Should endometriomas be treated before IVF–ICSI cycles?

Edgardo Somigliana¹,³, Paolo Vercellini¹,², Paola Vigano¹,², Guido Ragni¹ and Pier Giorgio Crosignani¹,²

¹Department of Obstetrics, Gynecology and Neonatology, Ospedale Maggiore Policlinico, Mangiagalli and Regina Elena and ²Università degli Studi di Milano, Milan, Italy
³To whom correspondence should be addressed at: Department of Obstetrics, Gynecology and Neonatology, Ospedale Maggiore Policlinico, Mangiagalli and Regina Elena, Via Commenda 12, 20122 Milan, Italy. E-mail: dadosomigliana@yahoo.it

The laparoscopic excision of ovarian endometriomas appears to increase the chances of spontaneous conception, but the value of this treatment in women selected for IVF–ICSI cycles is debated. Studies recruiting women with unilateral disease and comparing ovarian responsiveness in the affected and contralateral intact gonads indicate that excision of endometriomas is associated with a quantitative damage to ovarian reserve. There are no randomized trials comparing laparoscopic excision to expectant management before IVF–ICSI cycles. The idea that surgery increases IVF pregnancy rates is not supported by the available evidence. However, the chance of conception is not the only issue that has to be considered. Some potential drawbacks are associated with both therapeutic strategies. Specifically, costs and hazard of surgical complications support expectant management whereas oocyte retrieval risks, the possibility of missing occult malignancy and endometriosis progression due to ovarian stimulation would favour surgical treatment. Alternative therapeutic options include medical treatment and ultrasound-guided aspiration. Whereas prolonged GnRH agonist down-regulation may be beneficial, data on ultrasound aspiration are more controversial.

Key words: endometrioma/endometriosis/IVF/laparoscopy/ovarian reserve

Introduction

Endometriosis is a common gynaecological disorder in which endometrial tissue (glandular epithelium and stroma) is found outside the uterine cavity. It affects 20–40% of women who complain of subfertility, although it can be found also in 5–10% of fertile women. Other characteristic symptoms include dyspareunia, severe dysmenorrhoea and chronic pelvic pain (Hart, 2003). Endometriosis mostly presents as superficial and deep pelvic peritoneal implants, adhesions and ovarian cysts. Whereas detection of peritoneal implants and adhesions typically requires direct visualization of the pelvis through a laparoscopic examination, endometriotic ovarian cysts can be reliably identified by transvaginal ultrasound. A trained sonographer can easily distinguish endometriomas from other ovarian cysts for their characteristic echogenic appearance. Sensitivity and specificity of transvaginal ultrasound have been reported to be 84–100% and 90–100%, respectively (Mais et al., 1993; Kurjak and Kupesic, 1994; Alcazar et al., 1997; Eskenazi et al., 2001). The possibility of identifying endometriotic ovarian cysts without laparoscopic removal and histological confirmation and the development of IVF techniques have led to new therapeutic scenarios. A debated and still unsolved topic in this context is whether or not endometriomas should be treated before undergoing IVF cycles (Brosens, 2004; Garcia-Velasco and Arici, 2004; Gibbons, 2004; Sharpe-Timms and Young, 2004).

Current data and observations concerning the impact that ovarian endometriomas and/or their treatments may have on IVF outcome are herein summarized. The aim of this review is to clarify whether or not these cysts should be treated before IVF. Search strategies used were online query of the MEDLINE database and handsearching of relevant publications and reviews from January 1990 to December 2004. Key words used were endometriosis, endometrioma, endometriotic ovarian cyst combined with IVF or ICSI. Additional reports were collected by systematically reviewing all references from retrieved papers. Prospective and retrospective studies have been included.

Laparoscopic treatment of endometriomas and natural fecundity

The treatment of ovarian endometriomas in general has been exhaustively discussed in a recent review (Chapron et al., 2002b). This point is beyond the scope of this study, but some aspects deserve consideration and are thus briefly mentioned herein.

