Does laparoscopic excision of endometriotic ovarian cysts significantly affect ovarian reserve? Insights from IVF cycles

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BACKGROUND: Residual ovarian function after laparoscopic excision of endometriotic ovarian cysts is a major and still unsolved topic. Ultrasonographic evaluation of ovarian response to ovulation stimulation represents a simple yet poorly employed tool to assess residual ovarian function after surgery. METHODS: Data from patients referred for IVF or ICSI between January 2001 and December 2002 were reviewed. Patients were included who previously underwent laparoscopic excision of a monolateral endometriotic ovarian cyst. The operated ovary and contralateral intact ovary were compared in terms of number of follicles with a mean diameter >15 mm at the time of hCG administration. Basal volume of the two ovaries before initiating stimulation was also compared. A paired Student’s t-test was used to investigate differences between the two ovaries. RESULTS: In total, 32 patients and 46 cycles were identified. The mean (± SD) number of follicles >15 mm was 4.2 ± 2.5 in the control ovary and 2.0 ± 1.5 in the previously operated ovary (P < 0.001); this corresponded to a mean reduction of 53% (95% CI 35–72%) but did not seem to be related to the dimension of the excised ovarian cyst. The basal volume of the operated ovaries was also statistically significantly diminished, though this reduction was less relevant. CONCLUSIONS: Excision of endometriotic ovarian cysts is associated with a significant reduction in ovarian reserve. Further studies are required to clarify whether the damage is related to the surgical procedure or to the previous presence of a cyst.

Key words: cyst enucleation/laparoscopy/ovarian cyst/ovarian reserve

Introduction

Laparoscopic surgery is currently considered the treatment of choice in women with benign ovarian cysts and has gained increasing acceptance among gynaecological surgeons (Daniell et al., 1991; Donnez et al., 1996; Sutton et al., 1997; Canis et al., 2002). However, residual ovarian function after laparoscopic excision of ovarian cysts is a major and still unsolved topic in this field.

A body of literature has provided evidence that the pregnancy rate after laparoscopic removal of ovarian cysts is satisfactory (Donnez et al., 1996; Beretta et al., 1998; Hemmings et al., 1998). Moreover, results from IVF cycles suggest that, in general, the possibility of achieving pregnancy is not impaired by previous ovarian surgery (Canis et al., 2001; Donnez et al., 2001; Geber et al., 2002; Marconi et al., 2002). Nevertheless, it is worthwhile noting that the vast majority of operated patients had undergone monolateral excision of an ovarian cyst, leaving the contralateral ovary undamaged. In fact, the intact reserve of the unoperated gonad renders adequate estimation of damage to the operated ovary very difficult. Indeed, in these women, hormonal evaluation and spontaneous and/or assisted reproduction technique-mediated pregnancy rates cannot be considered reliable tools to assess residual ovarian function in the operated ovary. In this regard, results from ovarian stimulation for IVF cycles may represent an appealing possibility to test specifically the functional reserve of a single gonad. Specifically, monitoring ovarian response in the previously operated ovary and using the contralateral gonad of the same patient as a control should be considered an interesting and simple means of assessing residual ovarian function. Surprisingly, this method has been used previously in only four studies, and has produced controversial results (Nargund et al., 1996; Loh et al., 1999; Donnez et al., 2001; Ho et al., 2002).

The aim of the present study was to evaluate the response to ovarian stimulation in patients who had been referred to the authors’ infertility unit for IVF techniques and who previously had undergone monolateral excision of endometriotic ovarian cysts. Specifically, ovarian response was compared in the operated and intact ovaries, whilst factors that might influence the severity of the damage were also investigated.
Materials and methods

Patients
Data from patients referred to the Infertility Unit of the Department of Obstetrics and Gynecology of the University of Milan and selected for IVF or ICSI between January 2001 and December 2002 were reviewed. Patient were included who previously had undergone laparoscopic excision of an endometriotic ovarian cyst, regardless of cyst dimensions. Specifically, inclusion criteria were: (i) previous laparoscopic enucleation of an endometriotic ovarian monolateral cyst; (ii) availability of a detailed description of the surgical intervention; and (iii) age <40 years at the time of ovarian stimulation. Exclusion criteria were: (i) enucleation of more than one cyst; (ii) coagulation of the internal layer of the endometrioma without excision of the cyst wall; (iii) subsequent intervention(s) for other ovarian cyst(s) in the same or the contralateral ovary; (iv) presence of ovarian cyst(s) at the time of ovarian stimulation; and (v) cancelled cycles due to hyper-response (serum estradiol level >4000 pg/ml and/or more than 20 follicles before hCG administration) or low response (echographic evidence of fewer than three follicles during ovarian stimulation). Approval for the study was obtained by the local Institution review board. All patients referred to the authors’ unit provided an informed consent for their clinical data to be used for research purposes.

