Second surgery for recurrent endometriomas is more harmful to healthy ovarian tissue and ovarian reserve than first surgery

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Objective: To evaluate the excised specimen with histologic analysis and to assess the antral follicle count (AFC) at follow-up. This is to determine whether excisional surgery for recurrent endometriomas is more harmful to ovarian tissue and to the ovarian reserve than first surgery.
Design: Prospective controlled study.
Setting: University hospital.
Patient(s): Consecutive patients with pelvic pain and/or infertility undergoing laparoscopic excision of a monolateral ovarian endometrioma for the first time (17 patients) or for recurrence after previous surgery (11 patients).
Intervention(s): Laparoscopic excision of ovarian endometrioma and ultrasonographic evaluation 3 months after surgery.
Main Outcome Measure(s): Cyst wall histologic evaluation (specimen thickness, presence and morphology of ovarian tissue) and evaluation of ovarian reserve with AFC and ovarian volumes of both the operated and contralateral, nonoperated ovary at follow-up.
Result(s): The cyst wall specimen was significantly thicker in the recurrent endometrioma group than in the first surgery group (1.7 ± 0.3 mm vs. 1.1 ± 0.3 mm). Both main components of the cyst specimen (i.e., endometriosis tissue and ovarian tissue) were more represented in the recurrent endometrioma group than in the first surgery group. At sonographic follow-up, the operated ovary had a significantly lower AFC and volume than the contralateral nonoperated ovary in the recurrent endometrioma group, but not in the primary surgery group.
Conclusion(s): Surgery for recurrent endometriomas is associated with evidence of a higher loss of ovarian tissue and is more harmful to the ovarian reserve evaluated by AFC and ovarian volume, if compared with endometriomas operated for the first time. Indications to surgery for recurrent endometriomas should be reconsidered with caution. (Fertil Steril® 2015;103:738–43. ©2015 by American Society for Reproductive Medicine.)
Key Words: Endometrioma, laparoscopic surgery, ovarian cyst excision, ovarian reserve, recurrence

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Endometriosis is a disease characterized by the presence of endometrial glands and stroma outside of the uterine cavity. Endometriosis affects women of reproductive age, and is usually associated with dysmenorrhea, pelvic pain, and infertility (1).

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Ovarian endometriomas are present in 17%–44% of patients with endometriosis (2). In most cases it is associated with symptoms (3). Laparoscopic surgery with complete excision of the cyst wall is considered the gold standard for the treatment of endometriomas as it is associated with better outcomes in terms of subsequent pregnancies or recurrence of symptoms compared with drainage and ablation (4).

International guidelines on the management of endometriosis suggest

surgery in case of endometriomas larger than 3 or 4 cm. This is even in the absence of associated symptoms (1, 5).

Surgical excision is, however, associated with a considerable burden of recurrences, with reported recurrence rates after surgery between 6% and 67% (6–8). Recurrence of an ovarian endometrioma is, therefore, a common occurrence, and the clinician is often faced with the decision of whether undertaking a second surgical procedure or managing the recurrence expectantly or with medical therapy. Current guidelines on the management of endometriosis do not give specific indications for treatment of the recurrence as opposed to first diagnosis (1, 5), except for a more careful consideration of the decision to proceed with surgery in case of previous interventions (1).

Recently concerns have been raised as to possible damage to the ovarian reserve after laparoscopic excisional surgery (9–12), possibly determined by the inadvertent removal of healthy ovarian tissue in addition to the endometrioma wall (13). Surgery for the recurrence of an ovarian endometrioma may be even more detrimental to the ovarian reserve than primary surgery as the ovary with the recurrent cyst may already have a reduced reserve due to the damage from the first surgery.

The aim of the present study was to evaluate, with histologic analysis of the excised endometrioma wall and with ultrasonographic follow-up of operated ovaries and of contralateral, nonoperated ovaries, whether excisional surgery for recurrent endometriomas is more harmful to the ovarian reserve than the first excisional surgery.

