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ARTICLE

Laparoscopic stripping of endometriomas negatively affects ovarian follicular reserve even if performed by experienced surgeons

Chiara Perono Biacchiardi [a], Luisa Delle Piane [b], Marco Camanni [a], Francesco Deltetto [a], Elena Maria Delpiano [a], Gian Luigi Marchino [b], Gianluca Gennarelli [b], Alberto Revelli [b,*]

[a] *GINTEAM Unit of Minimally Invasive Gynaecology, Turin, Italy;* [b] *Reproductive Medicine and IVF Unit, Department of Obstetrical and Gynecological Sciences, University of Torino, OIRM-S. Anna Hospital, Torino, Italy*
[*] Corresponding author. *E-mail address:* alberto.revelli@unito.it (A Revelli).

Alberto Revelli born in Torino, Italy, in 1959, obtained the Degree in Medicine in 1984, the Specialization in Obstetrics and Gynecology in 1988 and the PhD in Obstetrical and Gynecological Sciences in 1996 at the University of Torino, Italy. Since July 1999 he has worked as Researcher in Obstetrics and Gynecology at S. Anna Hospital, University of Torino, and in 2006 he was nominated Aggregate Professor in Obstetrics and Gynecology in the same University. Since 1999 he teaches Reproductive Biotechnology and IVF at Torino University. Presently he is also Head of the Physiopathology of Reproduction and IVF Unit at the University of Torino, S. Anna Hospital and IVF consultant at LIVET (Italo-Swedish Clinic for Assisted Reproduction) in Torino, Italy. He is author or co-author of 66 publications in peer-reviewed journals (PubMed), 1 book and 21 book chapters.

Abstract In order to estimate the impact of laparoscopic stripping of endometriomas on the ovarian follicular reserve, 43 normo-ovulatory women were studied by endocrine (anti-Müllerian hormone (AMH), FSH, LH, inhibin B, oestradiol) and ultrasonographic (antral follicle count (AFC)) methods before surgery, and 3 and 9 months after surgery. The operation was performed by experienced laparoscopists, particularly aware of the need to avoid damaging the healthy part of the ovary. Serum AMH concentrations significantly decreased after the operation (1.4 ± 0.2 ng/ml after 3 months and 1.3 ± 0.3 ng/ml after 9 months versus 3.0 ± 0.4 ng/ml before surgery; $P < 0.0001$), whereas basal FSH, LH, oestradiol and inhibin B concentrations remained unchanged. The volume of the operated ovary significantly diminished after surgery ($P < 0.0001$), whereas the AFC was not significantly altered. Overall, the data show that laparoscopic stripping of endometriomas reduces ovarian reserve. The significant decrease of AMH after surgery confirms that part of the healthy ovarian pericapsular tissue, containing primordial and preantral follicles, is removed or damaged despite all the surgical efforts to be atraumatic. This must be carefully considered when laparoscopic cystectomy surgery is scheduled for patients with no relevant symptoms besides infertility or with already small ovarian reserve. RBMOnline

KEYWORDS: endometriotic cyst, laparoscopic cystectomy, ovarian endometriosis, ovarian reserve

Introduction

Endometriosis is a common gynaecological disorder characterized by the ectopic growth of endometrial tissue leading to ovarian and peritoneal implants. Its prevalence among women in the reproductive age is 10–15% and ovarian involvement is frequent, regarding 17–44% of affected patients (Busacca and Vignali, 2003; Redwine, 1999).