Investigations
According to the protocol used, all patients who had previously undergone pelvic surgery were requested to provide a copy of the chart referring to their intervention(s). This protocol provided the possibility of obtaining exhaustive information on previous surgical procedure(s). The dimension and histology of the cysts were obtained from surgical and pathological evidence. A detailed ultrasonographic monitoring before and during IVF-ICSI cycles was systematically applied and recorded. In particular, patients routinely underwent transvaginal ultrasound within day 8 of the cycle before ovulation stimulation. The ovarian volume was calculated as $6 \cdot \frac{1}{2}$ diameter, where the diameter was taken as the mean of the height, width and depth of the ovary. Moreover, the number and dimension of all follicles on the day of hCG administration were always available. The diameters of the follicles were calculated as the mean of three perpendicular diameters. All data are recorded separately for the two ovaries. hCG was administered when two or more leading follicles had a mean diameter >18 mm. If three or more embryos were available at the time of embryo transfer, the patients was informed about the severe risks associated with multiple gestation and offered the choice of transferring either two or three embryos. Clinical pregnancy was defined as the ultrasonographic demonstration of an intrauterine gestational sac 4 weeks after embryo transfer.

Statistical analysis
Analysis of the data was performed using the Statistics Package for Social Sciences (SPSS, Chicago, IL, USA). Data are expressed as mean ± SD. A paired Student’s t-test was used to investigate differences between operated and contralateral ovaries. Differences were confirmed using non-parametric Wilcoxon rank test for paired data. A P-value < 0.05 was considered statistically significant.

Results
A total of 32 patients and 46 cycles fulfilled the inclusion and exclusion criteria. Characteristics of the patients and cycles are shown in Tables I and II respectively. The number of follicles >15 mm was significantly reduced in the operated ovary when compared with the contralateral ovary (Figure 1). Specifically, the mean number of dominant follicles was 4.2 ± 2.5 in the control ovary and 2.0 ± 1.5 in the previously operated ovary ($P < 0.001$), a mean reduction of 53% [95% confidence interval (CI) 35–72%]. The number of dominant follicles was higher in the operated ovary compared with the contralateral ovary in only seven cycles (15%). The basal volume of the operated gonads was also statistically significantly diminished, although this reduction was less relevant. The basal volumes of the operated and contralateral ovaries were 7.4 ± 5.5 and 9.5 ± 6.5 cm$^3$ respectively ($P = 0.02$), a mean reduction of 23% (95% CI 3–42%). Since it could be hypothesized that the use of data per cycle rather than per patient might have resulted in the repeated inclusion of women with more serious ovarian damage, the analysis was repeated including only the first cycle for each patient. This analysis led to extremely similar results.

Table I. Characteristics of the 32 patients selected for IVF who had previously undergone monolateral ovarian cystectomy

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the time of surgery</td>
<td></td>
</tr>
<tr>
<td>Age (years)*</td>
<td>32.2 ± 3.7</td>
</tr>
<tr>
<td>Ovarian side</td>
<td></td>
</tr>
<tr>
<td>Left (n)</td>
<td>22 (69)</td>
</tr>
<tr>
<td>Right (n)</td>
<td>10 (31)</td>
</tr>
<tr>
<td>Cyst diameter (cm)*</td>
<td>3.9 ± 1.5</td>
</tr>
<tr>
<td>ASRM classification</td>
<td></td>
</tr>
<tr>
<td>Stage III (n)</td>
<td>21 (66)</td>
</tr>
<tr>
<td>Stage IV (n)</td>
<td>11 (34)</td>
</tr>
<tr>
<td>At the time of ovarian stimulation</td>
<td></td>
</tr>
<tr>
<td>Age (years)*</td>
<td>34.6 ± 3.2</td>
</tr>
<tr>
<td>Duration of infertility (years)*</td>
<td>5.4 ± 3.4</td>
</tr>
<tr>
<td>Time since ovarian surgery (years)*</td>
<td>2.4 ± 1.7</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)*</td>
<td>20.6 ± 3.2</td>
</tr>
<tr>
<td>FSH on day 2–3 of cycle (mIU/ml)*</td>
<td>7.2 ± 2.6</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. 
Values in parentheses are percentages. 
BMI = body mass index.

Figure 1. Number of follicles >15 mm on the day of hCG administration in the operated and in the contralateral intact ovary. Values are mean ± SD. *$P < 0.001$. 

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Specifically, the mean number of dominant follicles was $4.0 \pm 2.7$ in the control ovary and $1.8 \pm 1.4$ in the previously operated ovary ($P < 0.001$), while the basal volumes of the intact and operated gonads were $10.0 \pm 7.4$ and $7.7 \pm 6.0 \text{ cm}^3$ respectively ($P = 0.08$).