MATERIALS AND METHODS

From January 1, 2012, to December 31, 2012, all consecutive patients presenting at the Department of Obstetrics and Gynecology of "Sapienza" University in Rome with a preoperative ultrasound diagnosis of a presumed ovarian endometrioma were considered for the inclusion in the present prospective study. The study was accepted by the local Institutional Review Board, and all participating women signed an informed consent form.

Inclusion criteria in both study groups were: age between 18 and 38 years, monolateral endometrioma with a diameter more than 3 cm, presence of infertility, and/or moderate-to-severe pelvic pain as the main indication to surgery, and either no previous surgery or one single monolateral cystectomy on the same ovary of the recurrence performed previously to study enrollment.

Exclusion criteria were: bilateral endometriomas at study enrollment, medical therapy for endometriosis in the previous 6 months, more than one previous conservative surgery for endometriomas, previous excisional surgery performed on the contralateral ovary, previous nonexcisional surgery (fenestration and coagulation/ablation) or previous nonconservative surgery (adnexectomy) on either ovary, and any previous surgical treatment for bilateral endometriomas.

Among the scrutinized patients, 28 patients met the inclusion criteria, 17 were never operated on (primary surgery group), and 11 patients were previously operated on the same ovary using the stripping technique (recurrent surgery group). Mean interval from first surgery to surgery for recurrence in the second group was 15 months (range, 9–24 months). Five of the 11 patients recurred within 1 year from the first surgery, and 6 within the second year after surgery. In three of the seven patients not desiring pregnancy at the moment, a trial of medical therapy was attempted, but for either pain persistence or the presence of an enlarging endometrioma, medical therapy was interrupted and patients were put on the waiting list for the second surgical procedure. More than 6 months elapsed between medical treatment interruption and second surgery. No pregnancy occurred in the interval between the first and second surgery in any patient.

Both groups were comparable as to mean age, associated symptoms, mean diameter of the cyst, and mean revised American Society for Reproductive Medicine score (14) at surgery (Table 1). Patients in both groups were submitted to laparoscopic excision of the monolateral endometrioma using the stripping technique, as previously described elsewhere (15, 16). Briefly, after careful identification of the cleavage plane, the endometrioma wall was stripped off the remaining ovarian parenchyma by tractions exerted in opposite directions with two atraumatic grasping forceps. After stripping of the cyst wall, hemostasis, when necessary, was obtained with targeted, pin-point bipolar coagulation applied on the ovarian parenchyma after identification of small bleeders. No sutures were used for reapproximation of the ovarian edges. All surgeries were performed by the same operator. The cyst wall was sent for routine histology analysis. In addition, a 2 × 2 cm specimen from the cyst wall was selected for inclusion in the present study. This specimen was selected from the intermediate part of the specimen (i.e., midway between the initial part of the stripping, usually at the site of ovarian adhesion to the lateral pelvic wall, and the final part, usually near the ovarian hilus). A blinded pathologist evaluated the presence or absence of ovarian tissue adjacent to the endometriotic tissue in the excised specimen. The morphological characteristics of the ovarian tissue, when present, were graded on a semiquantitative scale of 0–4 (0, complete absence of follicles; 1, primordial follicles only; 2, primordial and primary follicles; 3, some secondary follicles; 4, pattern of primary and secondary follicles as seen in normal ovary) (17, 18). The pathologist also recorded the mean thickness of the total cyst wall from each specimen,

TABLE 1

Patient characteristics.

Characteristic	PS group (n = 17)	RS group (n = 11)	*P* value
Age (y)	32.8 ± 2.7	33.9 ± 2.3	.25
No. of patients with CPP (%)	17 (100)	11 (100)	1.00
No. of patients with infertility (%)	8 (47)	4 (36)	.70
Cyst size (cm)	5.7 ± 1.0	5.6 ± 1.4	.77
Revised ASRM score	38.7 ± 12.4	43.7 ± 16.2	.36

Note: Data are expressed as mean ± SD or number (%). ASRM = American Society for Reproductive Medicine; CPP = chronic pelvic pain; PS = primary surgery; RS = recurrent surgery.

