

Management of endometriomas in women requiring IVF: to touch or not to touch

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The classic, unproven dogma that ovarian endometrioma should be removed in all infertile women prior to IVF has been recently questioned. There is currently insufficient data to clarify whether the endometrioma-related damage to ovarian responsiveness precedes or follows surgery. Both endometrioma-related injury and surgery-mediated damage may be claimed to be involved and the relative importance of these two insults remains to be clarified. Convincing evidence has emerged showing that responsiveness to gonadotrophins after ovarian cystectomy is reduced. Conversely, the impact of surgery on pregnancy rates is unclear since no deleterious effect has been reported. Of relevance here is that surgery exposes women to risk related to a demanding procedure whereas risks associated with expectant management are mostly anecdotal or of doubtful clinical relevance. We recommend proceeding directly to IVF to reduce time to pregnancy, to avoid potential surgical complications and to limit patient costs. Surgery should be envisaged only in presence of large cysts (balancing the threshold to operate with the cyst location within the ovary), or to treat concomitant pain symptoms which are refractory to medical treatments, or when malignancy cannot reliably be ruled out.

Key words: ovarian endometriomas / surgery / IVF / ovarian responsiveness / pregnancy rates

Introduction

Endometriosis affects approximately 10% of the female population in their fertile years and 10–25% of patients requiring assisted reproduction treatment (ART). Endometriotic ovarian cysts are a common form of the disease and may be present in up to 20–40% of women with endometriosis scheduled for IVF (Jenkins *et al.*, 1986; Vercellini *et al.*, 2003).

Classical surgical management of endometriotic ovarian cysts in patients requiring IVF has been recently challenged by evidence questioning the benefits of surgery in many, if not all, of these cases. The old aphorism ‘when in doubt, cut it out’ has been replaced with a more evidence-based approach, that tries to balance carefully the advantages as well as the complications of cyst removal prior to ART (Somigliana *et al.*, 2006a; Garcia-Velasco, 2008).

In the present article, we will try to dissect what is the impact of endometriotic cysts on ovarian response and whether surgery may prove beneficial and we will try to balance the pros and cons of a surgical approach prior to ART.

For this purpose, we did an extensive search of the published English literature in Medline from 1990 to 2008, with the keywords ‘endometriosis’, ‘endometrioma’, ‘endometriotic’, ‘IVF’, ‘ICSI’ and

‘*in vitro* fertilization’ and relevance was evaluated after reading the abstracts. Manual search of review articles and cross references completed the search. Articles with an inappropriate design were rejected.

Endometriomas and ovarian responsiveness

Ovarian responsiveness to hyperstimulation plays a crucial role in determining the success rate of IVF. In women developing few follicles despite the use of elevated dosages of gonadotrophins, the prognosis is worse (Broekmans *et al.*, 2006; Van Voorhis, 2007).

In this regard, it is noteworthy that that ovarian responsiveness is damaged after the presence and excision of ovarian endometriomas (Gupta *et al.*, 2006; Somigliana *et al.*, 2006a). In a recent meta-analysis, Gupta *et al.* showed that the number of developing follicles and the number of retrieved oocytes are lower in affected women when compared with controls who were unaffected. Specifically, 0.9 (95% CI –1.4, –0.3) fewer follicles developed and 1.7 (95% CI –3.2, –0.2) fewer oocytes were retrieved in these women (Gupta *et al.*, 2006). Data emerging from subsequent studies on this issue tend to confirm these findings (Esinler *et al.*, 2006; Somigliana

et al., 2006b; Yazbeck *et al.*, 2006; Cirpan *et al.*, 2007; Matalliotakis *et al.*, 2007; Kumbak *et al.*, 2008). The harmful effect of endometriomas, and/or their excision, on ovarian responsiveness is further supported by studies focusing on women with monolateral disease and comparing responsiveness to hyperstimulation in the affected and in the contralateral intact gonad of the same patient (Ragni *et al.*, 2005; Somigliana *et al.*, 2006a; Duru *et al.*, 2007). Collectively, these studies strongly support a marked reduction in the number of developing follicles and retrieved oocytes in the previously operated ovaries.