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Endometriosis is frequently associated with infertility, especially if one or both ovaries are involved (Gupta et al., 2008; Somigliana et al., 2006; Suzuki et al., 2005; Wardle et al., 1985; Yoshida et al., 2004). Endometriomas are often removed in order to improve spontaneous fertility or the outcome of subsequent pro-fertility treatments (e.g. IVF) (Aboulghar et al., 2003; Coccia et al., 2008; Esinler et al., 2006). One of the most widespread surgical techniques to excise endometriotic cysts is laparoscopic stripping (Hart et al., 2005). The surgical treatment of endometriomas, nevertheless, has dualistic effects on fertility: on one hand it represents a way to immediately remove the disease and reduce relapse incidence, improve symptoms like dyspareunia and improve sexual life and finally give positive effects on the chances of spontaneous conception (Fuchs et al., 2007); on the other hand, it affects the so-called ovarian reserve, i.e. the pool of small antral follicles within both ovaries, potentially already compromised by the development of one or more endometriomas within the gonad (Benaglia et al., 2010; Busacca and Vignali, 2009; Esinler et al., 2006; Nakagawa et al., 2007). It has been shown that removing ovarian endometriomas does not increase success rates in IVF, as it worsens the ovarian responsiveness to superovulation (Aboulghar et al., 2003; Busacca et al., 2006; Matalliotakis et al., 2007; Ragni et al., 2005). One key point is the surgical approach at the moment of cyst stripping: indeed, a wide variability among surgeons still exists, as part of the healthy ovarian tissue may be inadvertently excised together with the endometrioma wall (Muzii et al., 2005).

Can a very cautious surgical technique and a minimal thermocoagulation on the stripping bed avoid any damage on the ovarian healthy tissue close to the cyst? The present study was designed to investigate the change in ovarian reserve after laparoscopic stripping of ovarian endometriomas when surgery is performed by experienced surgeons (about 500 laparoscopic interventions/year for ovarian endometriosis) particularly aware of the importance of a conservative approach toward the healthy part of the gonad (constant co-operation with the study centre). Ovarian reserve was estimated before and after laparoscopic surgery using the most reliable methods available to date: ultrasonographic antral follicle count (AFC) and ovarian volume (Frattarelli et al., 2001; Haadsma et al., 2007; Scheffer et al., 2003) and basal (day-3) FSH (Toner et al., 1991; Verhagen et al., 2008) and anti-miillerian hormone (AMH) assays (Visser et al., 2006).

Materials and methods

Patients

The study included 43 normo-ovulatory women aged 18–42 years that were enrolled between September 2007 and June 2009. They were affected by one or more ovarian endometriomas diagnosed by transvaginal ultrasound examination and histologically confirmed after surgery. The clinical characteristics of the enrolled patients are listed in **Table 1**. None of the patients had more than one endometrioma in the same ovary, those with bilateral endometrioma (10 patients) had one endometrioma each side.

Patients with polycystic ovary syndrome according to the Rotterdam criteria (Rotterdam ESHRE/ASRM, 2004), with basal FSH >15 IU/l, under any kind of hormonal treatment for at least 6 months, with body mass index >30 kg/m^2 and/or with other concomitant pathology affecting the ovary (e.g. benign theratoma) were excluded from the study.

All patients were submitted to laparoscopic excision of ovarian endometrioma(s) because they were symptomatic. A full ethical approval was given by the local ethical committee and all participants signed a written informed consent.

Methods

A blood sample was drawn to measure FSH, LH, oestradiol, inhibin B and AMH during the early follicular phase (day 3) of the month in which surgery was scheduled. Blood samples were processed within 1 h after sampling and sera were frozen at −20°C for subsequent centralized hormone measurements.

FSH and LH concentrations were determined using an immunofluorescence method (AutoDELFIA hFSH Spec; PerkinElmer, Wallac Oy, Turku, Finland) having inter- and intra-assay coefficients of variation (CV) of 3.1% and 1.4% for FSH and 2% and 1.7% for LH, respectively. Oestradiol was measured by immunofluorescence using the KRYPTOR kit (Brahms-GmbH Hennigsdorf, Germany), having intra- and inter-assay CV of 4.2% and 3.5%, respectively. Inhibin B was determined using a double-antibody ELISA kit (OBI MCA13112KZZ Inhibin B ELISA kit (OBI-DSL-Beckman Coulter, Heyford, Oxon, UK) having intra-assay and inter-assay CV of 9.7% and 21.5%, respectively. AMH was assayed using an enzyme immunoassay (EIA AMH A11893; Immunotech, Marseille, France) having intra-assay and inter-assay CV of 12.3% and 14.2%, respectively.