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measured in millimeters, the mean thickness of the endometriosis tissue, and the mean thickness of the ovarian tissue removed. The measurements obtained for the primary surgery group of patients were compared with the recurrent surgery group.

After surgery, patients in both groups had a follow-up visit 3 months after surgery, including bimanual pelvic examination, visual analogue scale assessment for evaluation of recurrence of pain, and transvaginal pelvic ultrasound scan by a single observer who was blinded to the side of the previously excised endometrioma and unaware of the previous surgical history. The ultrasound operator evaluated the presence or absence of cyst recurrence, and measured the antral follicle count (AFC) for both ovaries between day 2 and day 4 of the menstrual cycle. Antral follicle count was defined as the total number of follicles between 2 and 10 mm in diameter observed by the operator. Ovarian volumes were calculated on the same day, using the prolate ellipsoid formula (length × width × height × 0.523). Antral follicle count and ovarian volumes for the operated ovary were compared with the contralateral, nonoperated ovary in both the primary surgery and recurrence groups.

Statistical analysis was performed with the Fisher's exact test for categorical variables, with the unpaired *t* test for the comparison of histology measurements, of AFC and ovarian volumes of the primary versus the recurrent surgery group, and with the paired *t* test for comparisons of AFC and ovarian volumes measurements for the operated versus the contralateral ovary within both groups. A *P* value of less than .05 was considered statistically significant.

RESULTS

All 28 patients were operated by laparoscopy, with no major or minor intraoperative or postoperative complication. Histologic analysis confirmed the endometriotic nature of all excised cysts. At histology, the cyst wall specimen was significantly thicker in the recurrent endometrioma group than in the first surgery group (1.7 ± 0.3 mm vs. 1.1 ± 0.3 mm; $P=.00003$). Ovarian tissue was identified in at least part of all specimens. Both main components of the cyst specimen (i.e., endometriosis tissue and ovarian tissue) were significantly more represented in the recurrent endometrioma cyst wall group than in the first surgery group (Table 2). Histologic grade of the ovarian tissue inadvertently excised with the endometrioma wall did not differ significantly between the primary surgery and the recurrence group (mean grade, 0.4 ± 0.6 vs. 0.7 ± 0.3; $P=.35$), although a trend toward a higher functional grade for the recurrent cysts was present.

All patients completed the scheduled follow-up, performed 3 months after surgery. No recurrence of endometrioma was diagnosed during follow-up. Recurrence of significant pain (graded as at least 4 in the visual analogue scale) was reported by four patients, two in the primary surgery group (12%) and two in the recurrent surgery group (18%; $P=1.00$). Two of the four patients, who were not planning conception at the moment, were started on medical therapy.

At ultrasound scan evaluation performed 3 months after surgery, the operated ovary had lower AFC than the contralateral, nonoperated ovary only in the recurrent endometrioma group (Table 3). As to ovarian volumes (Table 4), also this marker of ovarian reserve was significantly reduced in the operated ovary versus the contralateral in the recurrence group, and not in the primary surgery group. At the comparison of the operated ovaries between the two groups, AFC was reduced in the recurrence group compared with the primary surgery group, although not significantly ($P=.07$). Ovarian volumes were also reduced in the recurrent versus primary surgery group ($P=.03$).

DISCUSSION

Laparoscopic excision is considered the gold standard for the surgical treatment of ovarian endometriomas (1, 4, 5). Excisional techniques are associated with lower recurrence rates when compared with nonexcisional techniques (4). After excisional surgery, however, significant recurrence rates (21.5% at 2 years; 40%–50% at 5 years) have been eported (6), ranging widely from 6% (7) to 67% (8). As many as 51% of the patients operated on for endometriosis undergo a second surgical procedure for a recurrence (19).

