

Surgery for endometriosis-associated infertility: do we exaggerate the magnitude of effect?

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Abstract

Objective: Surgery remains the mainstay in the diagnosis and management of endometriosis. The number of surgeries performed for endometriosis worldwide is ever increasing, however do we have evidence for improvement of infertility after the surgery and do we exaggerate the magnitude of effect of surgery when we counsel our patients? The management of patients who failed the surgery could be by repeat surgery or assisted reproduction. What evidence do we have for patients who fail assisted reproduction and what is their best chance for achieving pregnancy?

Material and methods: In this study we reviewed the evidence-based practice pertaining to the outcome of surgery assisted infertility associated with endometriosis. Manuscripts published in PubMed and Science Direct as well as the bibliography cited in these articles were reviewed. Patients with peritoneal endometriosis with mild and severe disease were addressed separately. Patients who failed the primary surgery and managed by repeat or assisted reproduction technology were also evaluated. Patients who failed assisted reproduction and managed by surgery were also studied to determine of the best course of action.

Results: In patients with minimal and mild pelvic endometriosis, excision or ablation of the peritoneal endometriosis increases the pregnancy rate. In women with severe endometriosis, controlled trials suggested an improvement of pregnancy rate. In women with ovarian endometrioma 4 cm or larger ovarian cystectomy increases the pregnancy rate, decreases the recurrence rate, but is associated with decrease in ovarian reserve. In patients who have failed the primary surgery, assisted reproduction appears to be significantly more effective than repeat surgery. In patients who failed assisted reproduction, the management remains to be extremely controversial. Surgery in expert hands might result in significant improvement in pregnancy rate.

Conclusion: In women with minimal and mild endometriosis, surgical excision or ablation of endometriosis is recommended as first line with doubling the pregnancy rate. In patients with moderate and severe endometriosis, surgical excision also is recommended as first line. In patients who failed to conceive spontaneously after surgery, assisted reproduction is more effective than repeat surgery. Following surgery, the ovarian reserve may be reduced as determined by Anti Mullerian Hormone. The antral follicle count is not significantly reduced. In women with large endometriomas > 4 cm the ovarian endometrioma should be removed. In women who have failed assisted reproduction, further management remains controversial in the present time.

Key words: Assisted reproductive technology, intrauterine insemination, endometrioma, endometriosis, ovarian, repeat surgery.

Introduction

A causal relationship between endometriosis and subfertility has not been established (D'Hooghe et al., 2003; Rizk et al., 2009) (Fig. 1-3). The arguments for the association of endometriosis and infertility are stronger than the arguments against it. High prevalence of endometriosis was observed in subfertile women (50%) with monthly fecundity rate (MFR) of 0.02-0.10, compared with women of proven fertility (5-10%) in whom the MFR is 0.15-0.20 (D'Hooghe et al., 2003) (American Society for Reproductive Medicine, 2004). Mahmood and Templeton (1991) emphasized that mild endometriosis is more commonly encountered in infertility patients compared to fertile patients during diagnostic laparoscopy. Furthermore, Marcoux et al. (1997) confirmed a significant improvement in the pregnancy rate following surgical management of mild endometriosis. Jansen et al. (1986) highlighted lower pregnancy rates after donor sperm insemination in women with mild endometriosis. Finally, Barnhart et al. (2002) in a meta-analysis confirmed lower pregnancy rates when IVF was performed for patients with endometriosis compared to women without endometriosis. The impact correlated with the endometriosis stage.

On the other hand, Berube et al. (1998) showed in their study that the fecundity of women with minimal or mild endometriosis was not significantly lower than that of unexplained infertility. Vercellini et al. (2009b) argued that although laparoscopic surgery for endometriosis-associated infertility is gaining widespread popularity, it is based on uncontrolled studies and the potential benefit of surgery may be overvalued. This is a rather interesting statement, especially given that expert surgeons formulate it. In a critical analysis of the evidence-based studies, Vercellini et al. (2009b) suggested that the increase in post-operative likelihood of conception over background pregnancy rate is estimated to be between 10-25%. The authors believe that the effect of surgery for peritoneal endometriosis is limited, and for ovarian endometriomas it is difficult to define. Furthermore, the role of surgery before, after, or as an alternative to assisted reproduction remains unclear.

