IVF–ICSI outcome in women operated on for bilateral endometriomas

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BACKGROUND: The influence of previous conservative surgery for endometriomas on IVF–ICSI outcome is debated. Conflicting information emerging from the literature may be consequent to the fact that endometriomas are mostly monolateral. The contralateral intact ovary may adequately supply for the reduced function of the affected one. To clarify this point, we assess IVF–ICSI outcome in women operated on for bilateral endometriomas.

METHODS: Women selected for IVF–ICSI cycles who previously underwent bilateral endometriomas cystectomy were matched (1:2) for age and study period with patients who did not undergo prior ovarian surgery. RESULTS: Sixty-eight cases and 136 controls were recruited. Women operated on for bilateral endometriotic ovarian cysts had a higher withdrawal rate for poor response (P < 0.001). In these patients, despite the use of higher doses of gonadotrophins, the number of follicles (P = 0.006), oocytes retrieved (P = 0.024) and embryos obtained (P = 0.024) were significantly lower. The clinical pregnancy rate per started cycle in cases and controls was 7% and 19% (P = 0.037) and the delivery rate per started cycle was 4% and 17%, respectively (P = 0.013). CONCLUSIONS: IVF outcome is significantly impaired in women operated on for bilateral ovarian endometriomas.

Keywords: cystectomy; endometriosis; endometriomas; IVF; ovarian reserve

Introduction

The influence of previous conservative surgery for endometriotic ovarian cysts on IVF–ICSI outcome is a matter of debate (Somigliana et al., 2006a). To our knowledge, 11 studies specifically investigated this issue, but conclusions were controversial. A reduced ovarian responsiveness to hyperstimulation was reported in six studies (Al-Azemi et al., 2000; Geber et al., 2002; Pabuccu et al., 2004; Loo et al., 2005; Suzuki et al., 2005; Esinler et al., 2006) while the remainder failed to document a detrimental effect in this regard (Canis et al., 2001; Donnez et al., 2001; Marconi et al., 2002; Wong et al., 2004; Nakagawa et al., 2007). A recent meta-analysis on this issue supports a reduced responsiveness in operated patients (Gupta et al., 2006). Conversely, there is a general consensus that the pregnancy rate is not significantly affected (Gupta et al., 2006; Somigliana et al., 2006a).

In this study, we have hypothesized that a key reason for explaining conflicting information on this point may be the fact that endometriomas are mostly monolateral. Both gonads are indeed affected only in 19–28% of cases (Vercellini et al., 1998; Prefumo et al., 2002; Al-Fozan and Toulandi, 2003). It may be speculated that, in women with monolateral disease, the contralateral intact ovary may adequately compensate for the reduced function of the affected one. If this hypothesis is true, the observation that IVF–ICSI outcome is not severely compromised in women operated for endometriomas in general should not be used to conclude that the function of the ovaries is not damaged after surgery. In line with our hypothesis, recent evidence suggests that women operated on for bilateral endometriotic ovarian cysts may be at risk of severe ovarian function impairment (Busacca et al., 2006; Esinler et al., 2006). Evidence on this point is, however, scanty. To clarify this issue, we have set up a large retrospective case–control study comparing patients operated on for bilateral endometriomas to those who had not undergone previous ovarian surgery.

Materials and Methods

Data from patients selected for 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 2002 and March 2007 were reviewed. All women who referred to the investigators’ unit routinely provided an informed consent for their clinical data to be used for research purposes. Local Institutional Review Board approval was obtained.
Inclusion criteria of cases were as follows: (i) previous laparotomic and/or laparoscopic enucleation of bilateral ovarian endometriomas (patients whose ovaries were operated separately in two different interventions were thus included); (ii) availability of a detailed description of the surgical intervention (in our unit, patients were systematically requested to provide a copy of the chart referring to their previous gynaecological interventions); (iii) histopathologically confirmed diagnosis of endometriomas and (iv) age ≤40 years at the time of IVF–ICSI cycle. Patients were included in the study only if they underwent stripping of the endometrioma. Cases undergoing drainage and coagulation of the cyst were excluded. Patients were included even if cyst enucleation in the two gonads was performed in two distinct surgical interventions. Patients who suffered from ovarian recurrence of disease at the time of the cycle were not excluded from the study group.