After secondary surgery, cyst recurrence rates have been reported to be similar to those after primary surgery (20, 21). Also, pain recurrence rates have been reported to be similar after primary and secondary surgery (22). Data for secondary surgery in case of associated infertility are inconsistent, with a study (20) reporting similar pregnancy

TABLE 2

Histologic parameters of the endometrioma cyst wall.

Specimen thickness and histology grade	PS group (n = 17)	RS group (n = 11)	*P* value
Total cyst wall (mm)	1.1 ± 0.3	1.7 ± 0.3	.00003
Endometriotic tissue (mm)	0.2 ± 0.1	0.3 ± 0.1	.007
Ovarian tissue (mm)	0.3 ± 0.2	0.6 ± 0.3	.0009
Histology grade	0.4 ± 0.6	0.7 ± 0.3	.35

Note: Data are expressed as mean ± SD. PS = primary surgery; RS = recurrent surgery.

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TABLE 3

Ovarian reserve evaluation by antral follicle count after surgical excision of ovarian endometriomas.

Antral follicle count	PS group (n = 17)	RS group (n = 11)	*P* value (PS vs. RS group)
Operated ovary	5.1 ± 2.8	3.5 ± 1.4	.07
Contralateral ovary	5.7 ± 2.2	4.6 ± 1.5	.17
P value (operated vs. contralateral ovary)	.2	.002	

Note: Data are expressed as mean ± SD. PS = primary surgery; RS = recurrent surgery.

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TABLE 4

Ovarian reserve evaluation by ovarian volume after surgical excision of ovarian endometriomas.

Ovarian volume	PS group (n = 17)	RS group (n = 11)	*P* value (PS vs. RS group)
Operated ovary (mL)	7.0 ± 2.0	5.3 ± 1.7	.03
Contralateral ovary (mL)	7.5 ± 1.9	6.6 ± 1.7	.23
P value (operated vs. contralateral ovary)	.08	.001	

Note: Data are expressed as mean ± SD. PS = primary surgery; RS = recurrent surgery.

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rates (PR) after primary and secondary surgery and another study (23) reporting worse results after surgery for recurrence.

Recently, excisional surgery for endometriomas has been associated with damage to the ovarian reserve, expressed as lower antimüllerian hormone levels after surgery (9, 24, 25). A meta-analysis by Raffi et al. (9) reported a significant reduction of 38% for antimüllerian hormone levels after surgery, for a weighted mean difference of −1.13 ng/mL (95% confidence interval −1.88 to −0.37) after cyst excision.

A recent meta-analysis (26), however, did not confirm a detrimental effect of surgery on the ovarian reserve evaluated with AFC, and therefore this issue remains a research priority. No study in the literature has evaluated the effect of repeated excisional surgery on the ovarian reserve compared with first surgery.

Donnez et al. (27) in 1996 reported the presence of oocytes in the vicinity of the endometrial stroma in biopsies from ovarian endometriomas, and cautioned against the excision of the endometrioma wall because of the risk of removing healthy ovarian cortex with the cyst wall. Subsequent studies on the histology of the excised endometrioma wall after primary surgery consistently reported that some ovarian tissue is inadvertently removed with the cyst pseudocapsule, giving some possible explanation for the diminished ovarian reserve after surgery. In the absence of an anatomically identifiable plane of cleavage, some ovarian tissue is excised with the endometrioma wall in 44%–81% of patients (13, 15, 16, 18, 28–30).

The only study reporting some data on the histology of the recurrence versus primary surgery is the study by Matsuzaki et al. (29). In that study, the investigators report no significant difference in the presence of ovarian tissue in the specimen from a recurrence (44%) compared with specimens from primary surgery (64%). No data were reported on the thickness and functional grade of the excised ovarian tissue (29).

In the present study we report on a series of consecutive patients operated on for the recurrence of a monolateral ovarian endometrioma, comparing this group with a concurrent group of patients operated on for the first time. The two groups were compared for both the histologic characteristics of the excised cyst wall, and for the evaluation of postoperative ovarian reserve with AFC.