In our manuscript, we will discuss the evidence for the impact of surgery on the pregnancy rate in early as well as advanced endometriosis. We will discuss the place of repeat surgery versus assisted reproduction after failed surgery as well as the options after failed assisted reproduction. The impact of surgery on ovarian reserve was critically analyzed.

Materials and methods

In our manuscript, we reviewed publications in the English language between 1984 and 2014 using PubMed and science direct. We also used the bibliography cited in those articles to search for additional information. Review articles and meta-analysis were also identified. Key words used for the search were endometriosis, ovarian endometriomas, surgery, assisted reproduction, and intrauterine insemination.

Surgical management

Women with minimal to mild endometriosis

It has always been debated whether minimal or mild endometriosis is a cause for infertility per se (Rizk et al., 2009) (Fig. 1A-1E). The Cochrane review analyzed the two well-publicized randomized control trials (RCTs) comparing laparoscopic surgical treatment with diagnostic laparoscopy only in minimal and mild endometriosis (Jacobson et al., 2010). In the multicenter Canadian (ENDOCAN) study, conception was achieved by 63/172 (36.6%) women undergoing laparoscopy with ablation of peritoneal implants and by 37/169 (21.9%) of women undergoing diagnostic laparoscopy only [odds ratio (OR), 2.06; 95% CI 1.28–3.33] (Table I) (Marcoux et al., 1997). However, in the multicenter Italian trial, pregnancy 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) (Parazzini, 1999). On pooling the results of live birth rate and ongoing pregnancy after 20 weeks from both studies, meta-analysis demonstrated an advantage of laparoscopic surgery when compared to diagnostic laparoscopy only (OR 1.64, 95% confidence interval 1.05-2.57) (Table II). The number needed to treat (NNT) by laparoscopic surgery to obtain one additional pregnancy is twelve (Al-Inany, 2001; Jacobson et al., 2010). Chang et al. (1997) recommended CO₂ laser vaporization of stage I and II endometriosis instead of monopolar coagulation, since laser vaporization is associated with higher accumulative pregnancy rate.

Women with moderate to severe endometriosis

There is less uncertainty that moderate or severe endometriosis can cause infertility (Rizk and Abdalla, 2003; Rizk et al., 2009) (Fig. 2A-2G). There are no RCTs or meta-analysis to address whether surgical excision of moderate to severe endometriosis enhances pregnancy rates (Kennedy

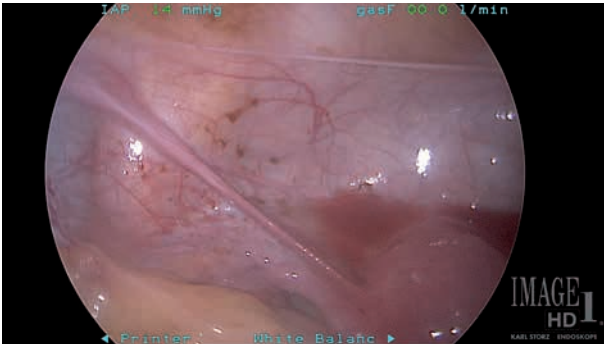


Fig. 1A. — Minimal/mild endometriosis seen as burnt powder and copper stains above and below the left round ligament. Small amount of old blood in anterior cul-de-sac, which is frequently observed in women with endometriosis.

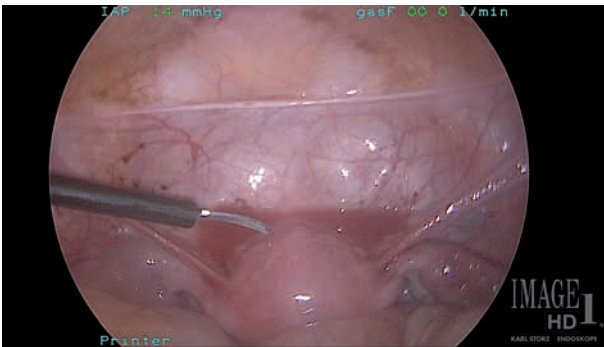


Fig. 1B. — Minimal/mild endometriosis seen as burnt powder and copper stains in the anterior cul-de-sac and surface of bladder.

