Endometriosis-associated infertility: surgery and IVF, a comprehensive therapeutic approach

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Abstract Infertility is a common problem presented by patients with endometriosis. At present, whichever treatment is chosen, half of patients with advanced stages of the disease will remain infertile afterwards. This observational study looked at the reproductive outcome achieved after treating a group of 825 patients aged between 20 and 40 years with endometriosis-associated infertility during the period 2001–2008. Of the 483 patients who had surgery as the primary option, 262 became pregnant (54.2%). Among the patients who did not become pregnant, 144 underwent 184 IVF cycles and 56 additional pregnancies were obtained (30.4% clinical pregnancy rate per retrieval). It is notable that, before any treatment, patients with endometriosis had a poorer ovarian reserve than the control group. The combined strategy of endoscopic surgery and subsequent IVF led to a total of 318 pregnancies, which represents a combined clinical pregnancy rate of 65.8%. This percentage is significantly higher than that obtained with surgery alone \( (P < 0.0001) \), with 173 patients who were not operated on and who went to IVF as the primary option \( (P < 0.0001) \) and with 169 patients who had no treatment and achieved 20 spontaneous pregnancies \( (P < 0.0001) \).

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Introduction

It is difficult to establish the real prevalence of endometriosis as it depends on the population under study. However, an estimate of data from women of childbearing age shows that around 10% may be affected by endometriosis, and the figure rises to above 40% among patients with symptoms such as dysmenorrhea, intermenstrual bleeding and dyspareunia (Meuleman et al., 2009; Practice Committee of the American Society of Reproductive Medicine, 2004). Nevertheless, in most studies, there is great heterogeneity relating to variables such as age and duration of infertility that makes it difficult to establish absolute figures for prevalence (Guo and Wang, 2006).
Epidemiological data suggest that the hypothesis of menstrual reflux is the origin of most cases of endometriosis (Viganò et al., 2004).

The association between endometriosis and infertility is especially evident for advanced stages of the disease. There are many reasons why endometriosis might compromise fertility but they are basically connected with ovulatory abnormalities and distorted pelvic anatomy (Gupta et al., 2008). Autoimmune disorders have also been implicated in the pathogenesis and possible association between endometriosis and periodontal disease (Kavoussi et al., 2009). A number of studies have shown the possibility of spontaneous pregnancy after 1 year of follow-up; in cases of mild endometriosis, this varies between 17% and 22% (Marcoux et al., 1997; Parazzini, 1999) and does not exceed 3% in severe cases (Adamson and Pasta, 1994).

For definitive diagnosis of endometriosis, laparoscopy has become the gold standard (Practice Committee of the American Society of Reproductive Medicine, 2004; Royal College of Obstetricians and Gynecologists, 2006), although, in the last decade, ultrasound diagnosis has made considerable progress and now plays an important role in the diagnosis of this disease (Alcázar et al., 1997). In fact, there are many studies that show that an accurate ultrasound diagnosis can be made, both of the ovarian affection (Eskenazi et al., 2001; Pascual et al., 2000) and of lesions that affect the rectum, bladder and other pelvic structures (Hudelist et al., 2009a,b). Now, the remaining indications where a laparoscopy must be practised are cases in which the painful symptoms and the clinical examination provide strong evidence of an endometriosis needing surgical treatment (Pouly et al., 2007).

The infertility that these patients suffer has classically been treated with surgery or a combination of medical and surgical treatment. It is currently accepted that the results from surgery are superior to those from medical treatment and, of course, from abstaining from therapeutic treatment (Pouly et al., 2007). New combinations of surgical and immunomodulation treatment with pentoxifylline with interesting preliminary results have been published (Creus et al., 2008).

Nowadays, IVF techniques represent a new therapeutic strategy for these patients. Although there are suggestions of worse results from IVF for cases of endometriosis than for other indications (Barnhart et al., 2002), there are many articles and national registries, such as the French National IVF Register (FIVNAT) and the US Society for Assisted Reproductive Technology Registry, that show the same results from IVF for endometriosis (Pouly and Larue, 2007; SART-ASRM, 2007).