The control group consisted of patients who did not undergo prior ovarian surgery and did not have any ultrasonographic sign of endometriotic and/or non-endometriotic ovarian cysts at the time of the cycle. Controls underwent the IVF–ICSI attempt in the same time period of the cases and they were matched with the cystectomized patients by age (±1 year) at the time of the cycle. Two controls were matched to each case. Specifically, they were recruited by identifying the nearest patient in a computerized IVF–ICSI database with the appropriate characteristics preceding and following each index case.

Exclusion criteria for both cases and controls were as follows: (i) previous ovarian surgery for endometrioma in only one gonad; (ii) previous ovarian surgery for non-endometriotic benign ovarian cysts and/or ovarian malignancy; (iii) previous mono/bilateral adnexectomy; (iv) use of cryostored spermatozoon and (v) previous IVF–ICSI cycles. Patients who suffered from extra-ovarian endometriosis were not excluded from the study. Patients of both groups were included only for their first IVF–ICSI attempt.

Day 3 serum FSH was routinely requested before starting a treatment cycle in our unit. In operated women, the included value was always obtained after the last surgery. The policy of our unit for the first treatment cycle is to use a protocol of stimulation starting GnRH agonist (Decapeptyl 0.1 mg, Ipsen, Rome, Italy) in the midluteal phase following by recombinant FSH (Gonal F, Serono S.P.A., Rome, Italy). Patients routinely underwent transvaginal ultrasound within Day 8 of the cycle before ovarian stimulation. The presence of ovarian cysts is systematically recorded at this time. The dose of gonadotrophins was determined on an individual basis according to the age, Day 3 FSH value and echographic characteristics of the ovaries. The precise protocol of ultrasound monitoring during IVF–ICSI cycles in our unit is reported elsewhere in further detail (Somigliana et al., 2003). Briefly, patients underwent serial transvaginal ultrasound starting on Day 6 of ovarian hyperstimulation. When three or more leading follicles with a mean diameter >18 mm were visualized, 5000 IU of HCG (Gonasi HP, AMSA Srl, Rome, Italy) was administered i.m. The same day, the number and dimensions of all the follicles with a mean diameter ≥11 mm were recorded. Oocyte retrieval was performed transvaginally 36 h after the HCG injection. All the follicles with a diameter ≥11 mm were aspirated. Embryo transfer was performed 48–72 h after the oocyte collection. Clinical pregnancy was defined as the ultrasonographic demonstration of an intrauterine gestational sac 4 weeks after embryo transfer. The delivery rate referred to the birth of at least one healthy children.

Ovarian endometrioma recurrence 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 (Somigliana et al., 2006a). When more than one cyst was diagnosed, the diameter of the bigger one was recorded. The diameter of the follicles and the endometriomas was calculated as the mean of three perpendicular diameters.

Cycles were cancelled because of low or hyperovarian response. We defined as hyper-response a serum estradiol level greater than 4000 pg/ml and/or more than 20 follicles identified at ultrasound scan before HCG administration. Low response was defined by the echographic evidence of fewer than three follicles during ovarian hyperstimulation.

Analysis of the data was carried out with the Statistical Package for Social Sciences (SPSS 14.0, Chicago, IL, USA). Statistically significant differences were determined using unpaired Student’s t-test, Wilcoxon test for unpaired data or Fisher’s exact test as appropriate. A P-value of ≤0.05 was considered statistically significant. Clinical pregnancy rate was used as the primary outcome to calculate the sample size. We assumed as clinically relevant a three-fold reduction of the chances of pregnancy in the study group. On the basis of an expected pregnancy rate per starting cycle in the control group of 20% (corresponding to the mean rate of success of our unit) and setting type I and II error at 0.05 and 0.20, we calculate that the number of cases to be recruited using a matched 1:2 strategy was ~70.

Results

Sixty-eight patients underwent bilateral excision of ovarian endometriomas. The control group consisted of 136 patients. Surgical characteristics of the cases are illustrated in Table I. Mean ± SD time between first surgery for endometriosis and IVF–ICSI was 3.9 ± 3.4 years. Thirty-seven patients (54%) were free of recurrence at the time of IVF–ICSI. Of 31 patients with recurrence of endometriomas, the disease was monolateral in 22 cases and bilateral in the remainder (n = 9). The mean ± SD diameter of the recurrent cysts was 22 ± 9 mm.