Transvaginal ultrasound examination was performed in the early follicular phase in order to estimate the ovarian volume and the AFC. Ovarian volume was calculated by transvaginal ultrasound using three orthogonal diameters combined in the ellipsoid formula ($D1 \times D2 \times D3 \times \pi/6$).

Table 1 Patient characteristics.

Characteristic	*Patients* (n = 43)
Age (years)	34.2 ± 5.4
Body mass index(kg/m^2)	21.4 ± 3.1
Endometrioma(s)	
Monolateral	33 (76.7)
Bilateral	10 (23.3)
Diameter of the endometrioma(s) (mm)	
First	36.8 ± 10.8 (21–53)
Second	35.2 ± 18.7 (23–52)
ASRM stage[a]	
Stage 2	7 (16.3)
Stage 3	26 (60.5)
Stage 4	10 (23.3)

Values are mean ± SD, mean ± SD (range) or *n* (%).
[a]American Society for Reproductive Medicine (1997).

AFC was determined by counting the follicles >3 mm diameter that were visible through a complete scanning of both ovaries. In order to avoid any operator-linked bias, all ultrasound examinations were done by the same investigators (CPB and LDP) using the same equipment (Accuvix XQ; Medison, Korea).

The blood sample and transvaginal ultrasound examinations were then repeated 3 and 9 months after laparoscopic cystectomy in the same cycle phase.

Surgical technique

All laparoscopic operations were performed under general anaesthesia by the same team of experienced pelvic endoscopists. The surgeons were aware of the need to induce the lowest damage possible to the healthy part of the ovary as all patients were still young, most of them wished to have children and some of them were also candidates to undergo ovarian stimulation for IVF.

A four-port laparoscopy technique was used: an 11-mm trocar was inserted through a short umbilical incision and connected to a video monitor (WideVieuw HD Karl Storz Endoscope); two additional lateral 5-mm operating ports and a central sovrapubic 5–10-mm operating port were also inserted. The pneumo-peritoneum was achieved by inflating with CO_2 (10 mmHg). First, inspection of the abdominal cavity was performed to check the presence of adhesions and endometriotic lesions; then, a sample of peritoneal fluid was aspirated from the Douglas pouch and sent for immediate cytological examination in order to exclude malignancy. Adhesiolysis and mobilization of the ovaries were performed when necessary. All visible endometriotic foci on the peritoneum, ligaments, etc., were excised.

To excise endometriomas, an incision was performed at the antimesenteric site of the affected ovary using bipolar cautery; then, the endometrioma was drained with aspiration and the pseudo-capsule was dissected by gentle traction and countertraction using two 5-mm grasping forceps ('stripping'). The bleeding at the stripping site was stopped by bipolar cautery only when necessary and very carefully in order to avoid unnecessary thermal damage to the healthy ovarian tissue. A complete excision of other peritoneal endometriotic lesions, both superficial and deep, was also performed following the technique described elsewhere (Camanni et al., 2009). Endometriotic lesions were given a score according to the revised American Society of Reproductive Medicine classification (American Society and for Reproductive Medicine, 1997).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 15.0 (SPSS, Chicago, IL, USA). Continuous variables with normal distribution (confirmed by Kolmogorov–Smirnov test) were compared with the paired Student's t-test after log transformation of some data to correct the heterogeneity of variance. Non-normally distributed parametric variables were analysed by the paired Wilcoxon's rank test after log transformation to correct the heterogeneity of variance. Correlations were calculated using the Pearson's test. A P-value <0.05 was considered statistically significant.

Results

The laparoscopic excision of endometriomas was performed in all cases without complications and patients left the hospital within 24–48 h. The resumption of a normal menstrual rhythm was observed in all patients within 6 weeks after the operation and all had a normal menstrual rhythm at the time of the first follow-up check (3 months).

