Surgery for endometriosis-associated infertility: a pragmatic approach

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Introduction

A causal relation between endometriosis and infertility has long been hypothesized based on a higher prevalence of the disease observed in subfertile women (up to 50%) compared with women of proven fertility (5–10%) (D’Hooghe et al., 2003). Moreover, the monthly fecundity rate of the former is reportedly 0.02–0.10 compared with 0.15–0.20 in fertile couples (The Practice Committee of the American

Laparoscopic treatment for endometriosis-associated infertility is gaining widespread popularity supported mostly by uncontrolled studies, but the purported benefit of surgery may be overvalued. We have therefore analysed the best available evidence with the aim of defining an approximate estimate of the effect size of conservative surgery for infertile women with endometriosis in various clinical conditions. The overall increase in post-operative likelihood of conception over background pregnancy rate may be estimated to be between 10 and 25%. The effect of surgery for peritoneal lesions is limited, and an estimate of benefit should be decreased by the fact that preoperative identification of the subjects actually with the condition is unfeasible. The benefit of excision of ovarian endometriomas is difficult to define due to multiple confounding factors and methodological drawbacks in the considered studies. Excision of rectovaginal endometriosis is of doubtful value and associated with worrying morbidity. The role of surgery before, after or as an alternative to IVF needs clarification. In conclusion, the absolute benefit increase of surgery for endometriosis-associated infertility appears smaller than previously believed. Complete and detailed information on risks and benefits of treatment alternatives must be offered to infertile patients to allow unbiased choices between possible options.

Key words: endometriosis / infertility / surgery / laparoscopy / pregnancy rates
Surgery for endometriosis and infertility (ASRM stage I–II)

Two randomized controlled trials (RCTs) were conducted to evaluate the effect of destruction of peritoneal endometriosis on pregnancy rate in infertile women. In the multicenter Canadian (ENDOCAN) study (Marcoux et al., 1997), conception was achieved by 63/172 (36.6%) women undergoing laparoscopy with ablation of peritoneal implants and by 37/169 (21.9%) of those undergoing diagnostic laparoscopy only [odds ratio (OR), 2.06; 95% CI 1.28–3.33]. At odds with these findings, in the multicenter Italian trial (Parazzini, 1999), pregnancy...
Figure 1 Cumulative 36-month probability of becoming pregnant by disease stage in 222 infertile women who underwent conservative surgery for endometriosis and had no other infertility factor (continuous line, stage I; dotted line, stage II; dashed line, stage III; dash-dotted line, stage IV). From Vercellini et al. (2006a), with permission.

Figure 2 Overview of RCTs comparing laparoscopic ablation of lesions with no surgery in infertile women with minimal or mild endometriosis. Diamonds represent odds ratio of conception and horizontal lines 95% CIs. Breslow-Day test for heterogeneity: $\chi^2 = 13.24, P = 0.42$. Data from Al-Inany et al. (2000).
was observed in 10/51 (19.6%) subjects in the operative laparoscopy group and in 10/45 (22.2%) in the diagnostic laparoscopy group (OR, 0.75; 95% CI 0.30–1.85). Pooling the results of the two trials (Fig. 2) gives an OR of 1.65 (95% CI, 1.06–2.58), which indicates a statistically significant difference of marginal clinical importance. Limiting the analysis to the main outcome of interest, i.e. late pregnancies, the experimental event rate is 26% versus a control event rate of 18%. The absolute benefit increase of 8% translates into a number needed to treat (NNT) of 12 (i.e., a dozen of laparoscopies should be performed to obtain one additional pregnancy compared with treatment abstention) (Al-Inany, 2000, 2001; Crosignani and Vercellini, 2000; Jacobson et al., 2002). However, this estimate should be doubled or tripled considering that preoperative identification of subjects with stage I–II disease is unfeasible, and that only one-third to one-half of the women undergoing laparoscopy for unexplained infertility actually have the condition. It has also been reported that excising or coagulating peritoneal implants seems un-influential (Tulandi and Al-Took, 1998).

**Surgery for ovarian disease (ASRM stage III-IV)**

In the European Society for Human Reproduction and Embryology (ESHRE) guidelines for the diagnosis and treatment of endometriosis (Kennedy et al., 2005), it has been pointed out that ‘no RCT or meta-analysis are available to answer the question whether surgical excision of moderate–severe endometriosis enhances pregnancy rates’.

Very different outcomes have been reported in uncontrolled studies evaluating the impact of laparoscopic treatment of ovarian endometriotic cysts on post-operative reproductive performance. Pregnancy rates vary from 30% (Marrs, 1991) to 67% (Beretta et al., 1998), with an overall weighted mean of about 50% (Fig. 3). This is most likely an overestimate due to multiple confounding factors, including selection bias (inclusion of women who did not try to conceive preoperatively and that are not necessarily infertile) and publication bias (surgeries with suboptimal outcomes may be less willing to submit their data and may be less likely to have them published). Moreover, exclusion from the analysis of subjects lost to follow-up may enflate the purported benefit of surgery, as drop-outs notoriously have a worse prognosis. The number of women with uni- or bilateral cysts is rarely specified. When a unilateral endometrioma was present, the operated gonad could have been damaged and pregnancy achieved as a result of the function of contra-lateral adnexa. Few authors indicate how many patients achieved a pregnancy post-operatively by means of IVF. In these cases it is questionable to attribute success exclusively to laparoscopy. Finally, lack of an adequately generated control group impedes measurement of the difference between post-operative and background spontaneous pregnancy rates. Noticeably, only such a difference, and not the total conception rate, may be ascribed to surgery.