Indication to IVF–ICSI cycles in the study group was endometriosis alone in 43 patients (63%) and mixed (endometriosis + male factor) in the remainder (n = 25, Table I. Patients operated for bilateral endometriomas: surgical characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%) or mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery (years)*</td>
<td>30.3 ± 4.5</td>
</tr>
<tr>
<td>Number of interventions</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43 (63%)</td>
</tr>
<tr>
<td>2</td>
<td>23 (34%)</td>
</tr>
<tr>
<td>3</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Surgical approach†</td>
<td></td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>76 (80%)</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>19 (20%)</td>
</tr>
<tr>
<td>Right ovary</td>
<td></td>
</tr>
<tr>
<td>Number of excised endometriomas:</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>64 (94%)</td>
</tr>
<tr>
<td>≥2</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Diameter of excised endometriomas (mm)‡</td>
<td>40 ± 16</td>
</tr>
<tr>
<td>Left ovary</td>
<td></td>
</tr>
<tr>
<td>Number of excised endometriomas</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>65 (96%)</td>
</tr>
<tr>
<td>≥2</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Diameter of excised endometriomas (mm)‡</td>
<td>43 ± 18</td>
</tr>
</tbody>
</table>

*If more than one surgical intervention was performed, age at first surgery is reported.
†Data refer to the total number of interventions performed (n = 95).
‡If more than one cyst was excised, the diameter of the bigger one is reported.
37%). Indications to treatment in the control group were as follows: male factor in 66 patients (48%), tubal-anatomic factor in 24 women (18%), unexplained infertility in 28 patients (21%) and mixed in the remainder (n = 18, 13%).

Baseline characteristics of recruited patients are shown in Table II. The age, BMI, duration of infertility and proportion of patients with primary infertility were similar in the study and in the control groups. Day 3 serum FSH and the proportion of patients with Day 3 serum FSH ≥ 12 IU/ml were remarkably greater in the cases.

Cycle characteristics are shown in Table III. Proportion of cancelled cycles in cases and controls were 26% (n = 18) and 21% (n = 28), respectively (P = 0.38). In contrast, the causes leading to cycle cancellation differed significantly. Poor ovarian response was higher in cases whereas hyper-response predominated in controls (Table III). In cases, dosage of gonadotrophin used was higher whereas number of follicles and number of retrieved oocytes were lower. No oocyte was retrieved in nine cases (18%) in the study group and in three cases (3%) in the control group (P = 0.002).

IVF and ICSI procedures were performed in 15 (37%) and 26 (63%) cycles in the study group and in 22 (21%) and 81 (79%) cycles in the control group, respectively (P = 0.09). The median (inter-quartile range) fertilization rate in the study and the control groups was 67% (50–100%) and 100% (67–100%), respectively (P = 0.06). The mean number of oocytes used and embryos obtained was significantly higher in the controls compared with the cases (Table III). The mean number of embryos transferred was, conversely, similar in the two groups. The clinical pregnancy rate and the delivery rate were significantly reduced in the study group (Table III). The odds ratios (OR) [95% confidence interval (CI)] for pregnancy and delivery in women affected were 0.34 (0.12–0.92) and 0.23 (0.07–0.78), respectively. The implantation rate was also significantly decreased in the study group (5/73, 7%) compared with the control group (33/202, 16%) (P = 0.048).

The same analyses were repeated within the study group comparing patients with (n = 31) and without endometrioma(s) recurrence (n = 37). For all variables considered, no significant difference was observed between the two groups (data not shown).

**Discussion**

In the present study, it was shown that the ovarian reserve of previously operated gonads is significantly damaged. Indeed,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 68)</th>
<th>Controls (n = 136)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.1 ± 3.8</td>
<td>34.2 ± 3.7</td>
<td>0.93</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.2 ± 3.3</td>
<td>21.7 ± 3.0</td>
<td>0.29</td>
</tr>
<tr>
<td>Previous pregnancies</td>
<td>13 (19%)</td>
<td>16 (12%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>3.1 ± 2.0</td>
<td>3.6 ± 2.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Day 3 FSH (IU/ml)</td>
<td>11.6 ± 6.5</td>
<td>7.6 ± 4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 3 FSH ≥ 12 IU/ml</td>
<td>26 (38%)</td>
<td>15 (11%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table III. Characteristics of the IVF–ICSI cycles in patients operated for bilateral endometriomas (cases) and controls.
et al. evaluated ICSI outcome in a small group of 23 cases using patients with tubal factor infertility as a control group. They reported a lower antral follicle count, a higher dosage of administered gonadotrophins and a lower number of retrieved oocytes. Conversely, Day 3 serum FSH did not significantly differ (Esinler et al., 2006). Busacca et al. highlighted that women operated on for bilateral ovarian endometriomas may be at increased risk of premature ovarian failure. Specifically, these authors reported this complication in 3 out of 126 patients, corresponding to a rate of 2.4% (95% CI: 0.6–6.8%). In all cases, ovarian failure occurred soon after surgery thus supporting a possible causal relationship (Busacca et al., 2006).

