Rate of severe ovarian damage following surgery for endometriomas

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BACKGROUND: There is growing and consistent evidence showing that ovarian reserve is affected following surgical excision of ovarian endometriomas. Of particular concern is the risk of severe ovarian damage leading to unresponsiveness to ovarian hyperstimulation. In this study, we aimed to determine the rate of this complication.

METHODS: Ninety-three women underwent surgery for monolateral endometriomas were recruited. Patients who underwent IVF were selected and, in all cases, follicular growth was monitored by serial transvaginal ultrasonography. The main outcome measure was the rate of ovaries remaining silent when stimulated after surgery for endometriomas.

RESULTS: Absence of follicular growth was observed in 12 operated ovaries although this event never occurred in the contralateral gonad (\(P < 0.001\)). The frequency (95% confidence interval) of severe ovarian damage following surgery was 13% (7–21%).

CONCLUSIONS: Severe ovarian damage, occurring in gonads operated on for ovarian endometriomas, is not a rare event.

Key words: endometriosis / endometrioma / ovarian failure / surgery / IVF

Introduction

There is growing and consistent evidence showing that ovarian reserve is affected following surgical excision of ovarian endometriomas (Gupta et al., 2006; Garcia-Velasco and Somigliana, 2009; Tsoumpou et al., 2009). Two main pathogenic mechanisms may explain this injury. Firstly, the presence of a cyst may per se distort and damage the adjacent ovarian tissue. Evidence from pathological specimens clearly supports this possibility (Maneschi et al., 1993). Moreover, responsiveness to ovarian stimulation in unoperated ovaries carrying an endometrioma is partially reduced (Somigliana et al., 2006) and two recent studies documented a lower rate of spontaneous ovulation in unoperated ovaries carrying an endometrioma (Horikawa et al., 2008; Benaglia et al., 2009). Secondly, there is also evidence supporting a surgery-mediated damage (Horikawa et al., 2008; Chang et al., 2009). A potential deleterious mechanism of surgery is the accidental removal of a significant amount of healthy ovarian tissue during cystectomy (Hachisuga and Kawarabayashi, 2002; Muzii et al., 2002), a surgery-related local inflammation following the intervention and a vascular compromise due to electrosurgical coagulation (Garcia-Velasco and Somigliana, 2009).

Regardless of the specific mechanisms leading to the damage, a crucial point is the magnitude of this deleterious effect. This is of relevance from a clinical point of view. A mild impairment of ovarian reserve is expected to be clinically unremarkable whereas a severe damage may compromise folliculogenesis and, ultimately, the capacity of the ovary to release competent oocytes. In this context, ovarian responsiveness during hyperstimulation may represent the best surrogate marker for ovarian reserve (Garcia-Velasco and Somigliana, 2009). Studies evaluating this outcome in women who underwent monolateral excision of endometriotic cysts generally documented a relevant reduction in follicular development in operated gonads when compared with contralateral intact ovaries (Table I; Loh et al., 1999; Ho et al., 2002; Somigliana et al., 2003; Ragni et al., 2005; Alborzi et al., 2007; Duru et al., 2007). The clinical relevance of this finding remains however debated (Gupta et al., 2006; Tsoumpou et al., 2009). Indeed, a recent metaanalysis confirmed a reduced responsiveness to hyperstimulation in women with ovarian endometriosis but failed to detect a detrimental impact on the rate of treatment success. The Odds Ratio (OR) [95% Confidence Interval (CI)] for pregnancy was 1.07 (0.63–1.31) (Gupta et al., 2006).