Assisted reproduction treatment should be seen not as competing with surgical treatment of endometriosis-associated infertility but as a complementary therapeutic strategy. Depending on the stage of the disease, the patient’s age and the duration of the infertility, physicians have to take the right decision for each case. In this regard, the aim here was to study final outcomes of obtaining a pregnancy following a holistic therapeutic approach to endometriosis-associated infertility in a large number of patients treated in the same private university centre.

Materials and methods

This is an observational study of reproductive outcome obtained by applying a holistic treatment that combined surgery and/or IVF to treat a population of 825 patients suffering from endometriosis-associated infertility, with a mean age of 35.3 ± 3.1 years (range 20–40) and mean length of infertility 3.2 ± 2.3 years. These patients were diagnosed with stage III–IV cystic endometriosis with endometriomas with a mean size of 5.8 ± 2.1 cm by means of ultrasound and/or laparoscopy in the study department during the period 2001–2005. In all cases, endometriosis was the major factor for infertility. Endoscopic surgery was used to treat 483 patients (group 1a), usually using cystectomy whenever possible, removing the whole capsule of the cyst, with later histological analysis to confirm its endometriotic origin. The follow-up of these patients continued until the end of 2008.

Apart from being infertile, the majority of the study group complained of dysmenorrhea and/or dyspareunia. The variables evaluated were the clinical pregnancies obtained directly after surgery as primary therapeutic strategy and the time interval elapsed to achieving the pregnancy, as well as other parameters such as a previous operation, the presence of unilateral or bilateral lesions and the recurrence of the disease.

Patients who did not become pregnant after surgery had the option of having IVF treatment (group 1b). There were also 173 patients who, although having endometriosis as the only factor, preferred to refrain from surgery and went directly to IVF (group 2). As a treatment control group (group 3), the study used 169 infertile patients who, in spite of being diagnosed with endometriosis, did not undergo any treatment. To study ovarian reserve in patients with endometriosis, the control group of patients with infertility unrelated to endometriosis consisted of 334 patients who underwent IVF for male factor infertility, mean age 34.3 ± 4 years and mean duration of infertility 2.9 ± 3.2 years. The endometriosis group and the male factor infertility group were comparable for age and duration of infertility.

Statistical analysis

The Student’s t-test was used to compare quantitative variables and chi-squared Pearson test or Fisher’s exact test were used to compare qualitative variables. A Kaplan–Meier survival analysis was applied to compare the pregnancy rates by time. All the tests were bilateral and with a level of significance of P = 0.05.

Results

Laparoscopic treatment was the first therapeutic choice in 483 patients (group 1a; 58.5%) and 262 achieved spontaneous pregnancies after surgery (54.2%). The mean time to pregnancy was 11.2 months (1–66 months). Of the 221 patients who did not become pregnant after surgery, 144 went on to IVF (group 1b) and underwent 184 oocyte retrievals and 56 additional pregnancies were obtained (30.4% clinical pregnancy/retrieval).

IVF was chosen as the primary therapeutic option by 173 patients who rejected surgery (group 2) diagnosed with
advanced endometriosis with endometriomas with a mean size of 5.4 ± 3.2 cm. This group was comparable with the group of 483 patients who had a laparoscopic treatment as far as the age of the patients and duration of infertility were concerned. In these patients, 211 oocyte retrievals were performed, 68 of which achieved pregnancy (32.2% clinical pregnancy/retrieval).

It is interesting to see the effect of age on the final outcome of the two therapeutic options. In group 1a, 61.6% (229/372) of patients aged <35 years became pregnant, doing so in a mean time of 12.5 months (1–66) and only 29.7% (33/111) of patients aged 35 years or over became pregnant (P < 0.05), in a mean time of 6.6 months (1–14) (Table 1, Figure 1). In group 2, with IVF as the primary option, patients aged <35 years achieved rates for clinical pregnancy/retrieval of 35.7% (51/143), which was significantly higher than the 25.0% (17/68) obtained in the patients aged 35 years or over (P < 0.05; Table 1).

For the treatment control group (group 3), patients with endometriosis who did not undergo any treatment, it was found by means of personal or telephone interviews, 11.8% (20/169) of patient had a spontaneous pregnancy during the period 2001–2008.