In light of the above considerations, it is not possible to exclude that the effect of endometriotic cysts removal is well inferior to the alleged 50%, and is presumably not much higher than that observed after treatment of peritoneal implants. Accordingly, the potential absolute benefit increase over background pregnancy rate 12 months after surgery in women with patent tubes could be hypothetically estimated to not greater than 25%. Based on this estimate, the NNT would be 4.

However, a major difference exists between peritoneal and ovarian lesions that may influence greatly the final practical outcome of surgery. In fact, whereas minimal and mild implants may not be diagnosed reliably before laparoscopy, endometriomas can be detected accurately with transvaginal ultrasonography (Mais et al., 1993; Eskenazi et al., 2001; Moore et al., 2002). Consequently, no ‘dilution’ of the effect of surgery related to disease prevalence in the population undergoing laparoscopy is observed in women with endometriotic ovarian cysts.

![Figure 3](image)

**Figure 3** Pregnancy rates observed after laparoscopic excision of endometriomas. Diamonds represent percentage point estimates and horizontal lines represent 95% CIs. Modified from Jones and Sutton (2002), with permission.
Whether the surgical modality adopted to treat endometriomas may influence the outcome has been extensively debated. Many authors assume that, as endometriomas are ‘extraovarian pseudo-cysts’ (Brosens et al., 1996), excising the so-called capsule means removal of a large part of ovarian cortex with the inherent reduction in follicular reserve. Consequently, only opening and vaporizing or coagulating the inner surface of the cyst has been suggested. However, several studies have consistently demonstrated that, independently of post-operative ovarian response, pregnancy rates do not seem to be negatively affected by excision (Somigliana et al., 2003, 2006). Pooling data from the two RCTs specifically conducted on this issue (Beretta et al., 1998; Alborzi et al., 2004) confirms a substantial benefit in favour of the excision technique (pregnancy rate, 60.9 versus 23.4%; rate difference, 37.5%) with an OR of pregnancy of 5.11 (95% CI 2.03–12.85; Fig. 4), and a NNT of 2.7. Moreover, an increase in risk of endometrioma recurrence has been repeatedly associated with the vaporization/coagulation technique (Vercellini et al., 2003a; Hart et al., 2008).

The significant difference in pregnancy rate observed in the above two treatment groups might be regarded as indirect proof of an effect of surgery for endometriomas. In fact, if vaporization/coagulation is considered not effective and hence equivalent to no treatment, excision should be deemed of benefit. The alternative explanation would be that excision is not effective and vaporization/coagulation is detrimental to the point of resulting in a reduction of baseline probability of conception. Although the latter hypothesis seems improbable, RCTs are badly needed to clarify whether, and how much, surgery for endometriomas improves the reproductive prognosis of infertile women.

Conservative surgery may be indicated in women with infertility and endometriotic ovarian cysts (stage III/IV) also because of the need for histological examination to rule out early ovarian cancer. However, patients must be informed that the effect of endometrioma excision on reproductive prognosis is poorly defined and that the chances of conception without surgery are currently unclear (D’Hooghe et al., 2003).

**Surgery for rectovaginal lesions**

Endometriosis infiltrating the posterior vaginal and anterior rectal walls usually causes severe symptoms (Vercellini et al., 1996, 2004; Vercellini, 1997), and studies on treatment of this particular form focus mainly on pain relief (Anaf et al., 2001; Chapron et al., 2001; Fedele et al., 2004a; Ford et al., 2004). Several conservative surgical techniques have been proposed to deal with this technically demanding condition (Poosover et al., 2000; Anaf et al., 2001; Chapron et al., 2001; Redwine and Wright 2001; Fedele et al., 2004a; Ford et al., 2004). Incomplete lesion resection generally does not achieve benefits, whereas radical interventions increase the risk of major complications, and ureteral and rectal injuries with associated sequelae are not exceptional (Table I).

Information on reproductive performance in infertile women is not very consistent, as reported pregnancy rates vary from 24% (Fleisch et al., 2005) to 54% (Chopin et al., 2005), with an overall weighted mean of slightly over 40% (Fig. 5). However, the drawbacks of reports on surgery for endometriomas also apply to uncontrolled studies on excision of deeply infiltrating lesions. To our knowledge, only one (non-randomized) study has been published on the effect

<table>
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<th>Source, year</th>
<th>Pregancies/Total</th>
<th>OR (95%, CI)</th>
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</thead>
<tbody>
<tr>
<td>Source, year</td>
<td>Experimental group</td>
<td>Control group</td>
</tr>
<tr>
<td>Beretta et al., 1998</td>
<td>4/17</td>
<td>6/9</td>
</tr>
<tr>
<td>Alborzi et al., 2004</td>
<td>7/30</td>
<td>19/32</td>
</tr>
</tbody>
</table>

**Figure 4** Overview of RCTs comparing vaporization/coagulation with excision of ovarian endometriotic cysts. Diamonds represent odds ratio of conception and horizontal lines 95% CIs. Breslow-Day test for heterogeneity: $\chi^2 = 0.08$, $P = 0.77$. 