The basal volume of the ovaries before stimulation and the number of follicles $>15 \text{ mm}$ at the time of hCG administration during ovarian stimulation was also evaluated according to the dimension of the excised cyst (Table III). To investigate the relevance of the diameter of the cyst, a cut-off of $3 \text{ cm}$ was chosen as previously described (Canis et al., 2001). Of note, the diameter of the cyst did not appear to play a relevant role in determining a lower number of dominant follicles, as the reduction in the number of follicles $>15 \text{ mm}$ resulted similarly in patients who were operated on for ovarian cysts $=3 \text{ cm}$ and $>3 \text{ cm}$ (Table III). Similar conclusions could be drawn when considering the basal volume of the ovaries. Finally, data were also analysed according to the gynaecological surgery unit where surgery was performed and the side of the operated ovary. Neither variable appeared to be a relevant factor (data not shown).

### Discussion

In the present study, it was shown that the functional reserve of previously operated ovaries is significantly impaired when compared with the contralateral intact gonads. Specifically, the number of follicles with a mean diameter $>15 \text{ mm}$ after ovarian stimulation was reduced by approximately $53\%$ (95% CI 35–72%). A reduction was also observed in the basal volume of the operated ovary, but this was less marked than the fall in the number of follicles, thus supporting the concept that the reduced response to ovarian stimulation cannot be merely ascribed to a reduction in the ovarian tissue.

The results observed in the present study were in perfect accord with those recently reported by others (Nargund et al., 1996; Ho et al., 2002), all of whom noted a marked reduction in the number of both dominant follicles and retrieved oocytes in the operated ovary. In contrast, when using a similar retrospective study design, others failed to observe this difference (Loh et al., 1999; Donnez et al., 2001). The results from these four studies are summarized in Table IV. There are at least two major reasons that might explain the discrepancies between the present results and those observed in these two recent studies. In the first of these studies (Donnez et al., 2001), the specific focus was on patients with endometriomas who were operated on using a specific and less frequently employed surgical technique comprising laser vaporization of the internal layer of the cyst wall. It might be speculated that this technique would be less deleterious for the residual normal ovarian cortex. The results from randomized trials comparing laser vaporization and stripping enucleation for the treatment of endometrioma are warranted to draw definitive conclusions on this topic. In the second study (Loh et al., 1999), the extremely small sample size (12 cycles) used was insufficient to evaluate
reliably whether ovarian reserve was impaired in the operated gonad. Of note, in the latter study the response in natural cycles and in stimulation cycles for non-IVF procedures was also analysed. Specifically, these authors reported a statistically significant reduction in terms of number of follicles in the operated ovary among the 11 patients who were monitored during a natural cycle and in 39 clomiphene citrate-stimulated cycles (Loh et al., 1999). Overall, it may be concluded that the results of the present study, and other currently available data on this topic, support the idea that laparoscopic excision of endometriotic ovarian cysts is associated with a significant reduction in the functional reserve of the operated ovary. This aspect may be of particular relevance for patients who undergo surgery for bilateral ovarian cysts.

The causes of the reduced ovarian reserve can only be hypothesized. At present, there are no definitive data available to clarify whether the damage is related to the surgical procedure and/or to the previous presence of a cyst. Indeed, it cannot be excluded that the cyst may damage the surrounding ovarian tissue per se. In this regard, based on histological analysis, it has been reported recently that the ovarian tissue surrounding the cyst wall in endometriomas is morphologically altered and possibly not functional, thus suggesting that a functional disruption may already be present before surgery (Muzii et al., 2002). Histological alterations involving endometriomas did not appear to be present when the ovarian cortex surrounding mature teratomas and cystoadenomas was studied (Maneschi et al., 1993; Muzii et al., 2002). In contrast, there are some findings which indicate that the surgical enucleation might, at least in part, be responsible for the injury. In particular, the presence of recognizable ovarian tissue adjacent to the wall of the enucleated endometriotic cyst has been shown in a consistent proportion of specimens (Hachisuga and Kawarabayashi, 2002; Muzii et al., 2003). Moreover, as cited above, it was reported that the ovarian reserve in the operated and in the intact ovary was similar when patients were treated with laser vaporization of the cyst wall (Donnez et al., 2001). The same group also documented that the overall response to gonadotrophin stimulation did not seem to be impaired using this technique (Wyns and Donnez, 2003). If confirmed, the finding that the damage may depend upon the surgical technique employed would support an iatrogenic origin of the injury. In this context, potential deleterious mechanisms are the accidental removal of a consistent amount of ovarian tissue during cystectomy and the damage that may be inflicted on the ovarian stroma and vascularization by both surgery-related local inflammation and electrosurgical coagulation during haemostasis. Of note, results from the present study suggest that the damage could not be ascribed merely to the amount of ovarian tissue removed during surgery as the decrease in basal volume of the operated ovary was less pronounced than the reduction in the number of follicles developing during ovarian stimulation. However, this finding needs to be confirmed in future prospective studies.

In conclusion, the results from the present study support the following observations: (i) the excision of ovarian endometriotic cysts is associated with a significant reduction in ovarian reserve; and (ii) the damage could not be merely ascribed to the amount of ovarian tissue removed during surgery. Further studies are required to clarify whether the injury is related to the surgical procedure per se or to the previous presence of an endometriotic cyst.

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References


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