It is interesting to note the yield from the combined strategy of surgical treatment plus IVF if they did not become pregnant 1 year after surgery, which made it possible to achieve 318 pregnancies in 483 patients, a rate of 65.8%, which is significantly higher than the 39.6% for surgery-only patients (P < 0.0001), the 32.2% achieved by the patients who did not undergo surgery and went to IVF as the primary option (P < 0.0001) and the 11.8% of spontaneous pregnancy observed in patients who underwent no treatment (P < 0.0001; Table 2).

An analysis of the results obtained from treating patients suffering from endometriosis-associated infertility with surgical treatment and/or IVF gives rise to a series of controversial points. In light of this data, therefore, additional analyses were performed.

### Ovarian reserve and response to stimulation

The ovarian reserve of the whole population of 825 patients before undergoing any treatment was compared with that observed in a simultaneous control group, made up of 334 patients who were going to have IVF for male factor infertility and adjusted for age. Patients with endometriosis had basal follicle-stimulating hormone concentrations on cycle days 3–5 of 8.8 ± 6.3 U/L, which was significantly higher than those observed in the control group 7.5 ± 3 U/L (P < 0.001). Also, the antral follicle count in these patients was 7.3 ± 4 antral follicles, which was significantly lower than the 10.2 ± 5.1 antral follicles observed in the control group (P < 0.004).

Comparing IVF treatments between patients with endometriosis (group 1b, n = 144; group 2, n = 173; total n = 317) and patients with male factor infertility, those with endometriosis had a poorer response to ovarian stimulation, needed larger doses of gonadotrophins and produced a lower number of follicles and mature oocytes. For this reason, the total numbers of embryos and of embryos frozen per patient in the study group were significantly lower than in the patients in the control group (P < 0.000 and P < 0.000, respectively). No significant differences were found between the live-birth rates in the study and control groups (Table 3).

### Does surgery for endometriosis have any effect on the final outcome of an IVF cycle?

Comparing the yield from the IVF cycles in group 2 (no surgery) with that obtained in group 1b (after surgery), the only differences found were that group-2 patients produced more follicles ≥16 mm (7.8 ± 5.1 versus 5.9 ± 6.1; P < 0.03) and more mature oocytes (10.1 ± 2.2 versus 7.3 ± 5; P < 0.03) than those in group 1b.

### Is there any difference between the IVF results obtained in patients operated on for bilateral or unilateral endometriosis?

This study showed that the 51 patients who came to an IVF cycle with an endometriosis that affected both ovaries produced fewer follicles ≥16 mm. (3.0 ± 2.8 versus 7.1 ± 6; P < 0.03) and fewer mature oocytes (4.1 ± 2 versus 8.7 ± 6; P < 0.03) than the 93 patients suffering from unilateral affection.

### Can IVF be attempted in a patient previously operated on for endometriosis who has a recurrence?

Among the 144 patients who went on to IVF after not becoming pregnant post surgery, 32 presented recurrence

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Table 1  Endometriosis-associated infertility: pregnancy rates after surgery and/or IVF.

<table>
<thead>
<tr>
<th>Age</th>
<th>Group 1a (surgery)</th>
<th>Group 1b (surgery and IVF)</th>
<th>Group 2 (IVF first option)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 483)</td>
<td>(n = 144)</td>
<td>(n = 173)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td>Pregnancy</td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>&lt;35 years</td>
<td>229/372 (61.6)</td>
<td>34/99 (34.3)</td>
<td>51/143 (35.7)</td>
</tr>
<tr>
<td></td>
<td>33/111 (29.7)</td>
<td>22/85 (25.9)</td>
<td>17/68 (25.0)</td>
</tr>
<tr>
<td></td>
<td>262/483 (54.2)</td>
<td>56/184 (30.4)</td>
<td>68/211 (32.2)</td>
</tr>
<tr>
<td>≥35 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are number/total (%) or mean ± SD (range).

a184 IVF cycles.
b211 IVF cycles.
cP < 0.05.
Figure 1 Age influence on pregnancy rate after surgery for endometriosis.

