Perspective

Women's Health

Exploring the relationship between endometriomas and infertility

Several clinical and epidemiological studies demonstrated an association between endometriosis and infertility. A role in the genesis of infertility may be played by endometriomas, which may interfere with ovulation or damage ovarian tissue. Unlike peritoneal implants, the availability of an accurate noninvasive sonographic diagnosis facilitates the investigation of endometrioma associated infertility. The laparoscopic excision of an endometrioma relieves the ovary from the damage caused by the cyst itself, which may be progressive over time, but at the same time is associated with a detrimental effect on ovarian reserve and with high rates of postoperative endometrioma recurrence. Therefore, the management of endometrioma-related infertility should not be based upon surgery alone, but upon a combination of surgery, with a refinement of the operating technique, long-term oral contraceptive, *in vitro* fertilization and oocyte cryopreservation.

Keywords: female infertility • *in vitro* fertilization • laparoscopic surgery • ovarian endometriomas • ovarian reserve

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The prevalence of endometriosis may approach 10% among women of reproductive age [1]. Several clinical and epidemiological studies have demonstrated an association between endometriosis and infertility; in fact, it has been estimated that 30–50% of women affected by endometriosis are infertile [2] and that the fecundity rate of women with stage III–IV endometriosis is 2–10%, compared with 15–25% of controls [3].

The pathogenic pathway that leads from endometriosis to infertility is scarcely known [4]. Since endometriosis is a polymorphic disease, it may negatively affect fertility in many ways, from the distortion of the pelvic anatomy to alteration of peritoneal fluid and the induction of a chronic inflammatory status. Moreover, a relevant role in the genesis of infertility may be played by ovarian endometrioma, either because it is a common clinical manifestations of the disease, being present in more than half of the women with endometriosis [5], and because it may negatively interfere with ovulation or possibly damage the ovarian tissue. In the present paper we sought to critically review the evidence suggesting a relation between endometriotic ovarian cysts and infertility.

Clinical characteristics of endometriomas

Endometriomas are pseudocysts in which the invaginated ovarian cortex is lined by endometrial mucosa that produces menstrual debris and blood; as a result, the pseudocyst is filled with a typical tarry, thick, chocolate-like fluid. Endometriomas are significantly more frequent in the left ovary (60%) than in the right ovary (40%) and this observation support the theory that endometriomas are generated by endometrial cells refluxed through the fallopian tubes during menstruation. In fact, an explanation for this epidemiological finding may be that on the left side the sigmoid colon constitutes a shelter preventing refluxed menstrual blood to be cleared by peritoneal circulation, thus prolonging the time in which refluxed

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endometrial cells and ovarian cortex remain adjacent to one another and favoring the implantation of the former onto the latter [6]. However, the pathogenesis of endometrioma is still controversial and other theories postulate the invasion of functional ovarian cysts by refluxed endometrial cells [7] and the metaplasia of the coelomic epithelium covering the ovary [8].

Unlike endometriotic pelvic implants, a reliable noninvasive diagnosis for endometrioma is available. In fact, at transvaginal ultrasound, endometriotic cysts present typical characteristics such as thick walls, regular margins and homogeneous low echogenicity of fluid [9,10], that allow a highly sensitive and specific sonographic diagnosis. As a relevant clinical consequence, based upon sonographic evaluation, it is possible to evaluate fertility outcome in all patients with endometriomas, including those not undergoing surgery, making the subgroup of infertile patients with endometriomas particularly suited for investigating the relationship between endometriosis and infertility.

When applying strict diagnostic criteria for the sonographic diagnosis of endometriomas, the risk of overlooking malignant lesions is very low [11]. On the other hand, a possible limitation of this approach is that the number of endometriomas diagnosed at ultrasound, in other words, without histologic evaluation, may be overestimated because a portion of lesions are actually luteal hemorrhagic cysts. Accordingly, a study evaluating the long-term sonographic followup of 72 asymptomatic patients with an ultrasound diagnosis of small to medium sized endometrioma (mean diameter 2.8 ± 1.1 cm), reported that the endometriomas disappeared after a mean time of 45 months in 22 (31%) patients [12].