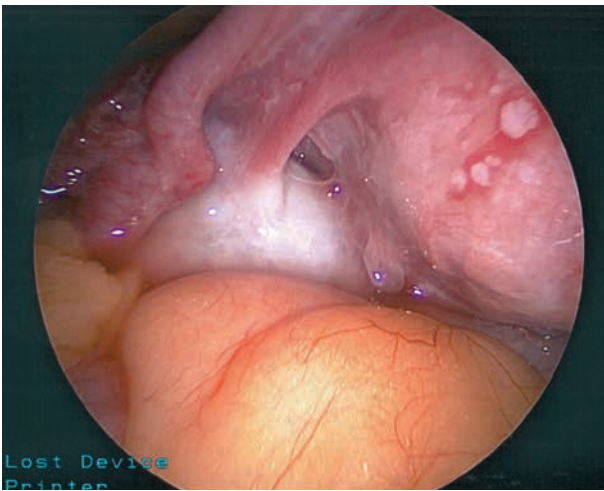


Fig. 1C. — Superficial endometriosis on the uterus or possible adenomyosis. Adhesions of left ovary and posterior surface of uterus on the left and left uterosacral ligament.

et al., 2005). Reports from uncontrolled studies on laparoscopic treatment of ovarian endometrioma on reproductive performance have different outcomes with pregnancy rates of 30% (Beretta et al., 1998) to 67% (Guzick et al., 1997). Overall, 50% of the patients conceived, which may be an overestimate of the real success rate (Table III). Vercellini et al. (2009b) estimated that no greater than 25% would



Fig. 1D. — Superficial endometriosis in right ovary.

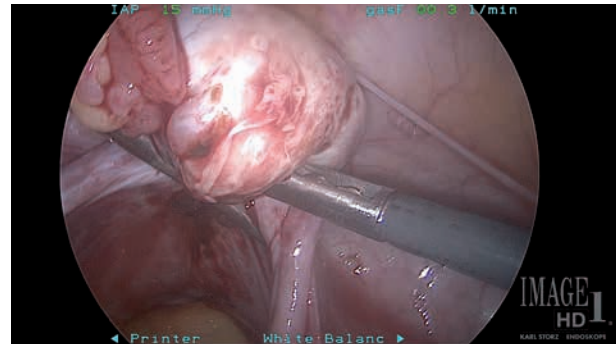


Fig. 1E. — Superficial endometriosis in right ovary as well as in cul-de-sac, in between the two uterosacral ligaments.

conceive and the NNT would be four. The study also concluded that the effect of surgery on peritoneal lesions is limited, and difficult to define in case of ovarian endometriomas due to multiple confounding factors and methodological flaws in these studies. Vercellini (2009b) highlighted the fact that many of the studies included patients who did not try to conceive preoperatively and therefore are not necessarily infertile (selection bias). It is also noted that surgeons with suboptimal outcomes will not publish these outcomes (publication bias). Despite all these limitations, based upon three outstanding studies, a negative correlation exists between the stage of endometriosis and the cumulative pregnancy rate after surgical removal of endometriosis (Adamson et al., 1993; Guzick et al., 1997; Osuga et al., 2002; Garcia-Velasco et al., 2010).

Excision versus ablation for ovarian endometriomata

Ovarian endometriomas are managed by laparoscopic procedures, like cyst aspiration alone, drainage and ablation of cyst wall by laser vaporization or electrocoagulation, or excision of cyst capsule (Aboughar et al., 1991, Rizk et al., 2008) (Fig. 3A-3B). In a Cochrane review, Hart et al. (2008) concluded from three RCTs that excisional