Further evidence supporting that ovarian reserve is damaged in operated gonads derives from studies investigating ovarian responsiveness in women who had been previously operated on for monolateral endometriomas. Valuable information may indeed be obtained from the comparison of the operated and unoperated ovaries of the same patients. This study design has been used in seven studies (Nargund et al., 1996; Loh et al., 1999; Donnez et al., 2001; Ho et al., 2002; Somigliana et al., 2003; Wong et al., 2004; Ragni et al., 2005). Overall, ovarian responsiveness appears to be significantly damaged in operated gonads (Somigliana et al., 2006a).

At present, the commonly accepted vision is that ovarian endometrioma and/or its surgical treatment may cause a quantitative but not a qualitative injury to ovarian reserve (Gupta et al., 2006; Somigliana et al., 2006a). In other words, even if the number of oocytes that can be retrieved from affected gonads is reduced, pregnancy rate is not affected. Results from our data do not support this conclusion. The pregnancy and delivery rates were indeed markedly reduced in women affected. The implantation rate was also decreased thus supporting a lower quality of the embryos obtained. Moreover, it is noteworthy that our study design may have led to underestimate the real difference between cases and controls. Indeed, the proportion of cancelled cycles due to hyper-response was 2% and 15% in the study and control groups, respectively. Thus, a significantly higher proportion of patients with a better prognosis were excluded from the control group. Our results are in contrast with those reported by Esinler et al. who employed a similar study design and failed to show significant differences in pregnancy rate between women with excised bilateral endometriomas and controls (Esinler et al., 2006); however, this study is underpowered to draw definite conclusions since the authors included only 23 cases in their analysis. Ragni et al. (2005) recently provided further evidence supporting the possibility that the pregnancy rate may be significantly hampered in women operated on for bilateral endometriomas. In this study, the authors highlighted that, in IVF–ICSI cycles, no oocytes could be retrieved from operated gonads in 29% of cases whereas this event occurred only in 3% of unoperated ovaries (Ragni et al., 2005).

Pathogenetic mechanisms leading to this insult have not been fully clarified. Surgery may directly affect ovarian reserve. A potential deleterious mechanism is the accidental removal of a consistent amount of ovarian tissue during cystectomy (Muzii et al., 2002). A further mechanism that may be responsible for the reduced ovarian reserve is represented by the damage that may be inflicted on the ovarian stroma and vascularization by both surgery-related local inflammation and electrosurgical coagulation during haemostasis. Adverse changes in ovarian artery blood flow have been reported following laparoscopic stripping (La Torre et al., 1998). Some evidence also supports that the injury may, at least in part, precede surgery. Using pathological sections of the ovarian cortex surrounding ovarian endometriomas, Maneschi et al. (1993) found a reduced number of follicles antecedent to surgery, suggesting that the disease may per se damage the ovary. Moreover, the presence of unoperated endometrioma is associated with a reduced responsiveness to gonadotrophins in IVF–ICSI cycles (Somigliana et al., 2006b). Finally, it cannot be excluded that the damage may also be determined by the superficial endometrioma implants and/or adhesions that typically surround affected ovaries. In this regard, Kaplan et al. demonstrated that, in the rabbit model, minimal superficial ovarian endometriosis impairs ovulation. This effect appeared to be mediated primarily through a mechanism related to periovular adhesions (Kaplan et al., 1989). Again, this detrimental effect would precede surgery and may persist after the intervention. In order to disentangle whether the damage documented in the present study precedes or follows surgery, a suitable control group would consist of women with unoperated bilateral endometriomas selected for IVF. In clinical practice, however, this is an exceedingly rare situation. Indeed, surgery represents the first-line treatment option in infertile women with endometriosis (Chapron et al., 2002) and, thus, women with unoperated bilateral endometriomas are rarely selected for IVF.

In conclusion, the results from the present study demonstrate that IVF–ICSI outcome is significantly impaired in women operated on for bilateral ovarian endometriomas. Future efforts should be aimed to develop therapeutic approaches able to prevent this damage.

References


Submitted on December 18, 2007; resubmitted on February 11, 2008; accepted on March 28, 2008