Effects of endometriomas on ovarian function

The pathogenic mechanisms through which an endometrioma might damage the ovary and consequently cause infertility are not known. The number of ovarian follicles might be reduced by the creation of a cytotoxic environment; in fact, due to hemolysis of entrapped blood, endocystic chocolate fluid contains a very high iron concentration, which determines a cytotoxic oxidative stress [13,14]. Alternatively, primordial follicles are lost due to the prolonged stretching of the ovarian cortex induced by the presence of the cyst, which may determine hypoperfusion and ischemic damage: the vulnerability of primordial follicles from this kind of insult is well known [15]. Another hypothesis may imply the disruption of the ovarian vascularization resulting in a reduced availability of gonadotropins and therefore a reduced stimulation of the follicular growth.

Regardless of the pathogenesis of the purported detrimental effect, several studies using different methods have analyzed ovarian function in women with endometriomas.

Histological evaluation

The follicular density in the healthy ovarian cortex of ovaries affected by endometriomas has been evaluated in two studies. The first study documented a reduced number of mature cortical follicles in presence of large endometriomas (mean diameter 6.5 ± 2.3 cm) as compared with the presence of nonendometriotic ovarian cysts of similar size [16]. The second, more recent study reported a reduced follicular density in the ovarian cortex surrounding smaller endometriomas (mean diameter 2.7 ± 1.0 cm) as compared with unaffected ovaries [15].

Therefore, histologic evaluation of the ovarian cortex supports the hypothesis that ovarian reserve is reduced in ovaries affected by an endometrioma.

Spontaneous ovulation

It has been reported that in ovaries affected by endometriomas measuring 3.1 ± 1.6 cm in mean diameter, spontaneous ovulation occurs less frequently when compared with the contralateral intact gonad with a proportion of about 1:2 [17]. However, this finding was not confirmed in a preliminary communication monitoring 1026 ovarian cycles in 214 women: according to this study endometriotic cysts, independently from their volume, did not influence the rate of spontaneous ovulation in the affected ovary [18].

Ovarian reserve

In order to assess ovarian function, it is crucial to estimating the amount of the remaining ovarian follicles, which constitutes the so-called ovarian reserve. During the past decade, it has been repeatedly demonstrated that the serum level of the anti-Müllerian hormone (AMH) is a reliable marker of ovarian reserve [19]. AMH is secreted by the granulosa cells of active growing follicles; with the progressive physiological reduction of ovarian follicles associated with increasing age, AMH concentration gradually declines until it becomes undetectable in perimenopause. Another useful diagnostic tool for evaluating ovarian reserve is the sonographic assessment of the number of antral follicles, the so-called antral follicle count (AFC).

Studies evaluating the ovarian reserve of women with endometriomas have reported conflicting results. In one study, significantly lower AMH and AFC were observed in 30 women with endometrioma >2 cm as compared with 30 healthy women of the same age without ovarian cysts [20]. Another study failed to observe lower serum AMH when comparing 77 women with

ovarian endometriomas to 413 controls without ovarian lesions [21]. A further study also failed to document significant differences in AMH concentration when comparing women with ovarian endometriomas (n = 102) and dermoid cysts (n = 48) to control groups matched for age and BMI [22].

It has to be noted that the concentration of serum AMH results from the sum of the production of this hormone by the two ovaries. This is a limitation for the evaluation of ovarian reserve in patients with unilateral cysts, because a normal AMH value might be observed, due to the compensatory function of the contralateral gonad, despite a reduction in ovarian reserve of the affected ovary.

Responsiveness to ovarian hyperstimulation

Ovarian responsiveness to hyperstimulation is the most informative tool in evaluating ovarian reserve in patients with monolateral cysts, because the contralateral unaffected gonad represents an optimal control [23]. A pilot study on ovarian hyperstimulation in women with unilateral endometriomas suggested a reduced responsiveness in the affected gonad [24]; however, this observation was not confirmed in two more recent and larger studies [25,26], which showed a comparable number of follicles in the affected as compared with unaffected ovary.

Among women with bilateral endometriomas, two studies reported a reduced responsiveness to ovarian hyper-stimulation when compared with women with intact gonads [27,28]. However, this difference reached statistical significance in only one study [27].

Altogether, the available data using different study designs suggest that ovarian endometriomas have a negative impact on ovarian function. However, the pathogenesis as well as the extent of such detrimental effect are still scarcely understood.

