation cycle for IVF treatment was not associated with a reduced number of oocytes retrieved from the affected ovary [18]. In a retrospective study, Benaglia *et al.* were also unable to demonstrate a significant difference in the number of

recruited dominant follicles in the ovary containing an endometrioma less than 4 cm compared with the contralateral normal ovary [19]. However, due to the retrospective nature of the study and the fact that larger endometriomas were most often treated surgically, generalized conclusions cannot be advanced.

Stripping of the cyst capsule is the preferred method for endometrioma removal due to a lower rate of recurrence compared with ablation by bipolar coagulation or laser [20]. However, irrespective of the surgeon's expertise stripping of the cyst capsule has been shown to reduce ovarian volume [21]. When taken together a great majority of the studies in the literature (six of eight) show a reduction in the number of recruited follicles in response to ovarian stimulation from ovaries subjected to cystectomy compared with unoperated contralateral ovaries [22]. Two studies that compared ovarian response to gonadotropins after laser vaporization of the endometrioma cyst capsule, however, failed to show a difference between operated and non-operated gonads. A three-step procedure that begins with laparoscopic cyst aspiration and biopsy, interval GnRHa treatment, followed by a second laparoscopy for laser vaporization of the cyst capsule was shown to be may be more advantageous compared with stripping in a recent randomized study [23]. However, the results should be corroborated in further trials, particularly for large endometriomas [24].

This effect of endometrioma removal on ovarian reserve has been measured using a variety of markers of ovarian response including the number of recruited follicles in response to ovarian stimulation, measurement of serum AMH levels and counting antral follicles (AFC). In a recent meta-analysis including eight studies and 237 patients, Raffi *et al.* showed a statistically significant decrease in serum AMH levels after removal of ovarian endometriomas (weighted mean difference: 1.13 ng/ml; 95% CI: 0.37–1.88) [25]. We recently published on the effect of unilateral endometrioma cystectomy on pre, immediate and remote postoperative AMH levels and showed an immediate and sustained reduction in AMH levels after surgery [13].

It may be argued that stripping of the cyst capsule yields more spontaneous pregnancies and decreases the likelihood of recurrence. However, it also decreases the ovarian reserve that may affect the outcome of IVF in patients failing to conceive spontaneously. Meta-analysis showed that oocyte yield is significantly lower in patients who were subjected to cystectomy. However, the decreased oocyte yield is not reflected upon the pregnancy rates as sufficient oocytes and embryos are available in most patients. When considering which treatment is more advantageous for the patient one should take into account spontaneous pregnancy rates as well as cumulative pregnancy rates with fresh and frozen embryos that fail to conceive spontaneously. The other pitfall of the studies in the literature was that patients with unilateral and bilateral disease were lumped together and data were not individually analyzed according to the laterality of the disease. A recent retrospective study of 93 women who underwent surgery for unilateral endometriomas prior to IVF showed a complete absence of follicular growth after gonadotropin stimulation in 13% of operated ovaries [26].

One should also be beware of the fact that our current practice is based on a few numbers of studies undertaken in a small number of subjects. Until results from well-designed studies are available, patients should be informed regarding pros and cons of all available treatment options. A proficiently executed complete surgery although may decrease the chance of recurrence may not always be in the best interest of the patient in terms of achieving a pregnancy. Particular attention must be paid in presence of bilateral endometriotic cysts. In fact, an increase in premature ovarian failure rate was reported when both the ovaries are involved in surgery [27].

Technical aspects & challenges of endometrioma surgery

The gold standard for endometrioma surgery today is laparoscopy. Laparoscopy provides an excellent view of the pelvis more so than laparotomy and once mastered, facilitates excision of endometriosis lesions deep in the pelvis that are not within reach through a small Pfannenstiel incision. Laparotomy is particularly more difficult in overweight patients. Laparoscopic endometrioma surgery is not for novices and should be only undertaken by expert surgeons. The reason for this is threefold. First, the surgeon while excising the disease should pay particular attention not to inflict undue damage to the neighboring tissue, which in case of endometriomas is the ovarian cortex. This requires expertise that comes with time and patient load. Second, endometriomas are commonly associated with deep infiltrating lesions that should be attended during surgery. Recognition and treatment of deep infiltrating disease is particularly challenging and requires a thorough knowledge of retroperitoneal spaces, blood vessels, the rectum, sigmoid colon and the ureter. Third, the extent of endometriosis cannot always be judged by pelvic examination and ultrasound. The disease may be much more extensive than anticipated that may require difficult adhesiolysis and entry into the retroperitoneal spaces during laparoscopy.

Bowel preparation prior to endometriosis surgery is controversial. One randomized study showed no benefit of mechanical bowel preparation prior to gyneco-

logical laparoscopic surgery showed no benefit in terms of patient discomfort, surgical difficulty, operating times and postoperative complications [28]. In another study, 83 women undergoing gynecological laparoscopic surgery were randomized into mechanical bowel preparation versus 1-week low-fiber diet that showed similar operative field exposure in both study arms [29]. However, patient discomfort was significantly less in women randomized to low fiber diet. We only advise bowel preparation when we anticipate deep infiltrative disease with possible bowel involvement.