Conversely, the potential impact of this endometrioma-related reduced responsiveness on the success rate of IVF is less recognized. In their meta-analysis, Gupta *et al.* reported an OR for clinical pregnancy rate in women with the disease of 1.07 (95% CI 0.63–1.81) (Gupta *et al.*, 2006). There are at least two main hypotheses to explain this contrasting result.

Firstly, the damage could be quantitative rather than qualitative. In other words, in contrast to women whose ovarian reserve has naturally declined, fewer oocytes but of unaffected quality might be retrieved in affected women. Interestingly, in the single available prospective study comparing responsiveness of ovaries operated for endometriomas to contralateral intact gonads of the same patient, Ragni *et al.* documented a marked reduction in the number of developing follicles and in the number of retrieved oocytes, but failed to observe differences in terms of fertilization rate between oocytes retrieved from affected and unaffected ovaries (Ragni *et al.*, 2005).

Secondly, ovarian endometriomas are mostly monolateral. Both gonads are involved only in 19–28% of cases (Somigliana *et al.*, 2008). The contralateral intact ovary may adequately compensate for the reduced function of the affected one. In this context, studies that have specifically focused on women with bilateral endometriomas should be considered more informative. Esinler *et al.* compared 23 women with bilateral disease to 99 unaffected controls (Esinler *et al.*, 2006). The pregnancy rate per started cycle was lower in the study group (35 versus 43%), but the difference did not reach statistical significance. In a larger study including 68 women operated on for bilateral endometriomas and 136 age-matched, unaffected controls, Somigliana *et al.* showed a statistically significant reduction in the chances of success (Somigliana *et al.*, 2008). The odds ratio (OR) for clinical pregnancy and delivery in the study group was 0.34 (95% CI 0.12–0.92) and 0.23 (95% CI 0.07–0.78), respectively.

Collectively, insights emerging from these observational studies support the conclusion that ovarian responsiveness is modified in affected gonads. Although the injury could be more quantitative than qualitative, in some cases the insult can be so relevant that no or only few oocytes are retrieved. In this regard, it is noteworthy that Ragni *et al.* documented a failure in the growth of codominant follicles in 34% of operated ovaries (Ragni *et al.*, 2005). This issue may assume great relevance in women with bilateral disease.

Endometrioma-related impact on ovarian responsiveness: a primary or a secondary event?

There is currently insufficient data to clarify whether the endometrioma-related damage to ovarian responsiveness precedes or follows surgery. Elucidation of this point is of utmost interest since it would strongly

impact on the decision of whether to operate on women with endometriomas and who are selected for IVF. At present, there appears to be evidence supporting both an endometrioma-related injury and a surgery-mediated damage. The relative importance of these two insults remains to be clarified.

Endometrioma-mediated damage

Using pathological sections of the ovarian cortex surrounding ovarian benign neoplasms, Maneschi *et al.* found reduced follicular numbers and activity antecedent to surgery in endometriomas when compared with teratomas or benign cystadenomas, suggesting that the disease *per se* may be detrimental to the ovary (Maneschi *et al.*, 1993). Moreover, in a rabbit model, Kaplan *et al.* showed that endometrial implants in the ovaries decreased the number of ovulation points (Kaplan *et al.*, 1989). Data regarding responsiveness to ovarian stimulation during IVF in unoperated gonads are unfortunately scanty. The vast majority of studies regarding the impact of endometriomas on IVF outcome have focused on previously operated women. Thus, they cannot clarify whether the damage is caused by the development of an endometrioma or by its surgical removal. To our knowledge, there is only one report specifically addressing this point (Somigliana *et al.*, 2006b). This study evaluated 36 unoperated women with monolateral endometriomas and who were selected for IVF. The number of codominant follicles in affected and contralateral unaffected gonads was 3.0 ± 1.7 and 4.0 ± 2.2 , respectively ($P = 0.01$). This difference corresponded to a mean reduction of 25% (95% CI 6–44) in affected ovaries (Somigliana *et al.*, 2006b).