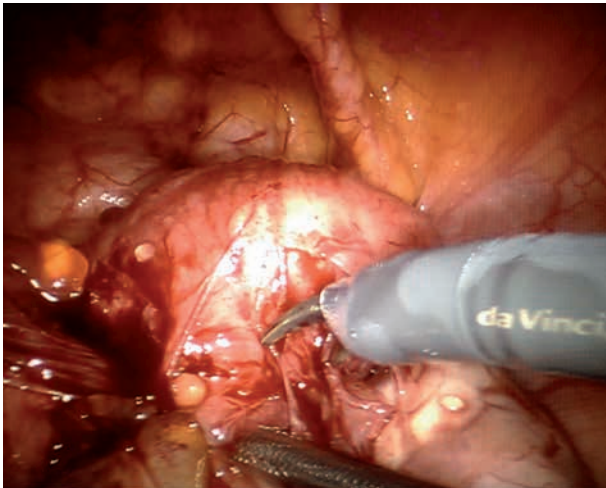


Fig. 2A. — Severe endometriosis demonstrating adhesions between the posterior uterine wall and colon and obliteration of posterior cul-de-sac.

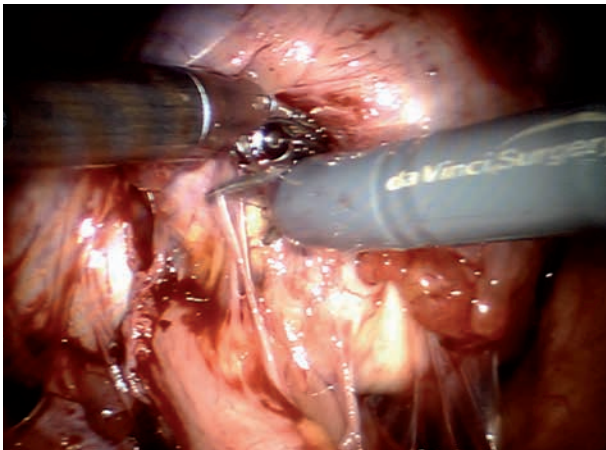


Fig. 2B. — Severe endometriosis with adhesions between right ovarian endometrioma and colon.

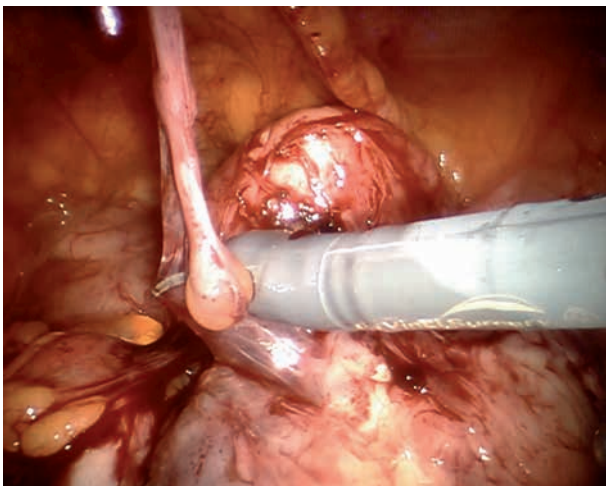


Fig. 2C. — Extensive deep peritoneal endometriosis.

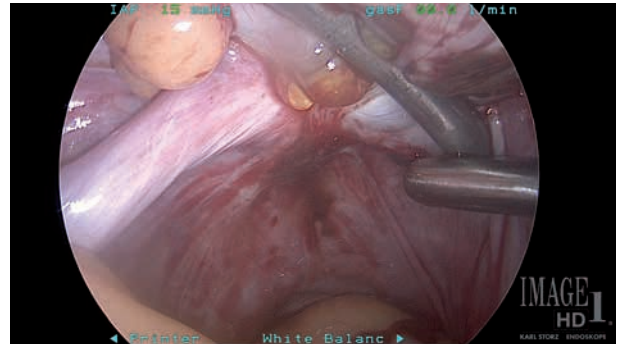


Fig. 2D. — Deep endometriosis in left ovarian fossa demonstrating scarring and burnt powder.



Fig. 2E. — Deep pelvic endometriosis around the left uterosacral ligament before surgery.



Fig. 2F. — Deep pelvic endometriosis around the left uterosacral ligament after surgery.