Hormonal serum concentrations before the operation and 3 and 9 months after surgery are shown in **Table 2**. Serum AMH concentrations significantly decreased after the operation (1.4 ± 0.2 ng/ml after 3 months and 1.3 ± 0.3 ng/ml after 9 months versus 3.0 ± 0.4 ng/ml before surgery; $P < 0.0001$). No significant differences were found in inhibin B, basal FSH, LH and oestradiol concentrations before and after surgery. Pre-surgery AMH concentrations were significantly inversely related to age ($r = -0.321$; $P < 0.018$), but this negative relationship lost significance 3 months after surgery ($r = -0.217$; not statistically significant) (**Figure 1**).

The ultrasonographic parameters before the operation and 3 and 9 months after surgery are shown in **Table 3**. Before surgery, the AFC in the affected ovary was significantly lower than in the healthy ovary (3.3 ± 3.2 versus 8.4 ± 6.0, respectively; $P < 0.0001$) and this difference was maintained 3 and 9 months after surgery (6.0 ± 4.5 and 5.1 ± 3.6 in the operated ovary versus 9.0 ± 6.2 and 8.1 ± 4.9 in the healthy counterpart; $P < 0.0001$). The AFC in the affected ovary appeared to be higher 3 months after laparoscopy than before the operation, although not to a statistically significant level. The volume of the operated, affected ovary was significantly reduced after surgery ($P < 0.0001$), whereas no difference was found in the healthy ovary, as expected.

A positive, significant correlation between AMH concentrations and AFC was observed in the affected ovary before surgery ($r = -0.312$; $P < 0.038$); this correlation was even more significant 3 months after the operation ($r = -0.819$; $P < 0.000$) (**Figure 2**).

Discussion

In recent years, several studies have weighted the beneficial or, conversely, the adverse effects of the laparoscopic excision of an ovarian endometrioma either on the spontaneous conception rate or on the outcome of a subsequent IVF (Demirol et al., 2006; Loo et al., 2005).

The presence of a space-occupying cyst inside the ovary has been shown to be itself a cause of a reduced ovarian follicular reserve: increased basal FSH concentrations (Hock et al., 2001) and reduced inhibin B concentrations (Dokras et al., 2000) were reported in patients with ovarian endometriosis, and circulating AMH concentrations were found to be lower than average in non-operated patients bearing an ovarian cyst (Lemos et al., 2008). Nevertheless, the laparoscopic excision of endometriomas using the classical 'stripping' technique that implies thermocoagulation of

Table 2 Hormone concentrations before laparoscopic stripping of ovarian endometrioma(s) and after 3 and 9 months.

Hormone	*Before LPS*	*After LPS*		P-*value*
		3 months	*9 months*	
FSH (IU/l)	6.6 ± 2.0	7.8 ± 3.4	8.0 ± 3.7	NS
LH (IU/l)	5.0 ± 2.0	4.5 ± 1.7	4.2 ± 2.0	NS
Oestradiol (pg/ml)	35.2 ± 24.5	33.5 ± 29.3	32.9 ± 26.6	NS
Inhibin B (pg/ml)	51.6 ± 31.3	47.4 ± 23.0	44.5 ± 26.0	NS
AMH (ng/ml)	3.0 ± 0.4	1.4 ± 0.2	1.3 ± 0.3	<0.0001

Values are mean ± SD. AMH = anti-Müllerian hormone; LPS = laparoscopic stripping; NS = not statistically significant.

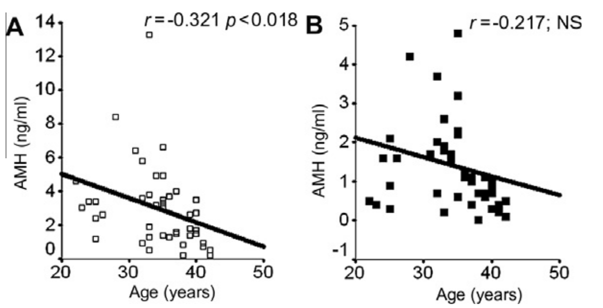

Figure 1 Correlation between anti-Müllerian hormone (AMH) serum concentrations and age (A) before and (B) 3 months after laparoscopic stripping of ovarian endometriomas. The negative correlation is significant only before the operation ($P < 0.018$). NS = not statistically significant.

