Sonographic changes after laparoscopic cystectomy compared with three-stage management in patients with ovarian endometriomas: a prospective randomized study

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BACKGROUND: Laparoscopic surgery is the gold standard treatment for ovarian endometriomas. The aim of this study was to evaluate the impact of two different laparoscopic methods on sonographic indicators of ovarian reserve in the treated ovary.

METHODS: In this prospective randomized clinical trial, 20 patients with endometriomas were randomly assigned to undergo either laparoscopic cystectomy (Group 1) or the ‘three-stage procedure’ (Group 2). All patients underwent ultrasound examination preoperatively and 6 months after laparoscopy. Another ultrasound examination was performed 12 months after intervention in order to detect any recurrence. We investigated the alterations in the residual ovarian volume, ovarian vascular supply and antral follicle count (AFC) on the ovary with the endometriotic cyst by transvaginal color Doppler ultrasonography.

RESULTS: The residual ovarian volume and the lowest pulsatility and resistance indexes were found to be similar between the two groups before and 6 months after laparoscopic intervention. The AFC of the operated ovary was increased significantly (P = 0.002) in Group 2 compared with Group 1 after 6 months. One year after laparoscopy, two recurrences of endometriomas were detected in Group 2, although none were detected in Group 1 (P = 0.47).

CONCLUSIONS: Ovarian volumes and vascularization were comparable among the two laparoscopic methods. On the contrary, functional ovarian tissue as determined by AFC was higher after the ‘three-stage’ procedure.

Key words: endometrioma / cystectomy / laser vaporization / transvaginal Doppler ultrasound / ovarian artery blood flow

Introduction
Endometriomas are defined as the cystic manifestation of ovarian endometriosis and represent 35% of benign ovarian cysts requiring surgery (Busacca and Vignali, 2003). Despite several proposed theories and pathogenic mechanisms for this enigmatic disease, invagination of ovarian cortex and metaplasia of the coelomic epithelium have been described as the main mechanism of ovarian endometrioma formation (Nisolle and Donnez, 1997).

Operative laparoscopy compared with laparotomy is considered the ‘gold standard’ for the treatment of ovarian cysts regarding the benefits in post-operative analgesia, hospitalization and de novo adhesion formation (Pados et al., 2006). Among the several proposed conservative laparoscopic methods for laparoscopic management of endometriotic cysts, laparoscopic stripping, also called cystectomy, seems to be the preferred surgical approach in terms of recurrence and symptoms relief (Hart et al., 2008). However, the impact of surgical injury on ovarian residual volume, ovarian artery blood flow and folliculogenesis after each laparoscopic approach for endometrioma treatment has not been widely investigated (Exacoustos et al., 2004; Muzii et al., 2005).

In recent years, transvaginal conventional color Doppler ultrasound has become a non-invasive and reliable diagnostic tool for evaluation of ovarian cysts and vascular impedance indices (Aleem et al., 1995; Alcazar, 2001). Sonographic assessment of the antral follicle count (AFC) has been strongly associated with the primordial follicle pool...
and is used as a reliable sonographic indicator of ovarian reserve (Matukrishna et al., 2005; Visser and Themmen, 2005).

According to recent reported studies, laparoscopic stripping has been questioned as an ideal surgical approach for endometriomas because it is associated with excessive removal of ovarian tissue and loss of ovarian follicles with subsequent reduction of ovarian reserve (Candiani et al., 2005; Busacca et al., 2006). An alternative to cystectomy is the ‘three-stage procedure’ which involves drainage of the cyst during laparoscopy, GnRH agonist treatments and then laser vaporization of the remains during a second laparoscopy. To the best of our knowledge, no retrospective or prospective studies have addressed the safety of laparoscopic stripping compared with the ‘three-stage procedure’ on preservation of normal ovarian tissue, vascularization and ovarian reserve as indicated by AFC.

In this study, we prospectively evaluated whether and to what extent any difference existed in sonographic findings such as ovarian volume, blood flow and AFC in natural cycles 6 months after laparoscopic stripping of endometriomas in comparison to the ‘three-stage procedure’.