It is well known that medical therapy alone has a limited role in the treatment of endometriomas. Conservative medical treatment,
Endometriomas and ovarian reserve: insights from IVF–ICSI cycles

Evaluation of ovarian reserve remains an elusive task of reproductive medicine. Since ovarian function cannot be measured directly, ovarian response to gonadotrophin stimulation is currently considered the most appropriate surrogate measurement for ovarian function. The use of serum markers (FSH, inhibin B, 17ß-estradiol (E₂), FSH/LH ratio, antimüllerian hormone) and/or ultrasound variables (ovarian volume, Antral Follicle Count, ovarian stromal blood flow) may be of help but are still considered less informative (Bukman and Heineman, 2001; Tarlatzis et al., 2003). However, the induction of ovarian stimulation in an unselected population of women with endometriomas (before and/or after surgical management) with the mere purpose to evaluate ovarian function is ethically debatable and has not been performed. As a consequence, results from IVF–ICSI cycles in patients with endometriosis has been used to infer the influence of endometriomas on ovarian function. It is important to underline that this population is biased since women who conceive spontaneously are not included.

Ovarian reserve and endometriosis

The influence of endometriosis on the results of IVF–embryo transfer (IVF–ET) cycles has been object of debate. Using meta-analysis methodologies, Barnhart et al. (2002) documented an odds ratio (OR) for pregnancy rate of 0.56 [95% confidence interval (CI) = 0.44–0.70] in patients with endometriosis. Pregnancy rates for women with severe endometriosis were significantly lower than for women with mild disease (OR = 0.60, 95% CI = 0.42–0.87) (Barnhart et al., 2002). More recent studies on this topic confirmed these findings (Azem et al., 1999; Al-Azemi et al., 2000; Norenstedt et al., 2001; Geber et al., 2002; Aboughar et al., 2003; Pabuccu et al., 2004) while others did not (Bukulmez et al., 2001; Canis et al., 2001; Donnez et al., 2001; Hickman, 2002; Marconi et al., 2002). The 2002 Report from the Center for Disease Control and Prevention (CDC) has documented that endometriosis is associated with highest live birth rate per cycle in IVF programmes when compared to other causes of infertility (Center for Disease Control and Prevention, 2002). Discrepancies among studies are surprising. Reasons to explain these conflicting results seem to be multifactorial because IVF outcome can be affected by patient management, stimulation protocols, laboratory procedures and other factors intrinsic to each institution (Garrido et al., 2002). Crucial roles should be attributed to the control group used and to selection criteria. The control group generally consists of women with tubal infertility. The adequacy of this choice is debatable considering that ovarian reserve and implantation may be reduced in these patients as well (Johnson et al., 2002; Carmona et al., 2003; Chan et al., 2003). Furthermore, it has to be noted that, in many centers, women with endometriosis and with a compromised ovarian reserve (elevated day 3 FSH, reduced Antral Follicle Count and older age) may have been excluded from IVF–ICSI cycles.

Ovarian reserve and endometriomas

Some studies have specifically focused on results of IVF cycles in patients with endometriomas (Nargund et al., 1996; Yanushpolsky et al., 1998; Loh et al., 1999; Al-Azemi et al., 2000; Tinkanen and Kujansuu, 2000; Canis et al., 2001; Donnez et al., 2001; Geber et al., 2002; Ho et al., 2002; Marconi et al., 2002; Suganuma et al., 2002; Somigliana et al., 2003; Garcia-Velasco et al., 2004; Pabuccu et al., 2004; Wong et al., 2004). In this context, we believe that at least three different clinical scenarios should be considered: (i) patients with endometriomas who have not undergone previous ovarian surgery, (ii) patients who have been previously operated for endometriomas who are disease-free at the time of IVF–ICSI and (iii) patients who have been previously operated for endometriomas who are found to have a recurrence at the time of IVF–ICSI. Findings from the first two groups may be of particular interest because they allow to distinguish the effects related to the presence of the endometriomas from those related to surgery. Further variables that have to be considered are bilaterality, dimension of the cysts and the specific surgical technique used. Unfortunately, the vast majority of available studies have not taken into consideration this distinction.