Effect of surgical removal of endometriomas on ovarian reserve

If data concerning ovarian reserve in unoperated ovaries are limited, more evidence is available regarding the effect of surgical removal of endometriomas on ovarian reserve. In fact, although a recent systematic review and meta-analysis has reported that AFC does not change significantly after surgical treatment of an andometrioma [29], during the last decade it has been repeatedly demonstrated that laparoscopic removal of ovarian endometrioma is *per se* a factor capable of determining a significant impairment of the ovarian reserve. Studies of different type have consistently supported this evidence: serum AMH levels are reduced after surgery [30–32], as reported in Table 1 [33–43], responsiveness to ovarian stimulation is markedly reduced in operated ovaries [44] and the onset of menopause may be anticipated in women who underwent excision of bilateral endometriomas [45,46].

Infertility as an indication to surgery

Based upon available studies, laparoscopic stripping of endometriomas has proved effective in improving spontaneous fertility, with an overall mean postoperative pregnancy rate of about 50%. However, adequately designed randomized controlled trials evaluating the

Table 1. Comparison of preoperative and postoperative serum anti-Müllerian hormone levels, literature data.

Study (year)	Cases (n)	Preoperative	4–6 weeks	3 months	6–9 months	Ref.
Ercan *et al.* (2010)	47	1.6 ± 1.1	1.4 ± 1.2 (p = ns)	–	–	[33]
Iwase *et al.* (2010)	29	3.0 (0.5–12.1)	2.2 (0.1–7.2)†	–	–	[34]
Chang *et al.* (2010)	13	2.0 (1.3–3.1)	1.0 (0.5–1.5)†	0.8 (0.7–1.6)	–	[35]
Tsolakidis *et al.* (2010)	10	3.9 ± 0.4	–	–	2.9 ± 0.2†	[36]
Biacchiardi *et al.* (2011)	43	3.0 ± 0.4	–	1.4 ± 0.2†	1.3 ± 0.3†	[37]
Hirokawa *et al.* (2011)	38	3.9 ± 2.5	2.1 ± 1.6†	–	–	[38]
Ercan *et al.* (2011)	36	2.0 ± 0.4	–	2.0 ± 0.6 (p = ns)	–	[39]
Hwu *et al.* (2011)	31	3.9 ± 0.4	–	2.0 ± 0.2†	–	[40]
Kitajima *et al.* (2011)	19	4.3 ± 3.0	–	–25 ± 29%‡	–	[41]
Lee *et al.* (2011)	13	4.7 ± 2.5	2.8 ± 1.5†	3.3 ± 2.1†	–	[42]
Celik *et al.* (2012)	65	1.8 ± 1.7	1.3 ± 1.3†	–	0.7 ± 0.8†	[43]

Data are presented as mean ± SD or median (range). AMH levels are reported in nanograms per milliliter.
†p < 0.05 versus preoperative AMH value.
‡p < 0.05 versus controls (% of AMH reduction).
AMH: Anti-Müllerian hormone; ns: Not significant.
Reproduced from [30].

impact of surgical excision of ovarian endometriomas on infertility are urgently needed, since most published studies are biased by at least two important confounding factors [47]. The first confounding factor is that the proportion of women who would have conceived spontaneously even without the operation, in other words, the background pregnancy rate in untreated women with ovarian endometriomas, has been poorly investigated. The second confounding factor is that the vast majority of women enrolled in observational studies have unilateral cysts. In these women, when a pregnancy is achieved, it is not known whether the ovulation occurred in the operated ovary, in which case surgery would have been effective, or in the nonaffected ovary, in which case the stripping of an endometrioma of the contralateral affected ovary would have probably had no influence on conception.

When excising a small ovarian endometriotic cyst, the surgeon relieves the ovary from the damage caused by the presence of the endometrioma *per se*, which may be progressive over time, but unfortunately determines a detrimental effect on ovarian reserve associated with the surgical procedure itself. Therefore, he or she should be cautious with the decision of excising an endometrioma with the sole aim of improving spontaneous fertility. In fact, in the absence of pelvic pain or other indications for surgery, infertile patients with small endometriomas are potentially eligible for IVF. Accordingly, two independent studies reported that pregnancy rates after IVF in women with bilateral, small (up to 3 cm) endometriomas and in those with unaffected ovaries are comparable [27,28].