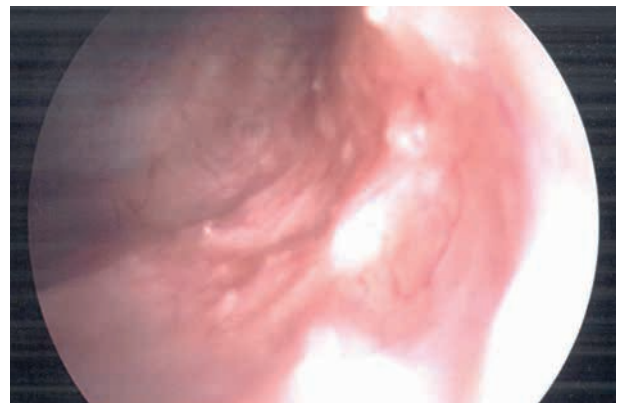


Fig. 2G. — Multiple vesicles of endometriosis in cul-de-sac and right uterosacral ligament.

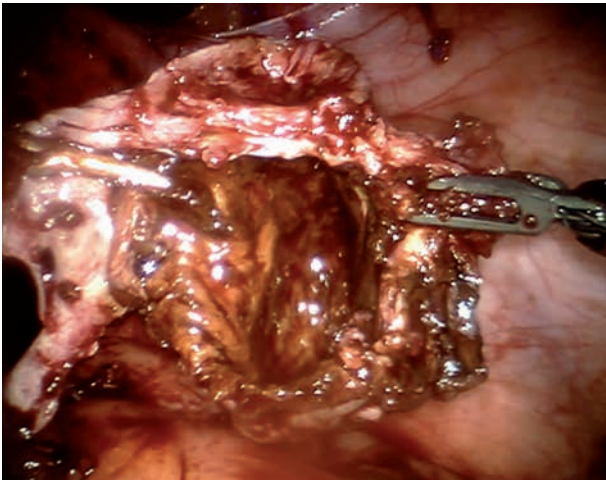


Fig. 3A. — Right ovarian endometrioma cyst wall.

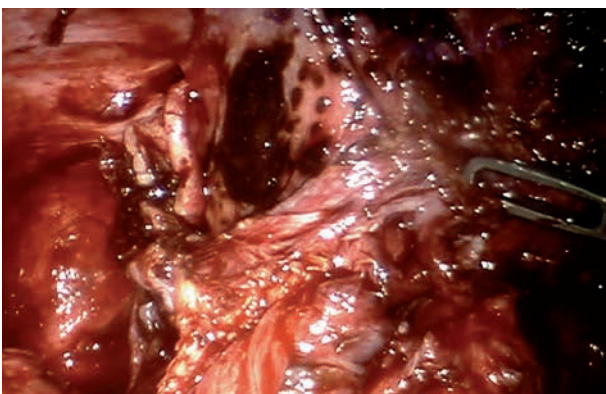


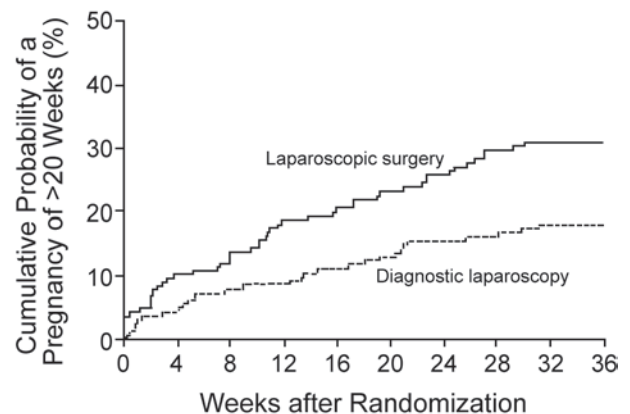
Fig. 3B. — Severe endometriosis on right pelvic wall.

surgery of ovarian endometriomas provides a more favorable outcome than drainage and ablation with regard to the recurrence of pain symptoms and subsequent spontaneous pregnancy in women who were previously subfertile (Beretta et al., 1998; Alborzi et al., 2004; Alborzi et al., 2007; Hart et al., 2008). However, they admitted that there is insufficient evidence to determine the favored surgical procedures in women planning fertility treatment, as there are no studies that compare the two surgical procedures prior to IVF treatment.