Studies investigating the influence of endometriomas on ovarian function have led to controversial results (Wardle et al., 1985; Tummon et al., 1991; Olivennes et al., 1995; Isaacs et al., 1997; Yanushpolsky et al., 1998; Tinkanen and Kujansuu, 2000; Garcia-Velasco et al., 2004). To the best of our knowledge, only one study has specifically compared unoperated women with endometriomas to women who previously underwent surgery for endometriomas (Garcia-Velasco et al., 2004). Lower peak E₂ levels and
higher gonadotropin requirements were documented in the operated patients. Conversely, number of oocytes retrieved, number of embryos obtained and pregnancy rate were similar in the two groups. Six studies specifically focused on women previously operated for endometriomas (Al-Azemi et al., 2000; Canis et al., 2001; Donnez et al., 2001; Geber et al., 2002; Marconi et al., 2002; Pabuccu et al., 2004). Results from these studies are summarized in Table I. Al-Azemi et al. (2000) did not observe any significant difference in terms of number of oocytes retrieved and embryos obtained at first treatment cycle while a marked reduced pregnancy rate became evident after the second treatment cycle.

**Table I. Studies evaluating response to ovarian stimulation in patients previously operated for endometriomas (EM)**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Surgical technique</th>
<th>Number of cases</th>
<th>Oocytes retrieved</th>
<th>Embryos obtained</th>
<th>Pregnancy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EM</td>
<td>Ctr</td>
<td>EM</td>
<td>Ctr</td>
</tr>
<tr>
<td>Al-Azemi et al. (2000)*</td>
<td>Not reported</td>
<td>40</td>
<td>80</td>
<td>6.9 ± 0.7</td>
<td>7.1 ± 0.5</td>
</tr>
<tr>
<td>Canis et al. (2001)</td>
<td>Cyst enucleation</td>
<td>41</td>
<td>59</td>
<td>9.4 ± 6.2</td>
<td>10.9 ± 6.5</td>
</tr>
<tr>
<td>Donnez et al. (2001)</td>
<td>Laser vaporization</td>
<td>85</td>
<td>289</td>
<td>10.6 ± 4.2</td>
<td>8.6 ± 6.3</td>
</tr>
<tr>
<td>Marconi et al. (2002)</td>
<td>Cyst enucleation</td>
<td>39</td>
<td>36</td>
<td>7.5 ± 3.9</td>
<td>8.7 ± 5.1</td>
</tr>
<tr>
<td>Geber et al. (2002)</td>
<td>Cyst enucleation†</td>
<td>37</td>
<td>46</td>
<td>9.8 ± 5.4‡</td>
<td>12.0 ± 5.9</td>
</tr>
<tr>
<td>Pabucco et al. (2004)</td>
<td>Cyst enucleation§</td>
<td>24</td>
<td>28</td>
<td>6.9 ± 6.5‡</td>
<td>11.9 ± 7.6</td>
</tr>
</tbody>
</table>

NA, not available.
Controls (Ctr) were women with tubal infertility.
*Only results from the first treatment cycle are reported. A statistically significant lower response in the endometriosis group became evident after the second treatment cycle.
†Age ≤ 35 years.
‡Statistically significant (P < 0.05).
§Age > 35 years.

Endometriomas and ovarian reserve: insights from IVF–ICSI cycles in women with unilateral disease

The studies on IVF–ICSI cycles in women with ovarian endometriosis are limited by the fact that, in most cases, only one gonad is involved. This limitation is important and poorly considered. Patients with a single ovary do not in general have a reduced fertility potential to conceive through IVF treatment (Lass, 1999). In women with unilateral disease, the contralateral intact gonad may adequately compensate for the reduced function of the affected ovary.

In this regard, we believe that a simple and reliable means to assess the influence of endometriosis and/or its surgical treatment on ovarian function is to monitor the response to ovarian stimulation during IVF/ICSI cycles in the affected ovary and to use the contralateral intact gonad of the same patient as a control. This study design has been employed by six independent authors to investigate the effects of surgery (Nargund et al., 1996; Loh et al., 1999; Donnez et al., 2001; Ho et al., 2002; Somigliana et al., 2003; Wong et al., 2004). Results from these studies are summarized in Table II. In three of them, the number of follicles developing in the cystectomized ovary was significantly reduced when compared to the contralateral intact gonad (Nargund et al., 1996; Ho et al., 2002; Somigliana et al., 2003). Loh et al. (1999) did not report any difference but they have included only 12 IVF–ICSI cycles. It is of note that the same authors documented a significantly reduced responsiveness of the operated gonad when considering 39 clomiphene citrate stimulated cycles for timed intercourse and/or intrauterine insemination (Loh et al., 1999). Wong et al. (2004) failed to detect any difference: unfortunately, number of recruited cases was not reported. A trend towards a difference can however be noted (Table II) (Wong et al., 2004). Conversely, the study from Donnez et al. (2001) failed to document any significant difference. As previously mentioned, these authors included only patients treated with drainage and laser-vaporization of the internal layer of the endometrioma.