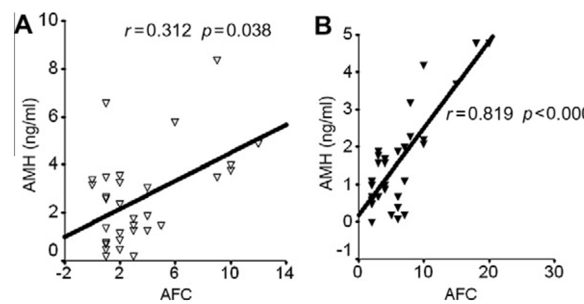

Figure 2 Correlation between anti-Müllerian hormone (AMH) serum concentrations and antral follicle count (AFC) (A) before and (B) 3 months after laparoscopic stripping of ovarian endometriomas. The positive correlation is significant both before and after surgery.

the stripping bed is likely to cause additional follicle loss. In fact, operated patients who later underwent ovarian stimulation for IVF showed increased resistance to hormonal stimulation and obtained less oocytes at retrieval (Busacca et al., 2006; Matalliotakis et al., 2007; Ragni et al., 2005). Some authors reported that after laparoscopic cystectomy of benign ovarian cysts (including endometriomas) the volume and the AFC of the operated ovary are both significantly lower than those of the contralateral ovary (Candiani et al., 2005; Exacoustos et al., 2004; Somigliana et al., 2003).

The presence of an ovarian cyst may distort and damage the adjacent healthy ovarian tissue (Maneschi et al., 1993), but the laparoscopic stripping of ovarian endometriomas may further worsen ovarian reserve through at least three ways: (i) the accidental removal of healthy ovarian cortex near the cyst's capsule; (ii) the thermal effect of diathermy coagulation of small bleeding vessels on the stripping area with consequent vascular compromise; and (iii) a surgery-related local inflammation. Some histological studies have indeed documented that ovarian tissue is excised together with the endometrioma wall in most cases of laparoscopic stripping (Hachisuga and Kawarabayashi, 2002; Muzii et al., 2005). So why is laparoscopic stripping of ovarian endometriomas still performed even in patients that do not have relevant symptoms to be relieved? Probably one of the reasons why surgeons still operate on such patients is that most of them are convinced that in their own hands

Table 3 Ultrasonographic variables before laparoscopic stripping of ovarian endometrioma(s) and after 3 and 9 months for patients with monolateral endometrioma ($n = 33$).

Ultrasonographic finding	*Before LPS*	*After LPS*		P-*value*
		3 months	*9 months*	
AFC (affected ovary)	3.3 ± 3.2	6.0 ± 4.5	5.1 ± 3.6	NS
AFC (healthy ovary)	8.4 ± 6.0	9.0 ± 6.2	8.1 ± 4.9	NS
Ovarian volume (affected) (ml)	10.5 ± 0.8	8.5 ± 0.6	8.6 ± 0.9	<0.0001
Ovarian volume (healthy) (ml)	8.1 ± 0.8	8.4 ± 0.6	8.2 ± 0.8	NS

Values are mean ± SD. AFC = antral follicle count; LPS = laparoscopic stripping; NS = not statistically significant.

(with minimal use of thermal coagulation, atraumatic equipment, very cautious behaviour, wide experience, etc.) the damage caused on the remaining ovarian tissue will be minimal. Is it true that a surgeon's experience may avoid any damage on the healthy ovary?

This study was designed together with a team of experienced laparoscopists belonging to a reference centre for the surgery of pelvic endometriosis. These surgeons were particularly aware of the need of being atraumatic and conservative on the ovary during excision of endometriomas. They applied a classical stripping technique that was performed with the highest level of cautiousness toward the healthy part of the gonad. Despite every effort, AMH showed a significant reduction after surgery. AMH is probably the most reliable tool to assess ovarian reserve (Fanchin et al., 2003; Nakhuda, 2008; Tremellen et al., 2005; van Rooij et al., 2002; Visser et al., 2006), being synthesized in the pre-antral and small antral follicles (Weenen et al., 2004), AMH provides information about the number of follicles relocated from the quiescent pool of primordial follicles to the pool of activated ones. AMH is more sensitive than basal FSH (Anderson et al., 2006; Laven et al., 2004; van Beek et al., 2007) or inhibin B (Bath et al., 2003) as a marker of ovarian reserve, since these reflect only FSH-dependent follicles at later stages of folliculogenesis.