Materials and Methods

This prospective study was conducted in ‘Papageorgiou’ University Hospital of Thessaloniki in Greece between January 2005 and March 2007. During the enrollment period, 37 consecutive women of reproductive age (22–40 years old) were found to be eligible for the study after examination in the outpatient department due to the diagnosis of an endometrioma of at least 3 cm in diameter. Subjects were required to give written informed consent and have no history of cancer, suspected malignancy, pre-surgical evidence of premature ovarian failure and no use of estrogen (E)-suppressive drugs, such as oral contraceptives, GnRH analogues, progestins or danazol in the preceding 6 months. In addition, pregnancy and a body mass index (BMI) of more than 30 kg/m² were among the exclusion criteria. Institutional review board approval was obtained before initiation of the study. Patients who refused to participate in this study, were treated by cystectomy.

Due to the absence of any relevant data, we initially performed a pilot study in order to determine the appropriate sample size, which was estimated to 10 patients at least in each study group, for a study power of 70%. Randomization was performed by choosing 1 of the 20 opaque envelopes and allocating them in proportion 1:1 either to Group 1 (laparoscopic stripping) or Group 2 (three-step procedure) by the clinical trials secretary. In all cases, pathology reports confirmed the pre-operative and intra-operative diagnosis of ovarian endometriomas. Neither patient dropped out from the study, nor was lost during the follow-up period. We ascertained demographic characteristics by questionnaire for each patient.

All subjects preoperatively and 6 months after surgery, during their follow-up, underwent transvaginal ultrasound examination (5–7.5 MHz transvaginal transducer, Sonoline G50, Siemens, Germany). The ultrasound examinations were performed by the same operator (D.T.) in the early follicular phase of the cycle (Days 3–6) to measure the ovarian size and, before surgery, the mean diameter of the three perpendicular dimensions of the cyst. The ovarian and cyst volumes were estimated by using the Prolate ellipsoid formula: \( V = 4/3 \times \pi \times (d/2)^3 \) where \( d \) is the mean diameter. Residual volume of the treated ovary was calculated by using the formula: ovarian volume – cyst volume.

AFC was recorded as the total number of recruited follicles with a diameter < 9 mm. Color Doppler examination followed B mode in order to rule out functional or malignant suspected cysts and to obtain flow velocity waveforms from ovarian artery at the hilus site of the affected ovary.

We, and other investigators (Kupesic and Kurjak, 2002), consider that intra-ovarian stromal vessels are thin and tortuous in relation to the main branch of ovarian artery and therefore it is difficult to obtain the correct angle between the ultrasound beam and intra-ovarian vessels. The calculation of resistance index (RI) and pulsatility index (PI) was therefore based on the following formulas: \( RI = (S - D)/S \) and \( RI = (S - D)/D \), where \( S \) is the peak systolic velocity, \( D \) is the end diastolic velocity and the mean is the averaged maximum velocity. When multiple signals were obtained, the lowest values were used for analysis. The sample volume was set at a 1–2 mm width. The pulse repetition frequency was set at 1.5–20 kHz and the high pass filter was set at 50 Hz.

Operative laparoscopy was performed during the late proliferative phase of the cycle through insertion of a 10 mm subumbilical trocar and three 5 mm trocars in the lower abdomen. In all patients, the pre-operative diagnosis of endometrioma was confirmed at laparoscopy. All endoscopic procedures were performed by the same endoscopist (G.P.) and assistant (D.T.) and followed the same protocol during the diagnostic phase of the laparoscopy. This included inspection of pelvic and peritoneal organs, peritoneal washings, staging of endometriosis and adhesiolysis to fully release the adhesive ovaries from the surrounding structures. If the ovarian cyst remained unruptured despite the manipulations during adhesiolysis, it was punctured to drain and aspirate its chocolate content. Further, extension of the incision into the anti-mesenteric edge facilitated meticulous inspection of the inner cyst’s wall for exclusion of possible suspicious areas. Endometriosis was staged according to the revised American Society for Reproductive Medicine classification.

For Group 1 patients, after identification of the cleavage plane, the wall of the cyst was stripped from the healthy surrounding normal ovarian tissue with the use of two atraumatic grasping forceps by traction and counteraction and sent for histological examination. Finally, hemostasis was achieved with application of a 30-W current using bipolar forceps on the cyst bed. Peritoneal endometriosis implants were electrocoagulated as well, with a power setting of 15 W.