In our opinion, albeit somewhat reassuring, this data requires more in-depth reflection. Of relevance here is that endometriomas are monolateral in the majority (72–81%) of women with the disease (Vercellini et al., 1998; Prefumo et al., 2002; Al-Fozan and Touandi, 2003). In these cases, the contralateral intact ovary may adequately...
Table I Studies comparing the number of follicles in the operated and in the contralateral non-operated ovaries during ovarian hyperstimulation for IVF.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of cycles</th>
<th>Operated ovary</th>
<th>Control ovary</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loh et al.</td>
<td>12</td>
<td>4.6*</td>
<td>3.6*</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ho et al.</td>
<td>38</td>
<td>1.9 ± 1.5</td>
<td>3.3 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Somigliana et al.</td>
<td>46</td>
<td>2.0 ± 1.5</td>
<td>4.2 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rago et al.</td>
<td>38</td>
<td>1.8 ± 1.8</td>
<td>4.5 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duru et al.</td>
<td>28</td>
<td>3.1 ± 1.8</td>
<td>4.4 ± 1.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Duru et al.</td>
<td>10</td>
<td>2.1 ± 1.4</td>
<td>5.0 ± 2.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Alborzi et al.</td>
<td>70</td>
<td>3.2 ± 1.1</td>
<td>3.2 ± 1.7</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Data are expressed as Mean ± SD. *SD was not reported. n.s., not significant; LPS, laparoscopy; LPT, laparotomy. Only studies referring to surgical excision of endometriomas were included.

compensate for the reduced function of the affected one. The endometrioma-related damage to ovarian reserve may thus become clinically evident in women with bilateral disease. In line with this view, studies investigating IVF outcome in women operated for bilateral ovarian endometriomas have documented a detrimental impact on pregnancy rate (Esinhin et al., 2006; Somigliana et al., 2008). In a recent study by our group on this issue, the OR (95% CI) for pregnancy and delivery in women with bilateral disease was 0.34 (0.12–0.92) and 0.23 (0.07–0.78), respectively, compared with controls (Somigliana et al., 2008). Furthermore, some cases of post-surgical ovarian failure following surgery for bilateral endometriomas have been described (Busacca et al., 2006; Di Prospero and Micucci, 2009). The frequency of this dreadful complication has been estimated to be 2.4% (Busacca et al., 2006) but this data warrants confirmation.

In order to further investigate this issue, we set up a retrospective study on women who have been operated for monolateral endometriomas. The primary aim of the study was to determine the rate of ovaries remaining silent when stimulated.

Materials and Methods

Data from IVF–ICSI cycles performed at the Infertility Unit of the Department of Obstetrics and Gynecology of the Ospedale Maggiore Policlinico, Mangiagalli and Regina Elena between January 2005 and December 2008 were reviewed. Inclusion criteria were as follows: (i) previous laparoscopic excision of one or more unilateral endometriotic ovarian cysts (women operated twice due to recurrences were excluded), (ii) No other adnexal interventions, (iii) availability of a detailed description of the surgical intervention, (iv) age ≤40 years at the time of ovarian stimulation, (v) More than three follicles with a mean diameter ≥11 mm at the time of hCG administration. This latter criterion was used to exclude women whose ovarian reserve was compromised for reasons unrelated to the presence of ovarian endometriomas. Only one cycle per patient was considered. Specifically, data exclusively refer to the first cycle performed in our Unit after surgery (women performing cycles prior to surgery and those who underwent cycles after surgery in other centers were not excluded). The presence of a recurrent endometrioma at the time of IVF was not an exclusion criterion. Patients were selected regardless of the period of time between surgery and IVF cycle. Information regarding surgical technique as well as dimension and histology of the cyst were obtained from surgical, ecographic and pathological records. All laparoscopic operations were performed using the stripping technique. Approval for the study was obtained by the local Institutional Review Board. All patients referred to our Unit give their informed consent to the use of their clinical data for research purposes.

The pharmacological regimen for controlled ovarian hyperstimulation used was the long protocol with daily 0.1 mg GnRH agonist (Triptoreline, Decapeptyl®, Ipsen Pharma, Pavia, Italy) combined with the use of recombinant FSH (Gonal-F®, Serono Laboratories, Inc., Rome, Italy). Dosage of recombinant FSH prescribed was decided based on age, hormonal tests, ultrasound characteristics of the ovaries and results from previous pharmacological ovarian hyperstimulation cycles. In all cases, follicular growth was monitored by serial transvaginal ultrasonography. Ovulation was triggered by administering 250 μg hCG (Ovitrelle®, Serono Laboratories, Inc., Rome, Italy) when two or more leading follicles had mean diameter ≥18 mm. On the day of hCG administration, a detailed transvaginal ultrasound scan was performed to record number and diameter of all follicles with a mean diameter >10 mm. This information was recorded separately for the two ovaries. Transvaginal oocyte retrieval was performed 36 h after hCG administration and transfer of the embryos 2–3 days later.