Prior to commencement of the surgery, bimanual examination under general anesthesia is strongly recommended as this may uncover previously undetected deep infiltrating lesions. Surgery begins with careful exploration of the abdomen and the pelvis. Following visual inspection, all adhesions precluding entry into pelvis should be lysed. It is often necessary to bring down the peritoneal attachments between the sigmoid colon and the pelvic sidewall for gaining better access to the left ovary. The cul-de-sac should be carefully inspected and palpated with a probe. The anterior compartment should also be inspected for possible deep infiltrating lesions involving the bladder reflection. The next step is to mobilize the ovaries from the pelvic sidewall. During this procedure, the contents of the cyst are usually drained. The cyst capsule is dissected from the ovary at its most dependent position and stripping is affected with traction and counter traction using atraumatic grasping forceps. Particular care should be taken not to exert excessive force that will inevitably cause bleeding from the ovary. The portion of the cyst close to the hilus and the utero-ovarian ligament can be preserved and ablated using bipolar coagulation or the laser. At these landmarks, the cyst is usually more adherent to the ovary and stripping will result in bleeding necessitating the excessive use of bipolar coagulation. Alternative to bipolar coagulation, one may consider suturing the ovary. This practice was associated with a lower rate of adhesion formation in a randomized study [30].

Due to concerns of endometriosis surgery on ovarian function, a three-step ablative technique has been described by Donnez that is comprised of the following steps: an initial laparoscopy is performed during which the cyst is drained, irrigated and inspected. A small biopsy is obtained from the cyst wall for pathological examination. Following this laparoscopy, GnRH agonists are administered for a period of 3 months with the intention to reduce the cyst diameter and to decrease stromal vascularization and the rate of glandular activity. A second laparoscopy is subsequently carried out to vaporize the internal cyst wall by CO_2 laser [31–33]. Tsolakidis, in a randomized study, looked at the affect of cyst capsule stripping versus the three-step technique on postoperative AMH levels in women with endometrioma [23]. A significantly greater reduction in AMH levels was recorded in women undergoing stripping. Similarly Var *et al.*, in a prospective randomized study found a significantly reduced ovarian volume and decreased antral follicle counts after stripping when compared with bipolar coagulation of the endometrioma cyst capsule [34].

Stripping of the cyst capsule has been associated with increased pregnancy and decreased recurrence rates when compared with cyst capsule ablation [20]. However, the two studies included in the Cochrane review did not take into account the effect of surgery on ovarian function. Ultimately this is very important, as patients who do not conceive will eventually be considered for treatment with assisted reproduction for which the most important variable of success is the ovarian reserve.

Single port laparoscopy is being increasingly performed for a variety of indications including benign adnexal masses [35,36]. Despite the attractiveness of reduced number of abdominal entry ports and purported cosmetic benefits, feasibility of single-port laparoscopic surgery for endometriosis and endometrioma remains to be shown. The benefits of single-port laparoscopy may be offset by the disadvantages related to the less than optimal performance of surgery due to difficulties encountered during cyst capsule stripping and resection of deep lesions.

Surgery should be completed with copious pelvic lavage and meticulous hemostasis. Adhesion barriers may be used after gynecological surgery, however, they should not be applied onto oozing surfaces [37]. Whether adhesion barriers are beneficial specifically for after endometriosis surgery should be defined in well-designed studies.

Surgical removal should be avoided in the asymptomatic young patients, in patients with a diminished ovarian reserve contemplating pregnancy, and in patients with bilateral endometriomas as the latter may result in a more severe insult on the ovarian reserve. Surgical removal should be reserved for the infertile patients with infertility and recurrent disease only in the presence of severe pelvic pain.

Postoperative management & recurrence

Postoperative administration of GnRH analogs following endometrioma removal is not recommended. Their use is associated with menopausal symptoms and irreversible bone loss [38,39]. Adding back therapy with a progestin should be considered if their use is contemplated.

Recurrence depends on many factors. Recurrence rates are higher in patients undergoing surgery at

an early age, in other words, adolescents, in patients who had incomplete removal of their pathology and also in patients who had undergone ablative surgery. Piecemeal removal of the endometrioma cyst capsule is associated with higher recurrence rates [40]. Endometrioma recurrence is higher in ovaries with a better reserve. Aggressive removal of endometrioma is associated with a decreased incidence of recurrence, however, may result in an ovary with a depleted reserve. Some residual disease with function may be better than no disease and no function.

The incidence of endometrioma recurrence can be decreased with the use of oral contraceptive (OC) pills. In a systematic review, Vercellini *et al.* assessed the absolute effect of postoperative OC use on endometrioma recurrence by comparing 'always' and 'never' users. A recurrent endometrioma was identified in 33 of 423 (8%) 'always' OC users and in 117 of 341 (34%) women who underwent expectant management [41]. Continuous OC use is associated with a lower recurrence rate compared with cyclic use (8.2 vs 14.7%) [42].

Conclusion & future perspective

Surgical treatment of endometriomas is indicated in the patient with pelvic pain and infertility. Expectant management may be adopted in the younger asymptomatic patients and adolescents provided that malignancy can be excluded. The gold standard for surgical approach is via laparoscopy. Stripping of the cyst capsule is associated with lower recurrence and higher pregnancy rates. However, this approach may be associated with a more significant surgical insult to the ovarian reserve. Expert surgeons who can deal with severe pelvic adhesions and deep infiltrating endometriosis should perform surgery, as these may frequently co-exist with endometriomas. Postoperative management should entail the use of OCs in patients who do not desire to conceive, as this practice is associated with a lower recurrence rate compared with expectant management.

The need for surgery stems from the limitations of medical treatment. Effective medical treatment options in the future will undoubtedly decrease the need for surgery and its associated complications. Future research should focus on the molecular and genetic basis of the disease.

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Executive summary

- Surgical treatment of endometriomas is indicated in the patient with pelvic pain and infertility.
- Expectant management may be adopted in the younger asymptomatic patients and adolescents provided that malignancy can be excluded.
- The gold standard for surgical approach is via laparoscopy. Stripping of the cyst capsule is associated with lower recurrence and higher pregnancy rates. However, this approach may be associated with a more significant surgical insult to the ovarian reserve.
- Postoperative management should entail the use of oral contraceptives in patients who do not desire to conceive, as this practice is associated with a lower recurrence rate compared with expectant management.

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