These retrospective studies have the merit to use the same patient as a control thus presumably reducing the inherent limits of this experimental design. Even if prospective trials are needed to confirm these findings, the obtained results support the vision that enucleation of endometriomas is associated with a significant damage to ovarian reserve. A recent study on a cohort of unselected women undergoing monolateral excision of an endometrioma documented that ovarian volume was reduced in operated gonads when compared to contralateral healthy ovaries (Exacoustos et al., 2004). The possibility that drainage and laser-vaporization of the internal layer may be less detrimental needs to be confirmed.

The observation that the responsiveness of cystectomized ovaries is reduced may be of particular relevance for women with bilateral endometriomas. Whereas the contralateral intact gonad may adequately compensate for the reduced function of the
affected gonad, women with bilateral endometriotic ovarian cysts may be at elevated risk of ovarian function impairment. Even if endometriotic cysts are monolateral in the majority of cases, both gonads are affected in 19–28% of cases (Vercellini et al., 1998; Prefumo et al., 2002; Al-Fozan and Tulandi, 2003). Moreover, in some cases, the two gonads may be affected in subsequent periods. Surprisingly, no study has specifically investigated the outcome of IVF–ICSI cycles in women with bilateral ovarian disease.

**Damage mechanisms**

*Endometrioma-mediated damage*

The causes of the reduced ovarian reserve in operated ovaries have been poorly investigated. In this regard, it is important to note that, at present, there are no definitive data to clarify whether the damage is related to the surgical procedure and/or to the previous presence of the cyst. Indeed, it cannot be excluded that the cyst *per se* may damage the surrounding ovarian tissue. 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 *per se* may be detrimental to the ovary. In a rabbit model, Kaplan et al. (1989) showed that endometrial implants in the ovaries decreased the number of ovulation points. This difference was primarily related to perilobar adhesions. Data in humans are lacking. No clinical studies have been set up in unoperated women with monolateral endometriomas to compare follicular growth in the affected and contralateral intact gonad. The relevance of the damage determined by the endometrioma *per se* remains thus to be determined. A further unsolved task would be to clarify whether this injury is permanent or transitory. Clarification of these points is utterly needed considering that they may have a relevant clinical impact.

*Surgery-mediated damage*

Apart from the potential injury related to the presence of the cyst *per se*, there are some evidence supporting the idea that surgery may negatively affect ovarian reserve. A potential deleterious mechanism is the accidental removal of a consistent amount of ovarian tissue during cystectomy. In a recent histological study performed on pathological specimens, Muzii et al. (2002) observed the presence of healthy ovarian tissue adjacent to the cyst wall in 14 out of 26 endometriomas (54%) compared to 1 case out of 16 non-endometriotic benign ovarian cysts (6%) (*P* = 0.002). The presence of recognizable ovarian tissue adjacent to the wall of enucleated endometriotic cysts has been documented in a substantial number of cases also by Hachisuga and Kawarabayashi (2002). The hypothesis that endometriomas may arise from the invagination of ovarian cortex would explain these findings. According to this aetio-pathogenetic model, ovarian cystectomy of endometrioma would imply the resection of healthy ovarian cortex with follicles rather than the excision of an intraovarian cyst (Brosens, 2004).

A further mechanism potentially responsible for the reduced ovarian reserve is represented by the damage that may be inflicted to 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). Although the relevance of this pathogenetic mechanisms still needs to be determined, we believe that bipolar coagulation should be performed with caution. The manoeuvre should be selective, facing the bleeding vessels and not widely grasping the entire ovarian tissue with bipolar coagulator (Marconi et al., 2002). Of note, a recent study has suggested that laparoscopic ovarian suture may be a less detrimental haemostatic procedure (Fedele et al., 2004).