**Table I** Summary of data on reproductive performance in infertile women.
of conservative surgery for rectovaginal endometriosis in which the reproductive outcome in operated patients was compared with that observed in women undergoing expectant management (Vercellini et al., 2006b). Among the 44 women who had resection of rectovaginal endometriosis at laparotomy, 15 (34.1%) became pregnant, as compared with 22 of the 61 (36.1%) women who choose expectant management. The 12-month cumulative probability of conception was 20.5% in the former group and 34.7% in the latter ($P = 0.12$). Corresponding figures at 24-month survival analysis were, respectively, 44.9 and 46.8% ($P = 0.38$). However, a statistically significant longer time to recurrence of moderate or severe pain recurrence was observed in the surgery group compared with the expectant management group for all of the symptoms considered. The benefit of surgery was particularly evident with regard to deep dyspareunia and dyschezia.

The above data suggest that excision of rectovaginal plaques does not improve the likelihood of pregnancy nor reduces the time-to-conception in women with endometriosis-associated infertility. These findings may be explained by a process of ‘pseudoretroperitonealization’ of implants leading to a reduction of the biochemical impact of deep lesions on fertilization processes. In fact, adhesion between the anterior rectal wall and the posterior vaginal fornix or uterine isthmus results in exclusion of the deepest portion of the pouch of Douglas, where infiltrating endometriosis originates and develops (Vercellini et al., 1996, 2000; Vercellini, 1997). Excision of deep endometriotic implants is unlikely to influence the probability of conception to a major extent if their burial limits the inflammatory consequences on the pelvic environment. Consequently, the

### Table I Major intra- and post-operative complications of radical surgery for rectovaginal endometriosis

<table>
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<tr>
<th>Complication</th>
<th>Observed incidence (%)</th>
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<tr>
<td>Neurogenic bladder dysfunction</td>
<td>4–10</td>
</tr>
<tr>
<td>Rectovaginal fistula formation</td>
<td>2–10</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>2–6</td>
</tr>
<tr>
<td>Inadvertent rectal perforation</td>
<td>1–3</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>1–2</td>
</tr>
<tr>
<td>Pelvic abscess</td>
<td>1–2</td>
</tr>
<tr>
<td>Temporary diverting loop ileostomy/colostomy</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>Intraoperative ureteral lesion</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Post-operative ureteral fistula formation</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Post-anastomotic rectal stenosis</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Post-anastomotic ureteral stenosis</td>
<td>0.5–1</td>
</tr>
</tbody>
</table>


### Figure 5

Pregnancy rates observed after excisional surgery of rectovaginal endometriosis at laparotomy or laparoscopy. Diamonds represent percentage point estimates and horizontal lines 95% CIs. Modified from Vercellini et al. (2006b), with permission.
purported benefit of excision of rectovaginal plaques in infertile women reported by several authors (Fig. 5) may be attributed to treatment of co-existent peritoneal and ovarian endometriosis. In fact, the three different lesion types are very frequently associated (Somigliana et al., 2004, 2007).

Radical excision of rectovaginal endometriosis is almost invariably a traumatic procedure that entails extensive adhesiolysis, systematic vaginal opening, occasional rectal perforation or incidental resection and wide pelvic deperitonealization. Because this is a benign condition and post-operative morbidity is not negligible (Koninckx et al., 1996; Camagna et al., 2004; Fedele et al., 2004a; Ford et al., 2004; Marpeau et al., 2004; Thomasin et al., 2004; Vercellini et al., 2004; Darai et al., 2005; Dubernard et al., 2006; Landi et al., 2006; Table I). Infertile women with rectovaginal endometriosis should be informed that radical conservative surgery could reduce algic symptoms but probably would not greatly improve reproductive prognosis (Kenneth and Davis, 2005; Vercellini et al., 2006b). The possibility of treating peritoneal and ovarian endometriomas only without excising rectovaginal plaques should be considered especially in women with limited pain. The role of IVF-ET as a therapeutic alternative in this specific clinical condition should be elucidated.

**Surgery for recurrent endometriosis**

Very limited information is available on the effect of second-line surgery for recurrent endometriosis in infertile women.

Candiani et al. (1991) evaluated the post-operative outcome in 42 women undergoing repetitive laparotomy for endometriosis. The disease was at stage IV in 14 women, stage III in 25 and stage I in 3. After a mean follow-up of 42 months, only 8 of the 28 women (28.6%) who attempted to conceive achieved a pregnancy. A third operation was necessary in six subjects.

Busacca et al. (1998) compared surgical results in patients re-operated at laparotomy (n = 41) or laparoscopy (n = 40). Of the subset of women who were attempting to conceive, 9 women in the former group and 10 in the latter conceived after mean follow-up times of 54 and 21 months, respectively. The 24-month cumulative probability of pregnancy was 45% after laparotomy and 54% after laparoscopy, without significant differences.