For infertile women, laparoscopic ovarian cystectomy sometimes may be recommended for endometriomas larger than 3 cm in diameter, because endometrioma fluid may damage the ovary and complications like peritonitis can arise in women with endometriomas undergoing assisted reproductive techniques [48]. Additional indications for laparoscopic surgery include: moderate to severe pain, a rapid growth in endometrioma size, the uncertainty regarding the precise nature of the cyst or the patient's preference to avoid IVF [49].

The decision to perform surgery must be shared with the patient after a detailed counseling and taking into account her needs and expectations. Along this line, the timing of the procedure is a critical factor. In fact, since it is well known that delaying conception after surgery is associated with a lower pregnancy rate and a higher rate of recurrence [50], it is advisable to postpone the surgical treatment until pregnancy is desired. Usually, hormonal therapy provides an adequate control of pain symptoms and prevent the increase in size of endometriotic cysts [51,52]. Surgical excision of endometriomas is advised in cases of unbearable pain not controlled by medical therapy.

Surgical technique

Presently, a widespread technique for the surgical excision of endometrioma is represented by the stripping of the pseudocystic wall from the surrounding ovarian cortex by means of a gentle maneuver of traction and counter traction using laparoscopic atraumatic forceps (Figure 1). Subsequently, pinpoint bipolar electrocoagulation allows achievement of hemostasis of the pseudocystic bed. The possible mechanisms of damage to the ovarian function associated with this technique are represented by the inadvertent removal of follicles together with the endometrioma pseudocapsule, by the thermic insult of electrosurgical coagulation and by an inflammatory reaction leading to a diminished ovarian vascularization and to ovarian fibrosis [53]. An alternative surgical treatment that does not imply the removal of the pseudocapsule from the ovary has been proposed with the aim of overcoming these limitations. This technique consists in the fenestration and drainage of the endometrioma followed by the selective ablation of the endometrial lining of the cystic pseudocapsule by means of laser vaporization or bipolar coagulation. Three randomized, controlled trials have compared the outcomes of these two surgical techniques for the treatment of ovarian endometrioma. In one trial, the postoperative reduction in serum AMH was limited in women who underwent the fenestration-vaporization as compared with the stripping of endometrioma, thus suggesting that the former technique is associated with a less severe impact on ovarian reserve [36]. On the other hand, data from the other two trials demonstrated that the stripping technique allows a higher rate of spontaneous pregnancy and a reduced risk of endometrioma recurrence as compared with the fenestration-vaporization technique [54,55]. Consequently, laparoscopic stripping is, at present, generally accepted as the standard technique for the surgical excision of endometriomas. A possible modification of this technique implies achievement of hemostasis by suturing the residual ovarian parenchyma after the stripping of the endometrioma, in order to possibly reduce the ovarian damage associated with bipolar electrocoagulation. Accordingly, in a study including 47 women with a single ovary, ovarian suture (n = 26) was associated with lower postoperative levels of day 3 serum follicle-stimulating hormone (FSH) as compared with ovarian electrocoagulation (n = 21) [56].

Based on the analysis of the characteristics and outcomes of cyst excision and coagulation, a new laparoscopic procedure has been proposed that would possibly minimize ovarian damage without being associated with a high rate of recurrences [57]. This is a mixed

technique that consists in the stripping of 80–90% of the cyst pseudocapsule, with sparing of the portion of the pseudocapsule adherent to the ovarian hilus, in other words, the remaining 10–20%. In fact, in the area of the ovarian hilus, the cleavage plane is less clear and the ovarian cortex is more vascular, making the stripping of the pseudocapsule at this site particularly traumatic and risky for the gonadal function. The pseudocapsule located close to the hilus is therefore left in place and treated by means of laser vaporization or bipolar coagulation of the inner endometriotic layer. Cumulative pregnancy rate and recurrence rate at 6 months in 52 women who underwent this partial cystectomy technique were 32 and 2%, respectively. Of note, postoperative AFC was similar in the operated ovary as compared with the contralateral unaffected gonad.