**Should endometriomas be excised before IVF–ICSI cycles?**

**The need for randomized trials**

*Why are randomized studies warranted?*

Laparoscopic excision is currently considered the first-line treatment for ovarian endometriotic cysts in subfertile women. It appears thus important to investigate whether or not this treatment would be valuable also in the particular condition of women selected for IVF–ICSI cycles who are found to have endometriotic ovarian cysts. Unfortunately, randomized trials specifically aimed to investigate this possibility are currently lacking. Of note, such study should be remarkably large to obtain subgroup analyses that may be clinically relevant. At least three variables should be considered: bilaterality of the endometriomas, dimension of the cysts and number of previous ovarian interventions. A further relevant variable is the length of follow-up; even if small, a certain percentage

---

**Table II. Studies comparing the number of follicles in the operated and in the contralateral non-operated ovary during ovarian stimulation for IVF–embryo transfer or ICSI**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Surgical technique</th>
<th>Number of cycles</th>
<th>Control ovary</th>
<th>Operated ovary</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nargund et al. (1996)</td>
<td>Not reported</td>
<td>90*</td>
<td>8.9 ± 5.1</td>
<td>6.3 ± 5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loh et al. (1999)</td>
<td>Cyst enucleation</td>
<td>12</td>
<td>3.6†</td>
<td>4.6†</td>
<td>NS</td>
</tr>
<tr>
<td>Donnez et al. (2001)</td>
<td>Cyst wall vaporization</td>
<td>87</td>
<td>6.6 ± 3.5</td>
<td>5.2 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ho et al. (2002)</td>
<td>Cyst enucleation</td>
<td>38</td>
<td>3.3 ± 2.1</td>
<td>1.9 ± 1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Somigliana et al. (2003)</td>
<td>Cyst enucleation</td>
<td>46</td>
<td>4.2 ± 2.5</td>
<td>2.0 ± 1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wong et al. (2004)</td>
<td>Cyst enucleation</td>
<td>Not reported</td>
<td>5.0 ± 0.8‡</td>
<td>6.3 ± 1.1‡</td>
<td>0.32</td>
</tr>
</tbody>
</table>

NS, not significant.

Data are expressed as mean ± SD.

* Both endometriotic (*n* = 36) and non-endometriotic (*n* = 54) ovarian cysts were included.

† SD was not reported.

‡ Data are expressed as mean ± SEM.
of patients with advanced stages of endometriosis scheduled for IVF is expected to conceive spontaneously (Kodama et al., 1996; Pagidas et al., 1996; Jones and Sutton, 2002). Natural fecundity is an aspect that should not be overlooked.

Given the lack of randomized trials aimed to establish benefits of the surgical treatment, some authors have tried to draw preliminary conclusions using retrospective studies. Such experimental design is debatable in this context since selection criteria may indeed play a crucial role. Size of endometriomas, presence of adhesions, pain symptoms, age, duration and cause of infertility are expected to be significantly different in women who did or did not undergo surgical treatment and in those who did or did not have recurrence. Taking into consideration these major limits, results from these studies are herein briefly reported.

Insights from non-randomized studies

Garcia-Velasco et al. (2004) compared IVF–ICSI outcome between 133 women who previously underwent laparoscopic cystectomy for an ovarian endometrioma and 56 women with ovarian endometriomas who had never undergone ovarian surgery. Number of oocytes retrieved (10.8 ± 0.6 versus 11.8 ± 0.9), number of embryos obtained (6.0 ± 0.4 versus 6.4 ± 0.6) and pregnancy rate (25% versus 23%) resulted extremely similar (Garcia-Velasco et al., 2004). Suganuma et al. (2002) observed a better response to ovarian stimulation in 20 patients (30 cycles) with unoperated endometriomas undergoing IVF–ICSI cycles when compared to 36 patients (62 cycles) previously operated for endometriomas. Number of oocytes retrieved and embryos obtained resulted 9.7 ± 6.7 and 7.2 ± 6.2 in unoperated women and 5.5 ± 4.9 and 4.1 ± 3.6 in operated women, respectively ($P < 0.05$). Pregnancy rate was similar (29 versus 37%). Tinkanen and Kujansuu evaluated ovarian response in 45 women with endometriomas at the time of IVF–ICSI (36 of the cases being recurrences) and in 45 women previously operated for endometriomas but without recurrence. A higher number of embryos and a better pregnancy rate were observed in women with ovarian endometriomas at the time of IVF (Tinkanen and Kujansuu, 2000). Two limitations of this study should be considered. First, the group of patients with endometriomas consisted of both operated and unoperated women. Second, a significantly higher frequency of bilaterality was observed in the group of patients who were disease-free at the time of IVF–ICSI (60 versus 13%). Wong et al. (2004) failed to document any difference using a similar study design. Oocytes retrieved, embryos obtained and pregnancy rate resulted similar in 38 cycles performed in women with endometriomas at the time of IVF–ICSI (nine recurrences) and in 36 women previously operated for endometriomas but without recurrence.