Patients allocated to Group 2 underwent the three-stage technique, which was first described by Donnez et al. (1996). During the first laparoscopy, only drainage of the cyst content, irrigation and inspection of its inner wall took place. From this, a biopsy from the cyst’s wall was sent for routine histological examination to confirm the diagnosis of endometriosis or for frozen section if suspicious or atypical lesions were encountered. Then, GnRH agonists were administered for 3 months to reduce the cyst diameter, stromal vascularization and the rate of glandular mitotic activity of endometriosis. After 12 weeks, a second laparoscopy was carried out to vaporize the internal wall by using a CO2 laser (Sharplan 1041S; Sharplan, Israel) at a power density of 14 000 W/cm². The other areas of superficial active endometriosis involving the other ovary or pelvic peritoneum were, also treated. Re-approximation of the edges of the ovarian tissue was achieved by a lower power density of CO2 laser in de-focus mode (8000 W/cm²).

No sutures were placed after either ovarian cystectomy or vaporization, and all patients were discharged the following day.

We compared the above two laparoscopic approaches for treatment of endometriomas to detect whether any difference exist in ovarian reserve (as determined by AFC), residual ovarian volume or ovarian blood flow (determined as PI and RI) 6 months after laparoscopy compared with that beforehand. Sonographically detection of endometrioma recurrence was performed 12 months after laparoscopic treatment.

Data analyses were performed with the software SPSS 15.0. The \( \chi^2 \) or Fischer’s exact test was used for comparison of categorical variables. Student’s t-test and the Wilcoxon–Mann–Whitney test were used for
comparison of continuous variables. P-values of < 0.05 were considered statistically significant.

Results

This prospective study was conducted in 'Papageorgiou' University Hospital of Thessaloniki in Greece between January 2005 and March 2007 and included 20 out of 37 eligible patients, who agreed to participate in this study and gave written informed consent. There were 17 of 37 patients who refused to participate in the study after being made aware of the benefits and treatment drawbacks of the two laparoscopic approaches for endometriomas. After the beginning of the study, no patients dropped out nor were any lost during the follow-up period and therefore, 10 patients were allocated and stayed in each group. As shown in Table I, baseline demographic and clinical features of patients in each group were not significantly different in terms of age, parity, BMI, length of menstrual cycle and presenting symptoms.

Also, the baseline sonographic and operative findings were comparable between the two groups, as summarized in Table II. The mean size of endometriomas was 37.9 mm in Group 1 and 36.8 mm in Group 2. There were bilateral endometriomas in three cases in Group 1 and in two cases in Group 2, and these were operated with the same technique (cystectomy or three-stage technique) as the contralateral ovary.

Comparisons of ultrasonographic findings between the two groups before and 6 months after treatment are presented in Table III. Of note, whereas residual ovarian volume and ovarian artery Doppler indices of the affected ovary were similar in both groups before and after treatment, a significant improvement of folliculogenesis was observed in Group 2 at 6 months follow-up. AFC of the operated ovary was found to be significantly higher (P = 0.002) in Group 2 (from 1.27 to 4.36) compared with Group 1 (from 2 to 2.38).

After cyst wall removal in Group 1 or laser ablation in Group 2, the residual ovarian volume of the treated ovary was similar in both groups, as demonstrated in Table III.

No complications were reported and all patients were discharged the following day. One-year after laparoscopy, two recurrences of endometriomas were detected sonographically in Group 2, although no recurrences were noted in Group 1.

Table I  Baseline demographic and clinical characteristics of the two groups of patients with ovarian endometriomas.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 10) stripping</th>
<th>Group 2 (n = 10) three-step procedure</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SE) age (year)</td>
<td>32.8 ± 1.7</td>
<td>29.9 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (± SE) cycle length (day)</td>
<td>29.4 ± 0.6</td>
<td>27.6 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.9 ± 1.5</td>
<td>22.9 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>No of nulliparous patients (%)</td>
<td>5 (50)</td>
<td>6 (60)</td>
<td>NS</td>
</tr>
<tr>
<td>No of patients with infertility (%)</td>
<td>1 (10)</td>
<td>3 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>No of patients with dysmenorrhea (%)</td>
<td>8 (80)</td>
<td>7 (70)</td>
<td>NS</td>
</tr>
<tr>
<td>No of patients with dyspareunia (%)</td>
<td>3 (30)</td>
<td>1 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>No of patients with chronic pelvic pain (%)</td>
<td>5 (50)</td>
<td>4 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>No of patients with dyschezia (%)</td>
<td>1 (10)</td>
<td>3 (30)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: values are means ± SE.
NS, not significant.