More recently, Fedele et al. (2006) compared the post-operative results observed after laparoscopic excision of primary (n = 305) versus recurrent (n = 54) ovarian endometrioma in the same ovary as the primary cyst. The 5-year cumulative pregnancy rate amongst the subset of infertile women who attempted to conceive was 40.8% after the first surgical procedure and 32.4% after the second, with crude rates of 32.2 and 20.8%, respectively. According to the authors, the effect of repetitive laparoscopic surgery is similar to that observed after first-line surgery. However, three of the five pregnancies (60%) observed after re-operation were obtained by means of ART. Interestingly, 12 of the 29 (41.4%) pregnancies observed in the infertile women who underwent first-line surgery were also obtained after ART (Fedele et al., 2006).

More data are urgently needed in this specific area of endometriosis management because the systematic performance of laparoscopy, combined with the relapsing tendency of the disease, has profoundly changed the clinical scenario of referral centers, where patients with recurrent lesions are now a burden in everyday clinical activity. It is a common tenet that re-operations for endometriosis are technically more demanding and potentially more risky. In order to offer adequate counselling to patients, these drawbacks should be balanced by acceptable post-operative results.

Based on the scanty available evidence, the effect of surgery appears smaller after second- compared with first-line surgery, and the potential absolute benefit increase in women with patent tubes and recurrent moderate to severe endometriosis is difficult to estimate but may be quite limited. According to the ASRM clinical guidelines, for infertile women who have moderate to severe endometriosis and have previously had one or more infertility operations, IVF-ET is often a better therapeutic option than another infertility operation (The Practice Committee of the American Society for Reproductive Medicine, 2004). However, data are so limited that drawing definitive conclusions seems inopportune. The final decision should be taken also considering the presence of pain symptoms and of large (>4 cm) endometriomas (Kennedy et al., 2005; Royal College of Obstetricians and Gynaecologists, 2006).

It has been suggested that ultrasound-guided aspiration may constitute an alternative to repeat surgery for patients with recurrent endometriomas (Aboulghar et al., 1991). However, difficulties may be encountered when aspirating thick chocolate-like fluid. More importantly, unacceptably high cyst recurrence rates (60–90%) have been reported (Zanetta et al., 1995; Chan et al., 2003). In order to reduce the incidence of endometrioma recurrence, several authors have combined ultrasound-guided aspiration with sclerotherapy by intracystic injection of tetracycline (Aboulghar et al., 1993; Chang et al., 1997; Fisch and Sher, 2004) and ethanol (Noma and Yoshida, 2001; Koike et al., 2002), or with instillation of methotrexate (Mesogitis et al., 2005; Agostini et al., 2007). Observed recurrence rates varied between 25 and 47% after tetracycline injection (Chang et al., 1997; Fisch and Sher, 2004), 13 and 15% after ethanol sclerotherapy (Noma and Yoshida, 2001; Koike et al., 2002) and 29 and 31% after methotrexate instillation.

Due to the small sample sizes, the short follow-up periods and the lack of control groups, data on reproductive performance after the procedure reported in most of the available studies are difficult to interpret. Pabuccu et al. (2004) conducted a RCT on the effect of aspiration of ovarian endometriomas before ICSI. Specifically, 41 women were allocated to cyst aspiration at the beginning of ovarian stimulation, whereas 40 women who did not undergo endometrioma aspiration were used as controls. Number of oocytes retrieved as well as fertilization, implantation and pregnancy rates were remarkably similar.

Unfortunately, endometrioma aspiration is not without risks. Leakage of chocolate-like material or fluid used for sclerotherapy may result in pelvic adhesion formation (Muzzi et al., 1995; Garvey et al., 1999; Okagaki et al., 1999). Moreover, transvaginal procedures are particularly associated with a definite risk of ovarian abscesses as old blood constitutes an excellent bacterial culture media (Zanetta et al.,
1995; Mikamo et al., 1998). Such a complication, which usually necessitates oophorectomy, is the most undesirable outcome in infertile women. Accordingly, ultrasound-guided aspiration of recurrent endometriomas with or without concomitant sclerotherapy should be limited to women with severe adhesions, increased anaesthetic risk or those unwilling to undergo further surgery (Chapron et al., 2002; Okaro and Condous, 2005; Somigliana et al., 2006).

**Adjuvant medical treatment**

Medical treatment for endometriosis is frequently combined with laparoscopic procedures, either preoperatively or post-operatively (Vercellini et al., 2003b).