Overall, this evidence suggests that surgery does not benefit asymptomatic women preparing to undergo IVF–ICSI who are found to have an endometrioma.

Risks and benefits of endometrioma excision prior to IVF–ICSI cycles

Risks of surgery

The chance of conception is not the only factor that a physician should consider before deciding whether or not the patient should undergo surgical treatment of an endometrioma before undergoing IVF–ICSI. Some risks of complications are associated with both therapeutic approaches (Figure 1). According to a recent meta-analysis, the rate of major and minor complications associated with laparoscopy is 1.4 and 7.5%, respectively (Chapron et al., 2002a). It should be noted that many patients with endometriosis selected for IVF have advanced stage disease and have had multiple previous surgeries. Most have developed pelvic adhesions and are thus at increased risk of complications from further surgery. Surgical treatment is also associated with higher economic costs. Minimum costs of operative laparoscopy for advanced endometriosis have been reported to be about £1735 (Philips et al., 2000).

Risks of expectant management

Five specific complications may be associated with the non-surgical approach: (i) risk of causing the rupture of the endometrioma and/or the development of a pelvic abscess, (ii) missing an occult early stage malignancy, (iii) difficulties during oocyte retrieval, (iv) follicular fluid contamination with endometrioma content and (v) progression of endometriosis. The exact impact of these risks has not been established. The hazard of causing pelvic abscess is presumably low though this complication has been repeatedly reported (Padilla, 1993; Yaron et al., 1994; Younis et al., 1997; Matsunaga et al., 2003). The risk of infection is real even if prophylactic antibiotics are used (Yaron et al., 1994; Younis et al., 1997). The possibility to induce the rupture of the endometrioma causing an acute abdomen has also been documented (Dicker et al., 1993). The fear of missing an occult early stage malignancy is another rare but severe concern. The role of endometriosis as a precursor lesion for ovarian carcinoma has been recently emphasized (Ness, 2003; Van Gorp et al., 2004; Dinulescu et al., 2005). The two largest available series concerning the risk of occult malignancy in endometriotic samples reported a frequency of 0.8% and 0.9% (Mostoufizadeh and Scully, 1980; Stern et al., 2001). Difficulties during oocyte retrieval in women with endometriomas are a well known problem. An affected ovary may be displaced in an uncomfortable and perilous position, follicles may grow beyond the endometrioma thus requiring puncture of the cyst to allow aspiration of the follicle content. Physicians may occasionally decide to avoid follicular aspiration in the affected ovary if a sufficient number of oocytes has been retrieved in the contralateral gonad. Accidental contamination of follicular fluid with endometrioma content is not a rare event during oocyte retrieval. This aspect is of particular interest considering that it has been reported that endometriotic fluid may significantly affect oocyte
quality (Dmowski et al., 1995; Suwajanakorn et al., 2001). This point is however debated (Khamisi et al., 2001). Little is known regarding the effects of ovarian stimulation on the progression of ovarian endometriosis. It cannot be excluded that, at least in a minority of cases, dimension of the endometriomas may significantly enlarge as a consequence of elevated \( E_2 \) levels. Even if rare, rapid growth of deep peritoneal endometriotic implants leading to harmful complications has been reported (Anaf et al., 2000). Data on endometriomas are lacking.

**Natural fecundity**

Finally, the possibility of natural fecundity should not be ignored in deciding the best treatment option in women selected for IVF–ICSI who are found to have an endometrioma (Kodama et al., 1996; Pagidas et al., 1996; Olive and Pritts, 2001). Even patients who have undergone previous ovarian surgery might benefit from a second intervention. Cumulative pregnancy rate after reoperation for stages III–IV endometriosis-related infertility after 3, 7 and 9 months have been reported to be 6, 18 and 24%, respectively (Pagidas et al., 1996).