Somigliana et al. (2011) compared excision/stripping surgery techniques to vaporization/coagulation technique. The excision/stripping surgery technique resulted in lower recurrence rate of ovarian endometriomas. The authors cautioned the surgeons to be aware that the excision/stripping surgery technique may result in damage to ovarian reserve.

Roman et al. (2011) performed a retrospective controlled study to compare the impact of plasma energy ablation of ovarian endometriotic cysts to excisional surgery. Fifteen women with comparable baseline characteristics were managed by each

Table I. — Cumulative probability of a pregnancy carried beyond 20 weeks in the 36 weeks after laparoscopy in women with endometriosis. Modified with permission Marcoux S, Maheux R, Berube S et al. Laparoscopic surgery in infertile women with minimal or mild endometriosis. *N Engl J Med.* 1997;337:217-22.



technique. The authors performed 3D ultrasound before and after surgery. When compared with plasma energy ablation, ovarian cystectomy resulted in statistically significant reduction in ovarian volume and AFC. The authors suggested that these findings should be considered in therapeutic decision-making concerning women with ovarian endometrioma and infertility (Rizk et al., 2008).

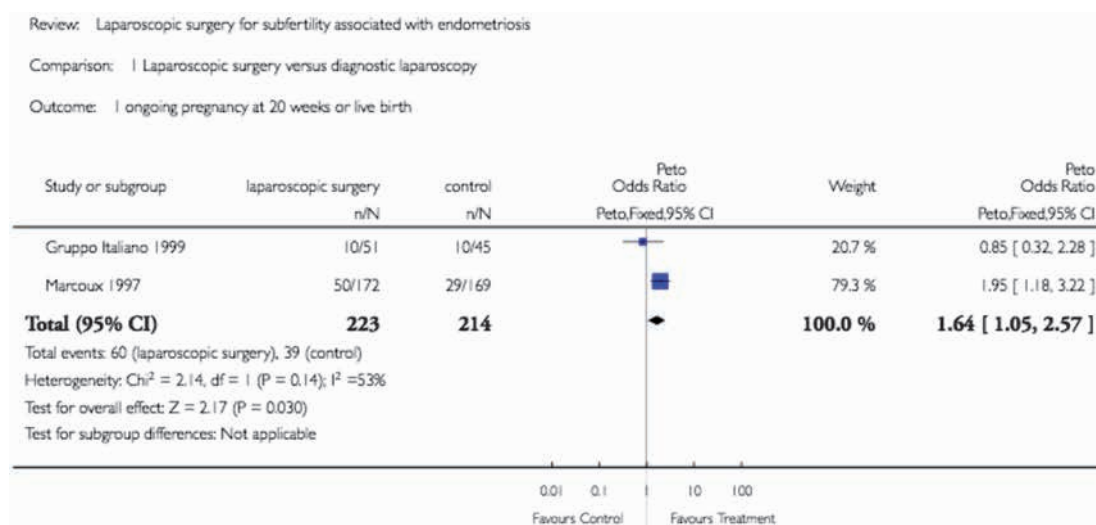
Var et al. (2011) performed a randomized prospective study to compare the effect of ovarian cystectomy versus ablation in patients with bilateral ovarian endometriomas. Forty-eight patients with bilateral ovarian endometriomas were randomized. The decrease in AFC and ovarian volume were observed for both coagulation and cystectomy. The decrease was statistically significantly more frequent in women who underwent ovarian cystectomy.

In a prospective randomized trial by Pados et al. (2010), twenty patients with bilateral ovarian endometrioma were randomized to either undergo laparoscopic ovarian cystectomy or the 3-stage procedure as first described by Donnez et al. (1996). Ovarian volume and vascularization were comparable among the two methods. However, functional ovarian tissue as determined by AFC was higher after 3-stage procedure.