The theoretical advantages of medical treatment before surgery are reduced inflammation and vascularization and shrinkage of implants. According to some authors, these effects may contribute to easier, quicker and less traumatic surgery, with more chance of complete eradication of the disease and a reduced risk of post-operative adnexal adhesions (Kettel and Murphy, 1989; Malinak and Wheeler, 1990; Thomas, 1992; Donnez et al., 1994a, b; Hemmings, 1998; Winkel, 1999). Practical advantages include avoidance of operating in the secretory phase with the disturbing presence of a corpus luteum, and the possibility of hospital admission at any time. This may be important in large, busy, public hospitals. The carry-over effect of most drugs used preoperatively prevents short-term ovulation in a recently traumatized gonad. Finally, with preoperative treatment lasting a few weeks, the differential diagnosis between endometriotic and corpus luteum cysts can be made easily, avoiding an untimely intervention when a functional formation is present. On the other hand, under medical suppression, small endometriotic foci may temporarily regress and thus escape laparoscopic recognition and ablation (Evers, 1987). Furthermore, delaying surgery may be inopportune in some circumstances, especially when the nature of the cyst is not completely defined and serum CA 125 levels are particularly elevated. Indisputable disadvantages are the increase in the overall cost of treatment and drug-related side-effects.

Apart from general considerations, the limited data available to evaluate the effect on reproductive outcome do not suggest any benefit from preoperative medical treatments (Vercellini et al., 2003b; Yap et al., 2004). Pre-surgical medical therapy decreases the endometriosis classification scores, but there is no demonstration that this leads to better outcomes for infertile patients.

The hypothetical advantages of post-operative medical treatment include resorption of residual visible lesions whose surgical removal was considered inopportune or not possible, ‘sterilization’ of microscopic implants and reduction in the risk of disease dissemination when endometriomas rupture during mobilization. The effect of systemic short-term medical treatment after surgery has been reviewed in Vercellini et al. (2003b). Assessment of outcome for the five considered trials is shown in Fig. 6. The overall conception rate was 18.1% in the post-operative medical treatment group and 22.9% in the conservative surgery only group. The pooled OR of pregnancy of 0.77 (95% CI 0.42–1.39) does not suggest any favourable effect of post-operative medical treatment on the likelihood of conception. Indeed, due to inhibition of ovulation for some months, one pregnancy would be precluded for every 21 women treated post-operatively with hormones. Based on the results of a similar systematic literature review, Yap et al. (2004) also maintain that there is insufficient

![Figure 6](https://example.com/figure6.png) Overview of RCTs comparing conservative surgery for endometriosis with or without post-operative medical treatment. Diamonds represent odds ratio of conception, and horizontal lines are 95% CIs. Breslow-Day test for heterogeneity: $\chi^2 = 0.95, P = 0.91$. Modified from Vercellini et al. (2003b), with permission.
available evidence to conclude that hormonal suppression combined with surgery for endometriosis is associated with a significant clinical advantage.

A high post-operative endometrioma recurrence rate ranging from 30% (Kikuchi et al., 2006; Koga et al., 2006; Liu et al., 2007) to 40% (Busacca et al., 2006; Vercellini et al., 2008) has been reported in the past few years. Therefore, tertiary prevention is an additional important objective of long-term medical treatment after surgery, especially in women desiring conception in the future.

The major reduction in risk of endometrioma recurrence demonstrated recently in post-operative oral contraceptives (OCs) users (Vercellini et al., 2008), constitutes an important benefit of prolonged ovulation suppression. In fact, a crude cyst recurrence rate of 9% (9/102) in OC users and of 56% (26/46) in never users was observed. The adjusted OR for OC use was 0.04 (95% CI 0.02–0.13). The 36-month cumulative proportion of subjects free from endometrioma recurrence was 94% in always users, compared with 51% in never users (log-rank test, χ² = 36.2; P < .001). The adjusted incidence rate ratio was 0.10 (95% CI 0.04–0.24). The absolute risk reduction of endometrioma recurrence in always users compared with never users was 47% (95% CI 37–57). According to this observational evidence, post-operative use of an estrogen–progestin combination prevented endometrioma recurrence in one out of two patients (95% CI 0.2–7) 3 years after surgery, with a relative risk reduction of 80%. However, the protective effect of estrogen–progestin combination tended to vanish rapidly after discontinuation.

**Surgery or IVF?**

**Surgery before IVF**

The role of operative laparoscopy before IVF is controversial and the available evidence on this issue is generally inconsistent. Garcia-Velasco et al. (2004a) did not observe a significant difference between the pregnancy rate of 133 women who underwent surgery for endometriomas before IVF (25.4%) and that of 56 subjects who proceeded directly to IVF without prior endometriotic cyst removal (22.7%). Wong et al. (2004) compared the outcome of 36 patients who underwent laparoscopic removal of an endometrioma before IVF/ICSI with that of 38 women who also had an endometrioma but went directly to IVF/ICSI. The authors observed a trend towards a more favourable pregnancy rate in the former group than in the latter (47 versus 34%), but the difference did not reach statistical significance.

According to Garcia-Velasco and Arici (2004b), the core question is whether surgery adds anything of value for infertile women with moderate to severe endometriosis or whether they undergo a surgical procedure simply because it is the so-called ‘gold standard’. De Hont et al. (2006) maintained that the simple truth is that we do not know and that RCTs are desperately needed to solve this issue.