In this study, basal FSH concentrations increased a little after the operation, but not significantly, whereas the circulating concentrations of LH, inhibin B and oestradiol remained practically unchanged. The fact that AMH significantly decreased after surgery while other hormones did not, may be explained by the higher sensitivity of AMH to ovarian damage and by the existence of a selective damage caused by surgery on the primordial and small antral follicle pool (secreting AMH) that are hosted in the tissue near the cyst. More developed ovarian follicles (secreting inhibin B and oestradiol and thus affecting FSH concentrations) are rarely detected near an endometrioma (Dilek et al., 2006; Hachisuga and Kawarabayashi, 2002; Muzii et al., 2005), and in this study, after surgery their concentrations changed only a little.

Interestingly enough, the significant inverse correlation between age and AMH concentrations (de Vet et al., 2002) that the present study observed before surgery lost significance after the operation, suggesting that the surgical damage on healthy ovarian tissue is independent of age and can lower ovarian reserve in the same way in both young and older women.

In this study, the ovarian volume of the cyst-containing ovary was significantly reduced by surgery, and after surgery became similar to the contralateral, healthy ovary. This is likely because of the small dimensions of most of the operated endometriomas and the attention that surgeons used toward limiting the quantity of the excised ovarian tissue. The AFC was significantly reduced in the affected ovary compared with the healthy one even before the operation, confirming the idea that the presence of an ovarian cyst can be itself a cause of reduced ovarian reserve. Paradoxically, the AFC of the operated ovary apparently increased after surgery, although not to a significant level: this effect can be likely explained by the limits of AFC, which is more difficult to perform and is inaccurate in the presence of the anatomical alteration caused by an endometrioma. Indeed, it was reported that both ovarian-volume measurement and AFC lose accuracy in the presence of ovarian cysts as well as in the presence of a corpus luteum (Broekmans et al., 2006; Hendriks et al., 2007). It was also reported that AFC can 'paradoxically' increase after excision of an ovarian endometrioma: this effect is linked to the possibility that it is more accurate calculating AFC after an ovarian cyst has been removed (Pados et al., 2010).

Overall, these data show that, even when performed by experienced laparoscopists with the highest level of cautiousness, the laparoscopic stripping of endometriotic cysts reduces the ovarian follicular reserve. The significant reduction of AMH after surgery confirms previous histological observations, suggesting that part of the healthy ovarian pericapsular tissue, containing primordial and preantral follicles, is removed or damaged despite every surgical effort to be atraumatic. This must be carefully considered when ovarian surgery is proposed to patients with one or more ovarian endometriomas, but no relevant symptoms besides infertility. Indeed, the European Society for Human Reproduction and Embryology guidelines state that the laparoscopic excision of ovarian endometriomas between 3 and 6 cm in diameter does not improve IVF outcome and significantly decreases ovarian reserve (ESHRE, 2007). It is true that the onset of an ovarian cancer from an endometrioma has been reported in rare cases (Kobayashi et al., 2011), but this is not a reason to operate on the patient before IVF, as laparoscopic excision of the cyst can be delayed until after she has completed her reproductive programme.

In cases where laparoscopic excision must be absolutely done (e.g. for relevant symptoms), alternative surgical techniques such as the combined cystectomy plus ablation (Hart et al., 2005) or the ultrasound-guided puncture with methotrexate (Agostini et al., 2007; Mesogitis et al., 2005) or alcohol injection (Hsieh et al., 2009; Koike et al., 2002; Yazbeck et al., 2009) could be considered, especially in patients who are aged over 38 years or who have an already small ovarian reserve.

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