Table 2 Endometriosis-associated infertility: pregnancy rate according to different treatment strategies.

<table>
<thead>
<tr>
<th>Group 1a (surgery) (n = 483)</th>
<th>Group 1b (surgery and IVF) (n = 483)</th>
<th>Group 2 (IVF first option) (n = 173)</th>
<th>Group 3 (no treatment) (n = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies after surgery (n)</td>
<td>262</td>
<td>262</td>
<td>–</td>
</tr>
<tr>
<td>Pregnancies after IVF (n)</td>
<td>–</td>
<td>56</td>
<td>68</td>
</tr>
<tr>
<td>Total pregnancies</td>
<td>262</td>
<td>318</td>
<td>68</td>
</tr>
<tr>
<td>Final clinical pregnancy rate (%)</td>
<td>54.2</td>
<td>65.8</td>
<td>32.2</td>
</tr>
</tbody>
</table>

Group I-a versus Group I-b: P < 0.0001.
Group I (a–b) versus Group II: P < 0.0001.
Group I (a–b) versus Group III: P < 0.0001.
Group II versus Group III: P < 0.0001.

Table 3 IVF outcomes in patients with endometriosis or male factor infertility after IVF treatment.

<table>
<thead>
<tr>
<th></th>
<th>Endometriosis (n = 317)</th>
<th>Male factor infertility (n = 334)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCG on day of oestradiol (pg/ml)</td>
<td>1843.2 ± 1368</td>
<td>1889 ± 981</td>
<td>N5</td>
</tr>
<tr>
<td>Follicles</td>
<td>8.3 ± 5.8</td>
<td>11.2 ± 3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MII oocytes</td>
<td>6.7 ± 5.2</td>
<td>10.3 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total embryos</td>
<td>4.0 ± 3.4</td>
<td>4.5 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Embryos frozen</td>
<td>1.9 ± 3</td>
<td>2.7 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Live births per patient</td>
<td>97/317 (30.6)</td>
<td>112/334 (33.5)</td>
<td>N5</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number/total (%).
HCG, human chorionic gonadotrophin; MII, metaphase II; N5, not statistically significant.
of the endometriosis. These patients had a worse ovarian reserve, as shown by the basal follicle-stimulating hormone concentrations of 12.5 ± 5.9 U/l being significantly higher than the values of 7.7 ± 3.3 U/l observed in the 112 patients who did not present any recurrence (P < 0.01). However, the clinical pregnancy rate obtained in the two groups showed no significant differences.

**Discussion**

There are a number of options in the therapeutic arsenal that are available to treat endometriosis-associated infertility and there is now sufficient information to clarify the best option for treatment. Primary-option medical treatment would be restricted to very painful cases and would be administered only in the pre-operative period (Darai et al., 2007).

It is accepted that surgery should be the primary therapeutic option because of its efficacy (Chapron et al., 2002; Marcoux et al., 1997; Moayeri et al., 2009; Ouahba et al., 2004; Pouly et al., 2007; Vercellini et al., 2009a,b) and also for its safety (Nezhat et al., 2005). The surgical indication is greater when there is intestinal affection. In these cases, laparoscopic resection of the affected intestinal segment improves subsequent reproductive performance (Darai et al., 2008; Ferrero et al., 2009; Stepniewska et al., 2009), although the improvement is not so evident in younger patients (Vercellini et al., 2006). As for recurrence, the current study observed a recurrence rate after surgery of 22%, which agrees with recurrence rates of 20–30% at 2 years in most studies, with greater frequency in younger patients presenting larger cysts, receiving additional medical treatment and not becoming pregnant (Guo, 2009; Koga et al., 2006). In these cases, the efficacy of IVF seems to be greater than that of a second surgical intervention (Aboulghar et al., 2003; Fedele et al., 2006; Vercellini et al., 2009a,b). There is one alternative that must be borne in mind for cases of repeated endometriomas; evacuating aspiration combined with ethanol sclerotherapy may contribute both to achieving spontaneous pregnancies and to protecting the ovary for later IVF attempts (Noma and Yoshida, 2001; Pabuccu et al., 2004; Yazbeck et al., 2009).