The effect of surgery for endometrioma on ovarian reserve

The impact of surgery for ovarian endometriomas on ovarian reserve has been a subject of great interest. Poor response to ovarian stimulation for assisted reproduction has been reported in patients who had undergone excision of ovarian endometrioma (Nargund et al., 1996; Somigliana et

Table II. — Comparing laparoscopic surgery versus diagnostic laparoscopy for subfertility associated with endometriosis. Modified with permission from Jacobson TZ, Duffy JMN, Barlow D et al. Laparoscopic surgery for subfertility associated with endometriosis. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD001398. DOI:10.1002/14651858.CD001398.pub2.



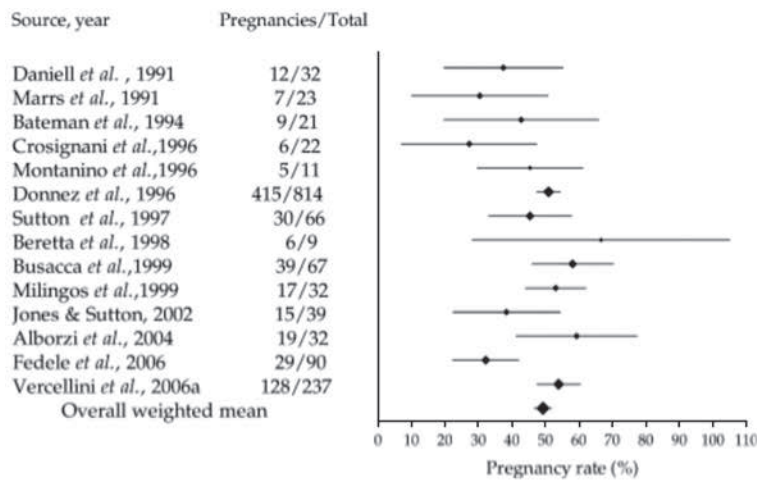
al., 2003; Shah et al., 2014). A younger age at menopause and premature ovarian failure has also been reported (Busacca et al., 2006; Coccia et al., 2011) respectively. Typically, AMH has been used as the marker for reduced ovarian reserve in these studies in two systematic views (Somigliana et al., 2012). Raffi et al. (2012) performed a meta-analysis to investigate the impact of surgery for endometriomas on ovarian reserve as determined by serum anti-müllerian hormone (AMH). All prospective cohort studies that analyzed changes of serum AMH concentrations after surgical treatment of endometriomas were eligible. Pooled analysis of 237 patients showed a statistically significant decrease in serum AMH concentration after ovarian cystectomy, although heterogeneity was high. Somilgiana et al. (2012) performed a systemic review from January 1990 to April 2012 to evaluate the AMH level after surgical excision of ovarian endometriomas. They identified eleven articles that supported surgery related damage to ovarian reserve. However, the decrease in the AMH levels caused by surgical excision of ovarian endometrioma could be recovered (Sugita et al., 2013).

Antral follicle is a reliable marker for ovarian reserve and has the advantage of correlating with the ovarian reserve of a single ovary. Muzii et al. (2014) in their meta-analysis, concluded that ovarian reserve evaluated with AFC was not significantly impaired by surgical excision of the ovarian endometrioma when it was performed with the stripping technique. Antral follicle of the operated ovary did not change significantly when compared with the preoperative values of the same ovary. They also concluded that non-excisional techniques did not affect AFC values after surgery.

Role of intrauterine insemination after surgery for endometriosis

The efficacy of intrauterine insemination after surgery for endometriosis depends on the patient's age, duration of infertility and stage of endometriosis. According to two prospective randomized controlled trials, intrauterine insemination after controlled ovarian hyperstimulation improved the pregnancy rates in infertility associated with endometriosis compared with expectant treatment 11% versus 2% (Deaton et al., 1990; Tummon et al., 1997). Werbrouck et al. (2006) noted though that not all women had undergone ablation of endometriotic lesions in these trials and intrauterine insemination did not restore fertility in these patients. Interestingly, intrauterine insemination and controlled ovarian hyperstimulation were reported to achieve lower pregnancy rates in mild endometriosis compared to unexplained infertility (Omland et al., 1998; Nuojuua-Huttunen et al., 1999). Again, in these two clinical randomized trials, the patients were not surgically treated before the insemination. Werbrouck et al. (2006) in Leuven designed a study to compare the pregnancy and live birth rate after surgical correction of endometriosis compared to unexplained infertility and showed no difference. They, therefore, proved that surgical correction might explain the difference in results between their trial and the two previous trials where some of the patients had undergone only the diagnostic part of the laparoscopy. In summary, so far, it appears that in the presence of confirmed but not surgically treated endometriosis, the pregnancy rates after intrauterine insemination are lower compared to women with normal pelvis and it is possible that