A prompt reply came from Demirol et al. (2006), who reported the results of the first available RCT on this issue. A group of 99 patients with endometriomas scheduled for an ICSI cycle were allocated to conservative surgery before ICSI (n = 49) or immediate ICSI without prior surgery (n = 50). No significant differences were observed in fertilization (86 versus 88%), implantation (16.5 versus 18.5%) and pregnancy (34 versus 38%) rates.
pregnancies and specific clinical conditions, in order to avoid discon-
tinuation of IVF after a single cycle to undergo an operative laparos-
copy. In fact, the probability of conception was lower in the IVF
group than in the repeat surgery group when only one cycle was per-
formed (Cheewadhanaraks et al., 2004), whereas the reverse was true
after two IVF cycles (Pagidas et al., 1996). In these circumstances, the
major advantages of laparoscopy are its effectiveness comparable to
one or two IVF cycles without increase in risk of multiple pregnancy,
the possibility of achieving subsequent pregnancies, alleviation of pain
and removal of endometriomas for histological diagnosis. The major
disadvantages are cost, morbidity, a potentially longer
time-to-conception compared with IVF and the paucity of skilled sur-
geons. Moreover, IVF treats multiple co-existing infertility problems at
the same time and may be performed without delay, making it particu-
larly attractive for older patients (Adamson, 2005).

International guidelines

The ESHRE (Kennedy et al., 2005), the ASRM (The Practice Comit-
tee of the American Society for Reproductive Medicine, 2004) and the
Royal College of Obstetricians and Gynaecologists (RCOG) (Royal
College of Obstetricians and Gynaecologists, 2006) published guide-
lines and recommendations for the management of women with
endometriosis. There is general agreement on most issues regarding
the suggested clinical conduct in the case of endometriosis-
associated infertility (Table II). The three organizations recommend
surgery for peritoneal endometriosis (stage I–II disease), although
ESHRE and ASRM acknowledge that the benefit is limited. Consensus
also exists on ovarian endometriomas (stage III-IV disease), as the
effect of surgery is always defined ‘possible’. In spite of this consider-
ation, ESHRE and ASRM suggest surgical removal of endometriotic
cysts, whereas the RCOG does not give a specific indication. Post-
operative adjuvant treatment is consistently discouraged, as no evi-
dence of efficacy is available in terms of increased pregnancy rate
with post-operative ovarian suppression. Surgery before IVF is
suggested by ESHRE and RCOG only when an ovarian endometrioma
of ≥ 4 cm in diameter is present, whereas ASRM does not give a rec-
ommendation, but emphasizes that the benefit of such a procedure is
doubtful. Recurrent endometriosis is addressed by ASRM which
suggests IVF instead of second-line surgery. The specific case of recto-
vaginal lesions has not been dealt with by any of the organizations.

Commonsense management
beyond the guidelines

Non-randomized studies studies versus
actual RCTs

According to Vandekerckhove et al. (1993), many infertile women will
eventually conceive independently of, or in spite of, medical remedies.
When patients are subfertile rather than sterile, it is tempting to give
undeserved credit to interventions when pregnancies occur. Standard
treatments aimed at eradication of endometriotic lesions have been
adopted largely on the basis of uncontrolled studies. Hughes et al.
(1993) confirm that such trials fail to take into account the potential
for spontaneous pregnancy in untreated patients and cannot be
used to assess the effectiveness of treatment.

The case of ablation of minimal and mild implants seems paradig-
matic to depict the fallacies deriving from the results of non-
randomized studies on the effect of conservative surgery for
endometriosis-associated infertility. A few years before publication

#### Table II

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<th>Source, year</th>
<th>Pregancies/ Total</th>
<th>OR (95%, CI)</th>
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<tr>
<td></td>
<td>IVF-ET group</td>
<td>Surgery group</td>
</tr>
<tr>
<td>Pagidas et al.,1996</td>
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<td>4/18</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Cheewadhanaraks et al., 2004</td>
<td>3/24†</td>
<td>6/32</td>
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<td>Common odds ratio</td>
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#### Figure 7

Results of studies comparing IVF-ET with second-line surgery in infertile women with recurrent moderate to severe endometriosis. Diamonds represent odds ratio of conception and horizontal lines 95% CIs. Breslow-Day test for heterogeneity: $\chi^2 = 2.58, P = 0.108$. *Results observed after one or two IVF-ET cycles. †Results observed after a single IVF-ET cycle.
of the results of the Canadian and Italian multicenter trials (Marcoux et al., 1997; Parazzini, 1999), findings of a meta-analysis based on cohort studies suggested a consistent benefit of laparoscopic surgery, with an OR of conception of 2.67 (95% CI 2.8–3.45). Based on these data, the authors fostered performance of large RCTs to verify the purported effect of physical destruction of limited endometriotic implants (Hughes et al., 1993). The common OR resulting after pooling of data from the two trials (1.65) is significantly less than that estimated (Marcoux et al., 1997; Parazzini, 1999; Evers, 1999; Al-Inany, 2000, 2001; Crosignani and Vercellini, 2000; Jacobson et al., 2002). The overall likelihood of conception derived from results of the cohort studies was 65% (439/677) in women who underwent ablation of endometriotic lesions versus 39% (154/396) in controls (Hughes et al., 1993), with a between group difference of 26%. Corresponding figures based on data from the formal RCTs are 33 (75/226) and 23% (50/216), with a between group difference in conception rates of 10, and 8% if only late pregnancies are considered (Marcoux et al., 1997; Parazzini, 1999).