Independently of the surgical technique adopted, it is important that the excision of ovarian endometriomas is performed by an experienced surgeon. In fact, an inverse correlation between ovarian damage and the surgeon experience has been demonstrated [58]. In particular, the surgeon has to identify and always follow the correct cleavage plane during the stripping of the cyst pseudocapsule. Moreover, he or she must be particularly cautious in the area of the ovarian hilus, where the ovarian cortex and the cyst wall are densely adherent, in order to avoid damage to the healthy ovarian tissue [59,60].

Recurrent endometriomas

Women experiencing postoperative endometrioma recurrences generally have a less favorable reproductive prognosis. A systematic review demonstrated that second-line surgical treatment for endometrioma-associated infertility is followed by a pregnancy rate of only 26% [61].

In infertile women with recurrent endometriomas, IVF is often a better therapeutic option than another infertility operation, as reported in the American Society for Reproductive Medicine clinical guidelines [2]. Indeed, in the two small randomized studies comparing pregnancy rate after IVF and repeat surgery, data were inconsistent: the probability of conception in the IVF group was lower than repeat surgery when only one cycle was performed [62], whereas the reverse was true after two IVF cycles [63].

The final decision to perform either repetitive surgery or IVF should be tailored on the basis of the patient's characteristics, keeping in mind advantages and drawbacks of each option [64]. Briefly, the advantages of reoperation include: relief of pain, removal of endometriomas for histological diagnosis and avoidance of the risk of multiple pregnancies. On the other hand, the advantages of IVF are: prevention of further potential damage to the ovarian reserve, a shorter time-to-conception as compared with reoperation and the simultaneous treatment of multiple co-existing infertility factors such as male infertility or tubal anomalies.

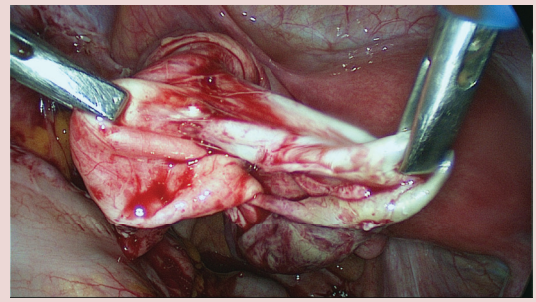

Figure 1. Laparoscopic stripping of an ovarian endometrioma. A gentle maneuver of traction and countertraction with atraumatic forceps is used for separating the endometrioma from the ovarian cortex along the cleavage plane.

Medical treatment is essential for the prevention of ovarian endometriotic cysts. In fact, recent studies demonstrate that the postoperative long term assumption of oral contraceptives (OC) is effective in reducing the recurrence rate of endometriomas. In particular, a meta-analysis of the available evidence showed an overall recurrence rate of 8% in women assuming postoperative OC as compared with 34% in women assuming no treatment [65]. Since endometrioma recurrence after first-line surgery may be associated with a particularly poor reproductive prognosis, the availability of an effective medical treatment for the prevention of this condition is of paramount importance.

Fertility preservation

A technique for fertility preservation that has recently gained attention is represented by oocyte cryopreservation [66]. Oocyte retrieval, in cases of bilateral endometriomas, may be performed before surgery, due to the risk of ovarian dysfunction associated with iatrogenic trauma to both gonads [46]. An alternative to oocyte preservation is the preservation of ovarian tissue collected during laparoscopic surgery. However, since in ovaries affected by endometrioma the follicular density in the remaining cortex may be reduced, the opportunity to collect and preserve a part of it may be questionable, especially when considering that ovarian tissue will subsequently undergo the freezing and thawing procedures that may further modify its structure. Therefore, at present, ovarian tissue preservation is indicated only in patients undergoing radical surgery in the form of oophorectomy. A possible future development in this field would be the isolation of follicles from ovarian tissue and their maturation *in vitro*.

Conclusion

There are multiple pathogenetic mechanisms that could explain the relationship between endometriomas and infertility, from the distortion of the tubo-ovarian anatomy to the reduction of ovarian reserve. Unfortunately, the pathogenetic mechanisms of the ovarian damage determined by an endometriotic cyst are poorly understood. The damage to the ovarian function may be progressive over time, in which case ovaries affected by an 'old' endometrioma would be more damaged than those containing a 'recent' endometrioma; or different kinds of endometriomas may exert different degrees of toxicity for the ovarian reserve. Further research focused in disentangling these issues may help in optimizing the management of endometrioma associated infertility.