Table II  Baseline sonographic and operative findings.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 10) stripping</th>
<th>Group 2 (n = 10) three-step procedure</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SE) volume of affected ovary (ml)</td>
<td>82.6 ± 29.6</td>
<td>77.7 ± 23.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (± SE) volume of endometrioma (ml)</td>
<td>44.2 ± 20.1</td>
<td>41.65 ± 15.4</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (± SE) diameter of cyst (mm)</td>
<td>37.9 ± 4.8</td>
<td>36.8 ± 5.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (± SE) residual volume of ovary (ml)</td>
<td>38.45 ± 10.2</td>
<td>36.09 ± 10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean revised AFS score</td>
<td>43 ± 5.5</td>
<td>38 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>No of endometriomas in right ovary (%)</td>
<td>6 (46.2)</td>
<td>7 (58.3)</td>
<td>NS</td>
</tr>
<tr>
<td>No of endometriomas in left ovary (%)</td>
<td>7 (53.8)</td>
<td>5 (41.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage of red color peritoneal lesions</td>
<td>80</td>
<td>82</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage of black color peritoneal lesions</td>
<td>5</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage of white color peritoneal lesions</td>
<td>15</td>
<td>17</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: values are means ± SE.
NS, not significant.
The ideal conservative laparoscopic approach of endometriomas is still controversial (Jones and Sutton, 2000; Brosens et al., 2002; Chapron et al., 2002; Vercellini et al., 2003; Aboulghar and Mansour, 2004; Alborzi et al., 2006; Dilek et al., 2006; Donnez et al., 2009). The impacts of cystectomy and of the ‘three-step procedure’ on ovarian reserve have not been examined previously by using sonographic markers. According to published randomized studies, the comparison between cystectomy and ablation favors excision of the cyst capsule in terms of recurrence of the cyst or of symptoms recurrence, as well in terms of the response to ovarian stimulation and subsequent pregnancy rates (PR) in infertile women (Beretta et al., 1998; Alborzi et al., 2004, 2007).

However, the assessment of ovarian reserve remains a challenge in the literature. Among the ultrasonographic markers of ovarian reserve, AFC is considered to be the most reliable indicator of the primordial follicle pool (Visser and Themmen, 2005). We have demonstrated that treatment of ovarian endometriotic cysts by the ‘three-step procedure’ as described by Donnez is associated with an increase in AFC in the treated ovary 6 months after laparoscopy (Donnez et al., 1996).

Ovarian volume has also been reported by several authors as a reliable indicator of ovarian reserve (Lass and Brinsden, 1999; Wallace and Kelsey, 2004), which can be used as a surrogate measurement of the remaining primordial follicle pool. It has been reported that diminished ovarian volume results in poor response to ovulation induction, low clinical PR (Syrop et al., 1995) and early menopause. Exacoustos et al. (2004) have found that ovarian stripping of endometriomas is associated with a significant decrease in residual ovarian volume. In the present study, post-surgical ovarian volume was influenced to the same degree irrelevant of the technique used.

Furthermore, adverse changes to vascular supply by measurement of PI and RI of the ovarian artery before and after laparoscopy of ovarian endometriomas have been reported with stripping (La Torre et al., 1998). A possible diminished ovarian blood supply due to ageing (Lass and Brinsden, 1999) or surgical injury (Busacca et al., 2006) could explain a further decrease in ovarian volume, as well as a reduction in the number of growing follicles or early ovarian failure. However, in our study both Doppler indexes of ovarian artery at the hilus level and residual ovarian volumes were comparable before laparoscopy and remained at similar levels after either laparoscopic stripping or the ‘three-stage procedure’ for endometrioma treatment. However, other investigators have reported post-surgical ovarian failure after laparoscopic excision of bilateral endometriomas (Reich and Abrao, 2006). Possible explanations of this rare complication are considered to be inadequate application of stripping by inexperienced hands or difficult dissection close to the ovarian hilus (due to endometriosis induced fibrosis) even by experienced laparoscopists (Canis et al., 2001). Such difficulties may provoke severe bleeding and excessive use of bipolar coagulation, so inducing irreversible severe damage of ovarian reserve.