Surgery-mediated damage

The impact of surgical removal of endometriotic cysts on ovarian reserve has attracted the interest of researchers in the last few years.

A potential deleterious mechanism of surgery is the accidental removal of a consistent amount of ovarian tissue during cystectomy. Conservative laparoscopic surgery of ovarian cysts with well-defined ovarian capsules (e.g. teratomas and benign cystadenomas) very seldom show healthy ovarian tissue being removed next to them (Hachisuga and Kawarabayashi, 2002; Muzii *et al.*, 2002). In contrast, in more than 50% of the endometriomas removed, primordial follicles are found, probably due to the lack of capsule that creates strong adhesions and to technical difficulties in the removal. This is in line with the most commonly accepted pathogenic theory stating that the endometrioma is a pseudocyst with the inverted ovarian cortex being its wall (Brosens *et al.*, 1996). In this regard, it is not surprising that removal of the cyst will inadvertently also include removal of healthy ovarian tissue with primordial follicles.

The damage inflicted by surgery to ovarian responsiveness may be due not only to the removal of healthy tissue by laparoscopic stripping, but also to surgery-related local inflammation or vascular compromise following electrosurgical coagulation. In contrast with open surgery (mini laparotomy), the laparoscopic procedure may involve more temptation for the operator to coagulate more often, which may have a detrimental effect on the remaining primordial follicle pool. In fact, bilateral disease with laparoscopic removal of endometriomas from both ovaries has a 2.4% risk of premature ovarian failure (Busacca *et al.*, 2006). The pathogenic mechanisms may reduce ovarian reserve and function afterwards by damaging ovarian stroma

as well as ovarian vascularization. Interestingly, power Doppler imaging of the ovaries after laparoscopic surgery for large endometriomas has shown a decreased ovarian stromal blood flow, suggesting a permanent insult to the gonad (Wu *et al.*, 2003).

Treatment prior to IVF

Non-surgical treatment

Ovarian endometriotic cysts respond poorly to medical therapy. Medical treatment is moderately effective in improving pain but absolutely inefficient in improving fertility in women with endometriosis (Ozcan *et al.*, 2008). Medical treatment may prevent further growth of the cyst or reduce the size, although shrinkage does not imply a reduction of the endometriotic tissue but mainly a diminution of the chocolate fluid within the cyst (Wood *et al.*, 2000). Thus, medical therapy by itself should not be considered in infertile women with endometriomas.

In contrast, it has been suggested that pituitary suppression with the administration of GnRH analogues for a few months prior to IVF may increase the success rate in women with endometriomas. The hypothetical beneficial effects may derive from the induced amenorrhea, a similar endocrine environment to hypogonadotropic hypogonadism, or to the effects of GnRH analogues on aromatase expression or on uterine NK cells, but this is all still speculative. A recent meta-analysis on this subject showed that a 3–6 month treatment period with GnRH analogues prior to an IVF cycle improved the odds of clinical pregnancy in women with endometriosis by 4-fold (Sallam *et al.*, 2006). As the results were extracted from only 165 patients and 78 pregnancies, they should be interpreted with caution. Moreover, the three trials included in the meta-analysis did not specifically focus on women with endometriomas. In any case, these results encourage further randomized trials to finally determine whether or not there is a benefit from this combined approach (Caihong *et al.*, 2007).

An alternative to surgery in some cases might be ultrasound-guided aspiration of ovarian endometriomas, a procedure first proposed by Aboulghar *et al.* (1991). Whether it is just cyst aspiration or, in order to reduce recurrence, aspiration plus *in situ* irrigation or injection with a sclerosing agent, the published evidence is still not very convincing. Sclerosing substances used vary from tetracycline (Aboulghar *et al.*, 1993) to methotrexate (Mesogitis *et al.*, 2000), recombinant interleukin-2 (Acien *et al.*, 2003) and/or ethanol (Noma and Yoshida, 2001). For those patients who decline surgery, or in whom surgery is contraindicated, cyst aspiration may facilitate oocyte retrieval, although the rates of disease recurrence are high.