The above phenomenon has been evaluated formally in the field of gynaecologic surgery by Johnson et al. (2008), who observed a general trend towards a reduction in effect size as a topic matured and trials got larger over time. It is not to be excluded that the situation might appear similar if and when RCTs are conducted on treatment of endometriomas.

### Pros and cons of surgery

By weighing the pros and cons of surgery, a balance should always be defined between the absolute benefit increase of a procedure and its related morbidity. As an example, enucleation of endometriotic cysts is generally uneventful, whereas excision of rectovaginal plaques is not infrequently associated with complications and serious morbidity, with a risk of rectovaginal fistula formation as high as 10% even in expert hands (Dariel et al., 2005; Dubernard et al., 2006). Consequently, even hypothesizing a similar effect size, the overall balance of surgery might appear advantageous in infertile women with endometriomas, but unfavourable in those with deeply infiltrating lesions. In addition, whereas the results reported after endometrioma removal are reasonably reproducible by many surgeons, those relative to rectovaginal endometriosis excision are strictly operator-dependent. Complication rates in the hands of surgeons not specifically trained in such particularly demanding interventions are likely to increase dramatically.

More in general, speculations on the role of different lesion types in determining a reduction in the likelihood of conception may obscure a possible simpler reality: in women with undamaged tubes, the effect of surgery for endometriosis-associated infertility may be similar for different clinical conditions and stages. This hypothesis is substantiated by data from a large database of 1037 women who underwent first-line surgery over a 12-year period (Busacca et al., 2006). The overall conception rate in women who tried to become pregnant was about 25% regardless of the site of the lesion (i.e. peritoneal, ovarian or deeply infiltrating). This proportion may seem low, but is consistent with the results of the few RCTs on the efficacy of surgery in infertile women.

The effect of surgery seems reduced in women with relapsing disease. This is conceivable for several reasons: endometriosis recurring after first-line surgery may constitute a particularly aggressive disorder with an adverse prognosis; surgically induced de-novo adhesions may impact on the likelihood of pregnancy and re-operation for endometriomas may further damage ovarian reserve. Importantly, two comparative, non-randomized studies demonstrated similar results after IVF compared with those after surgery (Pagidas et al., 1996; Cheewadhanaraks et al., 2004).

There is no convincing evidence that surgery before IVF enhances pregnancy rates. Accordingly, the choice of a laparoscopy before ART is based essentially on physical considerations (i.e. interference with pick-up) more than on improvement of results. An additional surgical procedure should be considered with caution in patients with multiple previous operations.

### NNT, OR and conflicts of interest

The expression of outcome in terms of NNT gives a different and more pragmatic view of the reproductive prognosis, and facilitates measuring the cost of an additional pregnancy. In fact, economic implications should play a greater role in the indication of medical interventions in infertile women with endometriosis. Heads of gynaecology department should have detailed knowledge of the advantages and drawbacks of different treatment options when analysing waiting lists and deciding on admissions. In countries with national health care systems, public hospital administrators should have knowledge of

### Table II International guidelines on surgical treatment of endometriosis-associated infertility in asymptomatic women

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>ESHRE 2005</th>
<th>ASRM 2006</th>
<th>RCOG 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal-mild endometriosis (stage I–II disease)</td>
<td>Limited benefit: surgery recommended</td>
<td>Small benefit: surgery recommended</td>
<td>Demonstrated benefit: surgery recommended</td>
</tr>
<tr>
<td>Moderate–severe endometriosis (stage III–IV disease)</td>
<td>Possible but unproven benefit: surgery recommended</td>
<td>Possible benefit: surgery recommended</td>
<td>Possible benefit: recommendation uncertain</td>
</tr>
<tr>
<td>Post-operative adjuvant treatment</td>
<td>No benefit: not recommended</td>
<td>No benefit: not recommended</td>
<td>No benefit: not recommended</td>
</tr>
<tr>
<td>Surgery before IVF</td>
<td>Recommended if endometrioma ≥4 cm</td>
<td>Doubtful benefit: no recommendation</td>
<td>Recommended if endometrioma ≥4 cm</td>
</tr>
<tr>
<td>Recurrent endometriosis</td>
<td>No recommendation</td>
<td>Second-line surgery not recommended</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>
data when distributing funds, and governmental health authorities should consider the magnitude of the benefit when reimbursing the procedure. The NNT in case of infertile women with minimal to mild endometriosis constitutes an emblematic clinical condition. The risk of wasting public money is substantial because a laparoscopy may be indicated by physicians to women for whom surgery has been deemed not cost-effective due to a poor cost–benefit ratio.

Additional concerns are caused by potential conflicts of interest. A conflict of interest is a set of conditions in which professional judgment regarding a primary interest (such as a patient’s welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain). Among the areas of concern are self-referral by physicians, which includes ordering diagnostic tests or indicating medical interventions in which they have a financial interest without regard to whether tests or interventions are in the patient’s interest. The severity of a conflict depends on the likelihood that professional judgement will be influenced by a secondary interest (Thompson, 1993). Given the somewhat vague scientific scenario, gynaecologists with personal interest in ART might be more prone to suggest IVF, whereas surgeons might push for laparoscopy. In the present undefined situation, more attention than ever should be paid to this issue.