The presence of a recurrent endometrioma was diagnosed when a round-shaped cystic mass with a minimum diameter of 10 mm, with thick walls, regular margins, homogeneous low echogenic fluid content with scattered internal echoes and without papillary proliferations was observed (Mais et al., 1993). The presence of the lesion had to be confirmed at least twice at two months’ interval. Diameter of follicles was calculated as the mean of three perpendicular diameters. Clinical pregnancy was defined as the ultrasonographic demonstration of an intrauterine gestational sac 4 weeks after embryo transfer.

Ovaries were considered severely damaged when no follicles with a mean diameter ≥11 mm were observed at the time of hCG administration. Analysis of the data were performed using the Statistical Package for the Social Sciences (SPSS 16.0, Chicago, IL, USA). A binomial distribution model was used to calculate the 95% CI of proportions. Numbers of follicles per ovary were compared using paired Student t-test and confirmed using non-parametric Wilcoxon test for paired data. The proportion of silent gonads was compared using a χ² test with one degree of freedom. Probability values <0.05 were considered statistically significant.

Results

Ninety-three women were eligible for the study. Clinical characteristics and cycle outcome of these patients are shown in Tables II and III. Recurrence of endometriomas at the time of IVF was observed in 43 (46%) women (ipsilateral in 19 cases, contralateral in 17 cases and bilateral in 7 cases). The mean ± SD diameter of the recurrent lesions was 22 ± 9 mm.

The mean ± SD number of follicles in the operated and contralateral gonads was 3.4 ± 2.4 and 5.7 ± 3.0, respectively (Paired Student t-test, P<0.001). This difference corresponded to a mean 42% reduction in the number of follicles (95% CI: 28–58%).
Absence of follicular growth was observed in 12 operated ovaries. This event never occurred in the contralateral gonad (Fisher’s exact test, \( P < 0.001 \)). The frequency (95% CI) of non-responsive ovaries following surgery was 13% (7–21%). A representative case is illustrated in Fig. 1. Six of these 12 women underwent a second IVF cycle. Absence of follicular growth in the operated ovaries was confirmed in all of them. Clinical characteristics and cycle outcome in these 12 cases were compared with those in the remaining 81 women. None of the considered variables was found to differ significantly by univariate and logistic regression analyses (data not shown).

Absence of follicular growth was observed in 4/43 women with endometrioma recurrence (9%, 95% CI: 3–20%) and in 8/50 in those without endometriotic cyst recurrence (16%, 95% CI: 8–28%; Fisher’s exact test, \( P = 0.37 \)).

### Discussion

On the basis of our findings, the rate of severe ovarian damage following surgery for endometriomas was 13% (95% CI: 7–21%). To our knowledge, this is the first report specifically aimed at clarifying this issue. Of relevance here is that this result is in line with a recent paper reporting a 2.4% (95% CI: 0.5–6.8) rate of post-surgical ovarian failure in women who were operated for bilateral ovarian endometriomas (Busacca et al., 2006). Indeed, if the risk of severe damage is considered independent for the two ovaries, the expected rate of ovarian failure following surgery based on our results would be 1.7% (0.132 ± 0.017).

A first needed consideration is that the present study aimed to clarify the impact of endometriomas and their removal on ovarian reserve. It was not designed to determine the impact of this pathology on the pregnancy rate in IVF. The reduced responsiveness of affected ovaries cannot indeed be used to infer a deleterious impact on the rate of success of the technique. In fact, as mentioned earlier, a recent metanalysis on this point reported a decreased folliculogenesis in women with ovarian endometriomas but failed to document an impact on pregnancy rate (Gupta et al., 2006). In this regard, it is important to remark that the pregnancy rate per transfer observed

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**Table II** Baseline clinical characteristics of the 93 selected patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD or number (%)</th>
</tr>
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<tbody>
<tr>
<td>At the time of surgery</td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>31.4 ± 3.4</td>
</tr>
<tr>
<td>Diameter of the excised cyst (cm)</td>
<td>4.2 ± 1.8</td>
</tr>
<tr>
<td>At the time of IVF</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.4 ± 3.4</td>
</tr>
<tr>
<td>Time since ovarian surgery (years)</td>
<td>3.0 ± 2.4</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>3.7 ± 2.2</td>
</tr>
<tr>
<td>Previous IVF cycles*</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.9 ± 3.4</td>
</tr>
<tr>
<td>Day 3 serum FSH (IU/ml)</td>
<td>8.6 ± 3.7</td>
</tr>
</tbody>
</table>

*Previous IVF cycles included cycles before and after surgery.