Surgery

Despite the lack of randomized controlled trials (RCTs), there is a general consensus that laparoscopic treatment of endometriomas increases the chances of pregnancy (Chapron *et al.*, 2002a). Following the procedure, pregnancy rate varies from 30 to 67%, with an overall mean of 50% (Jones and Sutton, 2002). Even if the possibility of an increased rate of spontaneous pregnancy also in women selected for IVF is a point deserving attention, it has to be underlined that the magnitude of the benefits of surgery in this context is poorly

defined but presumably very limited (Pagidas *et al.*, 1996; Adamson, 2005; Littman *et al.*, 2005; Fedele *et al.*, 2006).

The specific role of surgery in the management of women with endometriomas scheduled for IVF has been recently investigated in a RCT (Demiroglu *et al.*, 2006). In this study, 99 women were allocated to either conservative surgery ($n = 49$) or IVF without prior surgery ($n = 50$). Ovarian surgery resulted in longer stimulation, higher FSH requirements and lower oocyte numbers, but fertilization, pregnancy and implantation rates did not differ between the groups. Specifically, the pregnancy rate in the ovarian surgery group and the expectant management group was 34 and 38%, respectively. To date, this is the only published RCT on this issue. Of interest, results from a previous observational study led to the similar conclusions. Garcia-Velasco *et al.* (2004) compared IVF outcome for 133 women who had previously removed ovarian endometriomas and 56 women with an endometrioma present at the time of the procedure. In the former group, the gonadotrophin doses administered were significantly higher and the peak E_2 levels were significantly lower. Conversely, number of oocytes retrieved, number of embryos obtained and number of transferred embryos did not differ, and the pregnancy rate in the two groups was 25 and 23%, respectively ($P = NS$) (Garcia-Velasco *et al.*, 2004).

In this context, it is noteworthy that not all the different techniques used for surgical removal of endometrioma may have the same impact on the outcome. In particular, assuming that an endometrioma is an 'extra-ovarian pseudocyst', only opening and vaporizing or coagulating the inner surface of the cysts may prevent the inevitable removal of ovarian cortex associated with the use of the stripping technique. Some data in humans support this possibility (Donnez *et al.*, 2001; Somigliana *et al.*, 2006a). In this context, it is of note that the endometrioma wall contains endometriotic tissue covering the inner wall for 60% of the surface and it does not penetrate >1.5 mm (Muzii *et al.*, 2007), which is an interesting histologic observation to bear in mind while performing surgery. However, the repeatedly reported higher spontaneous pregnancy rates and lower recurrence rates associated with the stripping technique have limited the diffusion of the vaporization/coagulation approach (Beretta *et al.*, 1998; Alborzi *et al.*, 2004).

The risks of surgery or expectant management

Ovarian responsiveness and the chance of conception during ART cycles are not the only factors that a physician has to consider prior to deciding whether or not the patient should undergo surgical treatment of an endometrioma.

Surgery is costly and not free from complications. 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.*, 2002b). This aspect is particularly relevant here since the majority of patients with endometriosis selected for IVF have advanced stage disease and have generally been operated at least once before. Most have developed thick adhesions and are thus at increased risk of complications from further surgery. Albeit uncommon, ureteral and bowel injuries with associated sequelae have to be expected.

On the other hand, the expectant strategy is also associated with potential risks. They are the following:

- (i) *Missing an occult early stage malignancy.* Surgical removal and histological examination are considered mandatory to identify early ovarian cancer. Despite recent progresses in diagnostic tools (Visintin *et al.*, 2008), this risk cannot currently be definitely ruled out. The two largest available series concerning the risk of occult malignancy in endometriotic samples reported a frequency of 0.8 and 0.9%, thus suggesting that this event is rare but possible (Mostoufizadeh and Scully, 1980; Stern *et al.*, 2001). A careful sonographic evaluation and strict monitoring over time may nearly annul this possibility (Eskenazi *et al.*, 2001).
- (ii) *Development of a pelvic abscess.* The bloody content of an endometrioma may serve as an excellent culture medium and may facilitate the spread of an infection process. Not surprisingly, the development of a pelvic abscess following oocyte retrieval has been repeatedly reported (Tsai *et al.*, 2005; Benaglia *et al.*, 2008a). Clinical management of these cases is demanding and surgery may be necessary. The incidence of this frightful complication seems however rare. In an effort to determine the magnitude of this risk, Benaglia *et al.* have evaluated the frequency of this complication in women with endometriomas in a large consecutive series of 214 oocyte retrieval procedures (Benaglia *et al.*, 2008a). This complication was never observed (0.0%; 95% CI 0.0–1.7) suggesting that this risk is at least below 1.7%. In this regard, we however believe that prophylactic antibiotics should be routinely used and that every effort should be made to avoid the puncture of the endometrioma.
- (iii) *Progression of endometriosis.* Since endometriosis is an estrogen-dependent disease and ART cycles determine a substantial increase in the peripheral levels of this hormone, a certain degree of alarmism about possible detrimental effects is common among affected patients and appears theoretically justified. Benaglia *et al.* have recently reported reassuring data (Benaglia *et al.*, 2008b). These authors have prospectively evaluated 48 women with endometriomas undergoing IVF and measured the dimension of the cysts before and 2–6 months after the procedure. They failed to document any significant modification.
- (iv) *Other complications.* Other complications of unoperated endometriomas include risk of causing the rupture of the endometrioma (Dicker *et al.*, 1993; Garcia-Velasco *et al.*, 1998), possible follicular fluid contamination with endometrioma content, difficulties during oocyte retrieval (Somigliana *et al.*, 2006a) and increased obstetric complications such as preterm birth or intrauterine growth restriction (Fernando *et al.*, 2008). Data regarding the first risk is anecdotal, whereas the effects of endometriotic fluid on the oocyte quality are still debated (Dmowski *et al.*, 1995; Khamsi *et al.*, 2001; Suwajanakorn *et al.*, 2001). The benefits of surgery in facilitating oocyte retrieval may however be considered taking into account endometrioma location within the ovary, specially if healthy follicles are located behind the cyst and the ovary is fixed. Finally, there is no evidence that surgery may significantly overcome the reported increased obstetric complications.

Table 1 Clinical variables to be considered when deciding whether to perform surgery or not in women with endometriomas selected for IVF

Characteristics	Favours surgery	Favours expectant management
Previous interventions for endometriosis	None	≥ 1
Ovarian reserve ^a	Intact	Damaged
Pain symptoms	Present	Absent
Bilaterality	Monolateral disease	Bilateral disease
Sonographic feature of malignancy ^b	Present	Absent
Growth	Rapid growth	Stable

^aOvarian reserve is estimated based on serum markers or previous hyperstimulation cycles; ^bsonographic feature of malignancy refers to solid components, locularity, echogeniety, regularity of shape, wall, septa, location and presence of peritoneal fluid.

Conclusions and recommendations

In conclusion, what is the benefit, if any, of removing ovarian endometriotic cysts prior to IVF? There is convincing evidence that responsiveness to gonadotrophins after ovarian cystectomy is reduced and the number and quality of oocytes retrieved are at least not improved. Moreover, surgery exposes women to the dangerous risks inevitably related to a demanding surgery. In contrast, risks associated with expectant management are mostly anecdotal or of doubtful clinical relevance.

Overall, laparoscopic surgical removal of ovarian endometriotic cysts prior to IVF does not offer any additional benefit in terms of fertility outcomes. We thus recommend generally proceeding directly to IVF to reduce time to pregnancy, to avoid potential surgical complications and to limit patient costs. Surgery should be envisaged in specific circumstances (see Table 1), such as to treat concomitant pain symptoms which are refractory to medical treatments, or when malignancy cannot be reliably ruled out, or in the presence of large cysts. The diameter threshold for performing an operation before IVF should be adjusted according to the endometrioma location within the ovary. All decisions to operate a cyst beyond 3 or 4 cm are arbitrary, as there is no evidence to support one or the other. Surgeons should bear in mind that if all healthy growing follicles may be reached without damaging the endometrioma, cyst over 4 or even 5 cm do not require surgery in asymptomatic patients; however, smaller cysts that hide growing follicles, specially when the ovary is fixed, may require intervention.

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