An additional advantage of surgical treatment derives from the possibility that an early diagnosis of a neoplastic affection of the ovary could be missed otherwise (Somigliana et al., 2006b,c; Viganò et al., 2006). There are studies that suggest that endometriosis could be a risk factor for ovarian cancer (Brinton et al., 2004; Melin et al., 2006) and that the association of infertility and endometriosis could also increase the risk of other neoplasias such as melanomas and thyroid cancer (Brinton et al., 2005). For this reason, some authors suggest that a proper diagnosis, which is key in avoiding confusion between possible endometriosis and a neoplastic affection at the pelvic level (Banz et al., 2009; Goumenou et al., 2006), and complete surgical treatment are fundamental in reducing the risk of an ovarian neoplasia appearing in these patients (Nezhat et al., 2008).

Nevertheless, it would seem that, in treating infertility, the efficacy of surgery itself is less than that obtained in combination with IVF (this study; Coccia et al., 2008).

One important aspect to bear in mind is the ovarian reserve of patients with endometriosis. This study has shown that these patients have a poorer reserve even before surgery. The same observation has been published in patients presenting unilateral ovarian endometriomas who did not undergo previous ovarian surgery (Gupta et al., 2006; Somigliana et al., 2006a). Controversy surrounds the effect of endometriosis surgery on the ovarian reserve; some authors have shown that ovarian response in patients with severe endometriosis and surgical excision is lower than that of patients with minimal or mild endometriosis without ovarian surgery (Busacca et al., 2006; Horikawa et al., 2008; Matalliotakis et al., 2007; Yazbeck et al., 2006) while others have shown that laparoscopic ovarian cystectomy does not affect ovarian reserve and response to stimulation (Marconi et al., 2002; Tsolakidis et al., in press). The same findings have been published in a recent systematic review and meta-analysis of five studies that compared surgery with non-treatment of endometriomas before IVF (Tsoumpou et al., 2009). There is controversy as to whether response to stimulation after an operation to treat endometrioma is better (Somigliana et al., 2006a), worse (Esilier et al., 2006; Somigliana et al., 2008) or not affected (Garcia-Velasco et al., 2004). It is important to point out that it seems that unoperated endometriomas will not grow from the effect of the stimulation of the IVF cycle (Benaglia et al., 2009).

With the results from this study, IVF should be proposed as the primary option only in cases where there are additional infertility factors or where there is some contraindication to surgery. All studies agree that IVF should be recommended to infertile patients who have not become pregnant after operation for endometriosis. However, the question of when remain. From this study’s results, the answer varies with the patient’s age. Patients younger than 35 years of age can wait for up to 1 year post surgery to go for IVF while older patients are recommended to have IVF 6 months post surgery. With regard to the ovarian stimulation protocol, the usual protocols that combine gonadotrophins and gonadotrophin-releasing hormone agonists or antagonists obtain good responses if the ovarian reserve is normal (Zikopoulos et al., 2004). Accepting that the possibility of a low response is higher in these patients, whether or not they have been operated on, the yield of the IVF cycle is usually good, with pregnancy rates in the expected ranges and comparable with those attained in IVF cycles carried out for other indications. For patients who resort to IVF as their primary treatment option and do not become pregnant, laparoscopic surgery could be suggested to help to improve their chances of pregnancy, either spontaneously or before a new IVF attempt (Littman et al., 2005).

This study agrees with other reports that the progression of pregnancy with endometriosis presents no greater problems than pregnancies obtained with other indications (Kortelahi et al., 2003). However, some authors suggest that the pregnancies of patients suffering from endometriosis should be considered as high risk for preterm birth, antepartum haemorrhage, placental complications, pre-eclampsia and Caesarean section (Omland et al., 2005; Stephansson et al., 2009).

In conclusion, infertile patients with endometriosis should undergo surgical treatment as the primary option.
Those who do not become pregnant after surgery must be treated with IVF and their possibilities of pregnancy will be identical to those of patients who come to IVF for other indications. The combination of surgery and IVF offers the best chance of pregnancy for these patients.

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