In the histologic analysis of the excised cyst wall the specimens from patients with recurrent endometriomas were significantly thicker (1.7 mm) than the specimens from patients undergoing surgery for the first time (1.1 mm). Also, ovarian tissue was more represented in the cyst wall of recurrent endometriomas than in the cyst wall after primary surgery.

At follow-up, AFC and ovarian volumes for the operated ovary were significantly decreased compared with the contralateral, nonoperated ovary only in the recurrent endometrioma group. In patients undergoing surgery for the first time, AFC was not significantly different between the operated and the contralateral ovary. These results are in line with a recent meta-analysis of the literature (26) reporting no significant change in AFC after primary surgery for endometrioma excision. In the present study, no recurrence was observed in either group at sonography, whereas comparable pain recurrence rates were observed in the primary (12%) and recurrent surgery group (18%).

The histology and ultrasonographic data on the ovarian reserve from the present study, therefore, suggest that surgery for a recurrent endometrioma may be more harmful to the healthy ovarian tissue than primary surgery. There may be several possible reasons to explain these findings: [1] a recurrent endometrioma may represent a more aggressive form of the disease, which may in turn express a more aggressive behavior toward the healthy ovarian tissue; [2] the ovary with the recurrent endometrioma may be already damaged by the presence of the first endometrioma and/or by the first surgical procedure; [3] the fibrosis induced by the first surgery may render the second surgical procedure more technically challenging, with the plane of cleavage identifiable with more difficulty, thus provoking further damage to the ovarian reserve; and [4] the longer cumulative residence of an endometrioma within the ovary in a patient with a recurrence may cause greater damage on the adjacent ovarian cortical tissue due to the higher concentrations of free iron, reactive oxygen species, proteolytic enzymes, and inflammatory molecules (31). The long-term effect of the presence of an ovarian endometrioma within the ovary has not been investigated. Although medical therapy may seem advisable in some clinical situations, such as the recurrence of an endometrioma, the effects on the ovarian reserve of the persistent cyst within the ovary during medical therapy has never been evaluated. A nonsurgical approach in this clinical scenario must therefore be still validated. As to the histology data reported in the present study, thicker specimens are inadvertently excised with the cyst wall of the recurrent endometrioma. The tissue surrounding the endometrioma has been reported to have more fibrosis compared with the contralateral, unaffected ovary (32). When a recurrence happens, additional fibrosis may be present due to the cumulative damage of the two cysts and the healing process after the first surgery. Both of these mechanisms may cause a higher degree of fibrosis, which may in turn determine a more complex surgery where the plane of cleavage is more difficult to develop, and more ovarian tissue is inadvertently removed with the cyst pseudocapsule. In these patients, if surgery is indicated, a combined excisional/ablative technique may be preferred (33, 34). The

combined technique, consisting of cyst wall excision for most of its surface and of ablation of the last part toward the hilus, where most of the ovarian tissue is inadvertently excised with the conventional stripping technique (35), may in fact be more respectful of the ovarian reserve in the context of surgery for the recurrence.

In conclusion, this is the first study in the literature reporting on detailed histologic features of recurrent endometriomas, and on the evaluation of the ovarian reserve after a second surgery. A main limitation of the present study is the small number of included patients. Further studies with larger sample sizes are therefore needed to confirm its findings. Excisional surgery for recurrent endometriomas appears to be associated with histologic evidence of higher loss of ovarian tissue if compared with primary surgery, and may be more harmful to the ovarian reserve as evaluated by AFC. Indication for surgery for recurrent endometriomas should therefore be considered with caution. In case of recurrence, medical therapy may be preferred to surgery in case of associated pain, whereas IVF has been suggested as the preferred choice in case of associated infertility (36). Surgery may still be indicated when pain and infertility are present, when medical treatment is ineffective on associated pain, when the cyst is rapidly growing, or is suspect for malignancy. If surgery is deemed necessary in case of a recurrence, patients should be counseled as to the higher risk of damage to the ovarian reserve associated with a second surgery compared with first surgery, and the pros and cons of repeated surgery should be thoroughly discussed.

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