**Alternative treatment options in women with endometriomas selected for IVF–ICSI cycles**

**Medical treatment**

A series of studies have investigated the opportunity to prescribe medical treatment before IVF–ICSI cycle to increase the chance to conceive. These studies have been recently reviewed (Zikopoulos et al., 2004). Overall, there are evidence, though not robust, that the use of prolonged GnRH agonist down-regulation (2–6 months) is beneficial in patients with endometriosis in general (Remorgida et al., 1990; Dicker et al., 1992; Marcus and Edwards, 1994; Surrey et al., 2002; Zikopoulos et al., 2004). The only prospective randomized study comparing long agonist protocol (n = 26) to prolonged agonist down-regulation protocol (n = 25) documented a higher pregnancy rate in this latter group (Surrey et al., 2002). Advantages of this strategy in the subgroup of women who are found to have ovarian endometriomas at the time of IVF–ICSI cycle has not been specifically investigated.

**Ultrasound-guided aspiration**

Ultrasound-guided aspiration, with or without concomitant local or systemic therapy, is an alternative option that should be taken into consideration.

Dicker et al. documented a significant improvement in number of oocytes retrieved and embryos obtained in a cohort of women with ovarian endometriomas who failed to conceive during a previous IVF cycle and who subsequently underwent transvaginal ultrasound-guided aspiration (Dicker et al., 1991). In a retrospective study, Suganuma et al. compared treatment of endometriomas before IVF either by laparotomy-laparoscopy (n = 36) or aspiration (n = 23) to no treatment at all (n = 20). A higher fertilization rate was observed in the group of patients treated with aspiration (67%) as compared to those treated with surgery (57%) or those who did not receive any treatment (56%) (Suganuma et al., 2002). In contrast, these results have not been confirmed in a more recent randomized study comparing ultrasound-guided aspiration to no treatment before ICSI (Pabuccu et al., 2004). Specifically, 41 women were randomized for endometrioma aspiration at the beginning of ovarian hyperstimulation, whereas 40 women who did not undergo aspiration were used as controls. Number of oocytes retrieved, fertilization rate, implantation rate and pregnancy rate resulted similar. Potential benefits of adjuvant local or systemic medical treatment remains to be investigated. Fish and Sher recently reported promising results in a case series of 32 women treated with transvaginal-guided aspiration and successive intracystic sclerotherapy with 5% tetracycline (Fisch and Sher, 2004). Randomized studies are required to confirm these interesting preliminary results.

**Conclusions**

Drawing a definite balance of pros and cons regarding the opportunity to treat endometriomas before IVF–ICSI represents an arduous task. As shown in Figure 1 several factors should be taken into consideration. This analysis is further complicated since the relative importance of these aspects is unknown.

Briefly, the following conclusions can be drawn from current evidence. The presence of endometriomas per se may negatively influence ovarian function and may impose difficulties and risks during oocyte retrieval. The magnitude of the negative effect on ovarian reserve is unknown. On the other hand, there are no definite data clarifying whether the treatment of endometriomas increases (or decreases) the chances of success using IVF.

Results from large randomized trials are needed to elucidate whether or not ovarian endometriomas should be treated before undergoing an IVF–ICSI cycle and which treatment is more suitable. In the meantime, physicians should pursue a comprehensive and personalized approach in the decision-making process to identify the best option for the couple. At least five points have to be considered; the age of the woman, the presence/absence of pain, the number of previous interventions, ovarian reserve and the possibility of occult malignancy.

In conclusion, although the optimal treatment cannot presently be proposed, there is insufficient evidence to support a strategy of systematic surgical treatment of endometriomas before IVF–ICSI cycles.

**References**


Reviewer's comments:

- The review is comprehensive, covering various aspects of endometriosis and its treatment.
- The references are up-to-date, indicating active research in the field.
- There could be more emphasis on the impact of endometriosis on fertility outcomes.
- The discussion on surgical treatment before IVF could benefit from more recent studies.

Overall, the review is a valuable resource for researchers and clinicians involved in the treatment of endometriosis.


Submitted on April 1, 2005; revised on June 7, 2005; accepted on July 25, 2005