The need for unbiased and informative counselling
Gynaecologists ought to inform their patients that surgery has less effect on endometriosis-associated infertility than previously believed, and should define post-operative probability of conception in terms of absolute benefit increase (i.e. the benefit specifically attributable to surgery over the background likelihood of conception). Counselling based on rough overall pregnancy rates may be misleading and may persuade a patient to opt for surgery when she might have decided otherwise.

According to Copperman and DeCherney (2006), surgery for infertility is being rendered obsolete by advanced reproductive technologies. In fact, the IVF-ET success rates continue to increase, and are currently far superior to results only a decade ago (Diamond, 2005). Feinberg et al. (2008) maintain that ART has superseded surgery as first-line therapy for endometriosis-associated infertility, as the latter carries greater risks and less proven benefits than IVF. In these circumstances, it is unfortunate that even in large hospitals ART sometimes still plays only a marginal role (Somigliana et al., 2008).

Unbearable pain in women wanting a spontaneous pregnancy and refusing IVF, still constitutes an indisputable indication for excisional treatment of endometriosis in infertile subjects. If algic symptoms are tolerable, bowel and ureteral stenosis are absent, and no endometriomas larger than 4 cm or with alarming ultrasonographic characteristics are observed, surgery and ART should be both offered to infertile patients while explaining clearly the advantages and drawbacks of the two therapeutic options.

The patient role in medical decisions
Detailed and thorough patient information is always of utmost importance when choosing among therapeutic alternatives. This is especially true when dealing with benign chronic diseases not interfering with general health, in case of major differences in terms of risks and morbidity between treatment options, and when the purported benefits of an invasive procedure are undetermined. Uncertainties deriving from lack of reliable evidence should be discussed, and consent to operation should never be obtained by frightening women if they choose not to be operated on (e.g. anticipating lesion progression or malignant degeneration). Poor communication and failure to inform can lead to unrealistic expectations, and women will be unprepared to face problems and treatment failure if they arise (Coulter, 2001).

According to Deyo (2001), many medical decisions, typically including elective surgical procedures for benign chronic diseases, fall into a grey area where the optimal choice for an individual patient may be unclear and where reasonable people might choose differently. When well informed with the best available evidence, patients often make different decisions from their physicians (Deyo, 2001). This is especially important when dealing with younger women (under 40 years of age) who are particularly motivated in playing an active role in medical decision making (Coulter, 2001).

Conclusions
In the past two decades, the growing popularity and widespread diffusion of operative laparoscopy has resulted in an increase of surgical procedures in women with endometriosis. However, the role of laparoscopy appears to have changed from a technique originally developed to obtain results similar to laparotomy but at reduced morbidity, into a method on which to base the therapeutic strategy for endometriosis.

Gradually, convictions developed regarding several aspects of disease management, including the need for visual diagnosis, staging, excision/destruction of lesions and follow-up investigation. Unfortunately, such management modalities were introduced in standard practice based mainly on uncontrolled studies, and today the treatment of endometriosis is still based more on clinical opinion than fact (Gibbons, 2004). Nevertheless, surgery is currently proposed as the more appropriate therapeutic approach to most of the problems caused by, or associated with, endometriosis (Redwine et al., 2000).

However, infertile women with endometriosis constitute a paradigmatic situation in which the therapeutic approach should be ‘problem-oriented’ and not ‘lesion-oriented’, and before suggesting systematic resection one should be reasonably confident that the chances of overcoming the main clinical problem would be substantially increased. Pregnancy is here the main outcome of interest, independently of other variables (Farquhar, 2000).

Regrettably, given the scanty methodological quality of most of the available studies on the effect of surgery for endometriosis-associated infertility, only limited conclusions can be drawn.

(i) The absolute benefit increase in terms of enhancement of pregnancy rates seems lower than the previously suggested 38% (Adamson and Pasta, 1994) being reasonably between 10 and 25%. This estimate is largely based on the results of observational or non-randomized trials and appears to be partly independent of specific lesion types.

(ii) The practical impact of surgery for stage I–II disease, as well as the calculation of the NNT, are greatly influenced by prevalence of the condition in the population undergoing laparoscopy.
(iii) The effect of surgery for peritoneal disease is small. Harm is also limited, but the cost/benefit ratio is unfavourable. Excision of rectovaginal lesions is of doubtful value and associated with severe morbidity. First-line surgery for large ovarian endometriomas seems to be the procedure with the most favourable balance between benefits, harm and costs.

(iv) A practical advantage of surgery is temporary pain relief in symptomatic patients. This may render feasible spontaneous attempts at conception in women who refuse or prefer to postpone IVF.

(v) Complete and detailed information on risks and benefits of treatment alternatives must be offered to patients, in order to allow unbiased choices between different possible options.

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**Authors role**

P.V. contributed to the conception of the review, took part in the analyses and completed the first draft and subsequent amendments. E.S., P.V. and P.G.C. contributed to the conception of the review and subsequent amendments. A.A. and G.B. performed the literature search and conducted the statistical analyses.

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