In recent years a great body of evidence has accumulated demonstrating that the laparoscopic excision of an endometrioma is associated with a reduction of ovarian reserve [30–46]. Therefore, at surgery, the benefits of removing the endometrioma from the ovary are opposed to the inadvertent damage caused to the ovary by the surgical procedure itself. In infertile women, laparoscopic stripping of the pseudocystic capsule may be indicated for endometrioma larger than 3 cm [48]. A randomized controlled trial would be advisable evaluating the role of surgery as compared with IVF in infertile patients with small endometriomas, in the absence of pelvic pain or other surgical indications.

Another limitation of surgical excision of endometriomas is the high postoperative recurrence rate [67,68]. In order to prevent endometrioma recurrence after surgery, however, OC are highly effective [52], thus minimizing the number of surgical procedures and the consequent postoperative reduction of ovarian reserve.

Executive summary

Background

- Endometriomas may negatively interfere with ovulation or possibly damage the ovarian tissue and therefore reduce fertility.

Clinical characteristics of endometriomas

- There are three different theories on the pathogenesis of endometriomas: the metaplasia of the coelomic epithelium covering the ovary and the implantation of refluxed endometrial cells that either cause invagination of the ovarian cortex or invade functional ovarian cysts.
- Unlike peritoneal implants, the availability of an accurate noninvasive sonographic diagnosis facilitates the investigation of endometrioma associated infertility.

Effects of endometriomas on ovarian function

- The number of ovarian follicles might be reduced by the creation of a cytotoxic environment, due to the very high endocystic iron concentration, by the prolonged stretching of the ovarian cortex or by the disruption of the ovarian vascularization.
- Available data suggest that ovarian endometriomas have a negative impact on ovarian function.

Effect of surgical removal of endometriomas on ovarian reserve

- During the last decade it has been repeatedly demonstrated that laparoscopic removal of ovarian endometrioma is *per se* a factor capable of determining a significant impairment of the ovarian reserve.

Infertility as an indication to surgery

- The indications to surgery for an ovarian endometrioma in an infertile patient include: large cysts, the presence of pain, a rapid growth in endometrioma size and the uncertainty regarding the precise nature of the cyst. As for an asymptomatic small endometrioma ≤ 2 cm, a randomized comparison of IVF versus surgery would be advisable.

Surgical technique

- At laparoscopy, the endometrioma is either removed by stripping of the cystic pseudocapsule or fenestrated and left in place after the laser vaporitation or bipolar coagulation of the inner endometriotic layer.
- A mixed technique has also been proposed with the aim of reducing both the damage to ovarian function associated with the former technique and the high recurrence rate associated with the latter technique.

Recurrent endometriomas

- In infertile women with recurrent endometriomas, IVF is often a better therapeutic option than another infertility operation.
- The postoperative long-term assumption of oral contraceptive is effective in reducing the recurrence rate of endometriomas.

Conclusion

- Clinical management and research on endometrioma associated infertility should focus on the integration of surgery, with a refinement of the surgical technique, *in vitro* fertilization, long-term oral contraceptive assumption and oocyte cryopreservation.

Nowadays, in our opinion, an accurate counseling of women in reproductive age with ovarian endometriotic cysts and immediate or future desire for childbearing, should stress the risk of reduction of the ovarian reserve and inform about the possibility of oocytes retrieval and preservation.

Future perspective

In the near future, research may focus on the pathogenesis of the damage to the ovarian function associated with the presence of an endometrioma. In fact, it may well be hypothesized that not all endometriomas are equally detrimental for the ovarian reserve. Different endometriomas may be associated to a different degree of ovarian damage in relation to their size, pathogenesis or characteristics of endocystic fluid. Furthermore, it would be of paramount importance to know whether the reduction of the ovarian function in affected ovaries is stable or progressive over time, definitive or possibly reversible.

Surgery alone is inappropriate for the management of endometrioma related infertility, because it is associated with the reduction of the ovarian reserve and the recurrence of endometrioma. Therefore, research concerning this issue should focus on the integration of surgery, with a refinement of the surgical technique, long term OC, *in vitro* fertilization and oocyte cryopreservation.

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