Interestingly, in our randomized study, despite the absence of any difference in post-surgical ovarian volume and vascularization between the two groups, the AFC improved significantly only in the group treated by the ‘three-stage procedure’. This may be ascribed to a less destructive effect of laser energy than of electrocoagulation on healthy ovarian tissue adjacent to the endometriotic cyst wall (Wyns and Donnez, 2003). It has been documented that CO2 laser is an alternative safe and effective modality because it provides precise tissue dissection, ablation, controlled depth of tissue penetration and thermal damage without sacrificing the adjacent healthy ovarian cortex (Donnez, 1987; Brosens et al., 1996; Sutton and Jones, 2002). Furthermore, it has been suggested that only the internal lining of the cyst wall should be vaporized with a depth of ablation not exceeding 1.0–1.5 mm and there is no need to destroy the entire fibrotic capsule surrounding the endometrioma (Donnez et al., 2001). Another explanation, other than the detrimental effect of electrocoagulation on functional ovarian cortex during hemostasis, is the inadvertent removal of healthy ovarian tissue even by experienced laparoscopists, due to endometriosis induced fibrosis and consequent absence of cleavage plane. Our results are consistent with those of Kupesic and Kurjak (2002) who found that some patients may have diminished ovarian reserve without evident changes in ovarian volume.

In our study, the ovarian reserve was assessed in an unselected population in contrast to other conducted trials (Loibl et al., 1999; Ho et al., 2002; Somigliana et al., 2003; Alborzi et al., 2007) which have shown conflicting results concerning the assessment of the remaining ovarian reserve only in infertile women who underwent ovarian stimulation after laparoscopy.

Although our study was a prospective randomized one, it had several limitations. The power of study was only 70% since only 10 patients were recruited in each group, as it is difficult for a patient to accept the possibility of undergoing two operations instead of

### Table III Comparison of the sonographic findings of affected ovary of Group 1 and 2 patients before and 6 months after laparoscopy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 10) laparoscopic stripping</th>
<th>Group 2 (n = 10) three-step procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Residual ovarian volume</td>
<td>38.45 ± 10.02</td>
<td>11.45 ± 0.78</td>
</tr>
<tr>
<td>RI</td>
<td>0.87 ± 0.02</td>
<td>0.89 ± 0.03</td>
</tr>
<tr>
<td>PI</td>
<td>2.35 ± 0.19</td>
<td>2.51 ± 0.23</td>
</tr>
<tr>
<td>AFC</td>
<td>2.00 ± 1.00</td>
<td>2.38 ± 0.78</td>
</tr>
</tbody>
</table>

Note: values are means ± SE.

NS, not significant.
one. Another disadvantage was the inability to evaluate the thermal damage of ovarian reserve by histological examination and correlate it to any sonographic marker.

From the clinical point of view, our study demonstrated that in women of reproductive age, folliculogenesis based on AFC measurement was better restored, after choosing the ‘three-stage procedure’ instead of stripping for conservative laparoscopic treatment of endometriotic cysts. Our results reinforce those of Muzzi et al. (2005) who found that ovarian stripping is associated with inadvertent loss of ovarian tissue and of Donnez et al. (2009) who reported an AFC similar to that in the contralateral ovary after using a combined excisional and ablative laparoscopic technique. However, the ‘three-stage procedure’ was associated with a higher rate of recurrence and with two laparoscopies instead of one. Pre-operative counseling of patients with endometriomas should take into consideration the risks and benefits of each method. Further, studies are needed to evaluate the best technique for laparoscopic treatment of endometriomas, taking into account, among the others, the assessment of ovarian reserve. The results of this small randomized study need to be addressed in further trials enrolling larger number of patients.

Authors’ Roles


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