**Table III** IVF cycle outcome.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD (n = 93) or number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of stimulation (days)</td>
<td>11.1 ± 2.0</td>
</tr>
<tr>
<td>Total rFSH (IU)</td>
<td>3196 ± 1372</td>
</tr>
<tr>
<td>Number of oocytes retrieved</td>
<td>5.9 ± 3.3</td>
</tr>
<tr>
<td>Number of embryos transferred</td>
<td>2.2 ± 0.7</td>
</tr>
<tr>
<td>Number (%) of transfers not performed</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>Number of clinical pregnancies and PR per transfer</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>Number of implanted embryos and implantation rate</td>
<td>20 (12%)</td>
</tr>
</tbody>
</table>

rFSH, recombinant FSH; PR, pregnancy rate.
Ovarian damage and surgery

in our cohort was 19%, which is lower compared with the success rate observed in our Unit for other indications during the same study period (25% per transfer). Reasons to explain this lower rate of success are unknown. At least, we cannot exclude that it is just a random effect. In fact, the calculated 95% CI based on a binomial distribution model for this 19% varied between 11 and 28% (thus including the 25% rate of success observed for other indications).

Some limitations of the study should be considered. First of all, failure to detect follicular growth during ovarian hyperstimulation cannot be used to state that ovarian reserve is definitively compromised. Some follicular growth may be observed in a subsequent cycle or, alternatively, higher doses of gonadotrophins may result in some ovarian response. However, we failed to observe follicular growth in all the affected patients who underwent a second IVF cycle. Moreover, as shown in Table III, the amount of gonadotrophins used in our series was quite high. Finally, the overall conclusions of our study are not refuted by this potential criticism since the magnitude of the damage would remain of utmost importance even if some follicular growth would be obtained using higher gonadotrophins doses.

Second, the studied cases may not properly reflect the entire population of women with endometriomas. In fact, we selected infertile women who failed to get pregnant following surgery. Inferences can thus be made only from this specific group. In this context, it is also important to note that fertility and monolateral damage to ovarian reserve may be considered two separate concepts. One may also speculate that, in women with monolateral disease, it would be even better to allow ovulation to occur in the contralateral ovary. Endometriomas are typically associated with peri-ovarian and peritu-beral adhesions that are known to recur frequently and rapidly after surgery and that may interfere with sperm migration, ovum retrieval, fertilization and embryo transportation. Overall, even if a selection bias has to be considered, we do not believe that it may have a crucial impact on our results. The above-mentioned similarity of our results with those reported by Busacca et al. (2006) who used a different study design tends to support this assumption. Finally, even if confirmation of our results in an unselected population would be of great interest, it must be pointed out that it would be unethical to perform ovarian hyperstimulation in an unselected group of consecutive women operated for monolateral endometriomas with the exclusive aim to identify women with a silent ovary.

A further limitation of the study is that we were unable to identify risk factors for this event. The relatively small number of cases included and the retrospective study design do not allow us to perform reliable analyses aimed at resolving this issue. This is a crucial aspect because the identification of causes leading to this insult may allow us to establish preventive strategies. Of particular relevance here is the potential impact of the size and location of the endometrioma and the specific type of surgery performed (puncture/aspiration, ablation, bipolar or laser, excision in one or two stepsurgery) since all these can explain the ovarian damage. In this regard, and as mentioned in the introduction, it has to be pointed out that available scientific evidence supports different pathogenic mechanisms for the ovarian damage. First, the development of an endometrioma may affect ovarian reserve per se. Using pathological sections of the ovarian cortex surrounding ovarian benign neoplasms, Maneschi et al. (1993) found a reduced follicular number and activity antecedent to surgery in endometriomas when compared with teratomas or benign cystadenomas. Moreover, in unoperated women with unilateral disease, responsiveness to ovarian hyperstimulation is reduced in the affected gonad by about 25% (Somigliana et al., 2006) and spontaneous ovulation occurs more frequently in the intact gonad with a ratio of 2:1 (Horikawa et al., 2008; Benaglia et al., 2009). Second, surgery may also injure the ovarian reserve. Given the above-mentioned cases of post-surgical ovarian failure occurring soon after the intervention for bilateral endometriomas (Busacca et al., 2006; Di Prospero and Micucci, 2009), this aspect appears to be of utmost importance. A potential deleterious mechanism of surgery is the accidental removal of a consistent amount of ovarian tissue during cysctectomy. Conservative laparoscopic cystectomy in cases with well defined ovarian capsule (e.g. teratomas and benign cystademo-nas) very seldom implies removal of healthy ovarian tissue (Muzii et al., 2002; Hachisuga and Kawarabayashi, 2002). In contrast, primordial follicles are found in more than 50% of the endometriomas removed, probably due to the presence of 'pseudocapsule' which is, in fact, invaginated ovarian cortex (Brosens et al., 1996). Finally, the damage inflicted by surgery may be due not only to stripping and removal of healthy ovarian tissue, but also to the local inflammation and/or vascular injury secondary to electrosurgical coagulation (Wu et al., 2003; Garcia-Velasco and Somigliana, 2009).

Finally, the inclusion of women with recurrent endometriomas in our series may also be a possible concern. In this regard, a consistent proportion of women in our series had recurrences (46%). This may reflect a selection bias since we cannot exclude that this rate may be partly inflated in our study by the fact that we specifically selected infertile women for whom surgery has failed. In particular, we may have recruited women who received an inappropriate or incomplete surgery. On the other hand, it has to be underlined that the rate of recurrences observed in our study is in line with the 40–50% cumulative recurrence rate at 5 years reported in a recent metaanalysis on this point (Guo, 2009). This tends to exclude a selection bias.

A possible criticism to the inclusion of recurrent cases is that, in fact, we cannot separate whether the weaker response to ovarian stimulation is due to the previous surgery or to the new endome-trioma. We however decided to present data regardless of the presence of a recurrent endometrioma for at least one main reason: over the last few years, there is cumulative evidence supporting the view that ovarian endometriomas may develop from ovulatory events. The transformation of a corpus luteum into an endometrioma has been recently documented in 11 cases by our group (Vercellini et al., 2009). In the past, Jain and Dalton (1999) also reported the transformation of a follicle into an endometrioma in 12 cases. Moreover, oral contraceptives have been shown to be extremely effective in preventing endometriomas recurrences (Vercellini et al., 2008; Serrachioliet al., 2009), thus indirectly supporting a critical role of ovulation in the pathogenesis of these cysts. On the other hand, it is noteworthy that the rate of ovulation may be reduced in a damaged ovary (Candiani et al., 2005). The contralateral intact gonad compensates for this function in most cases. On this basis, it may be speculated that a damaged ovary may be at lower risk of recurrences than an intact one since the injury may lead to a reduction in the number of ovulatory events. Excluding cases with recurrences would have thus exposed our results to the risk of over-estimation of the real rate of silent ovaries. Notably, although the difference did not reach statistical significance, there is a trend for a
higher rate of silent ovaries when considering exclusively the cases without recurrences (16 versus 9%).

In conclusion, severe ovarian damage may occur in gonads operated for ovarian endometriomas. Even if our results would need to be confirmed in an unselected population, they at least allow us to state that this event is not rare. At present, there is evidence supporting that this damage may both precede and follow surgery, but the relative importance of these two pathogenic mechanisms has yet to be fully clarified. This point is of utmost relevance since the demonstration that surgery may be mainly responsible for the damage would strongly caution against systematic surgical removal of these lesions. In particular, a more conservative attitude would have to be considered in women with bilateral cysts, in those with small asymptomatic lesions and in those selected for IVF. Finally, our findings also emphasize that there is an obvious need to develop effective therapeutic strategies aimed at preventing the development of endometriomas or their recurrence.

References


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