Table III. — Pregnancy rates observed after laparoscopic excision of endometriomas. Diamonds represent percentage point estimates and horizontal lines represent 95% CIs. Modified with permission from Vercellini P, Somigliana E, Vigano P et al. Surgery for endometriosis-associated infertility: a pragmatic approach. Hum Reprod. 2009;24:254-69.



surgical management improves the rates so that they are equal after surgical treatment followed by insemination.

What is the real efficacy for and does it depend on the age of the patients and the stage of endometriosis. In a retrospective cohort study from the clinic studied ninety-six women who had undergone for infertility associated with endometriosis according to the stage of the disease (Gandhi *et al.*, 2014). In stage I and II the pregnancy rates 45% and 42% for spontaneous attempts and controlled ovarian hyperstimulation and intrauterine insemination. In stage III and IV the pregnancy rates were 20% and 10% after spontaneous attempts and intrauterine insemination coupled with controlled ovarian hyperstimulation respectively. The monthly fecundity rates in stages I and II were 3.81% for spontaneous and 4.59% for COH /IUI and in stages III and IV were 3.05% and 1.68% for spontaneous and IUI respectively. The authors concluded that COH /IUI did not improve pregnancy rates in any stage of endometriosis. The authors recommended that in stage II and IV we proceed to IVF. We agree with their opinion that in moderate and severe endometriosis proceeding to IVF is the next step. In clinical practice other factors play a significant role. What should the clinician decide or advise in many patients who could not afford IVF. We counsel them about the low fecundity and allow the couples to decide.

It is therefore that over the last three decades the place of IUI in moderate and severe endometriosis after surgical correction is limited to those who do not have the resources for ART.

Surgery before in vitro fertilization

The role of operative laparoscopy before in vitro fertilization (IVF) has been controversial. One of the important studies that started this debate is that of Garcia-Velasco *et al.* (2004) demonstrating no difference between the pregnancy rate of 133 women who underwent surgery for endometriomas before IVF (25.4%) and 56 women who underwent IVF without prior endometriotic cyst removal (22.7%). Wong *et al.* (2004) compared the outcome of 36 women who underwent laparoscopic endometrioma removal before assisted reproductive technology (ART) with that of 38 women who underwent ART without prior endometrioma removal. The authors noted a favorable trend in pregnancy rates in those who underwent surgery, but the difference did not reach statistical significance (37% vs. 34%).

Demiroglu *et al.* (2006) reported the first prospective randomized trial comparing the outcome of 99 patients with ovarian endometriomas who were randomized to surgery before ICSI in 49 women or ICSI alone in 50 women with similar pregnancy rates of 34% and 38%, respectively. They also noted no difference in fertilization rates or implantation rates. Somigliana *et al.* (2006) emphasized that the presence of ovarian endometriomas larger than 4 cm may cause difficulties during oocyte retrieval, as well as potential pelvic infection and follicular fluid contamination. Filippi *et al.* (2014) in prospective cohort study investigated 29 patients undergoing IVF, who have unilateral endometrioma (less than 5 cm) with no history of ovarian surgery.

Table IV. — Laparoscopy after failed IVF. Modified with permission from Littman E, Giudice L, and Lathi R et al. Role of laparoscopic treatment of endometriosis in patients with failed in vitro fertilization cycles. *Fertil Steril.* 2005;84:1574-8.

| Comparison of patients with a history of prior failed IVF cycles, who underwent laparoscopic treatment of endometriosis to patients who did not undergo laparoscopic treatment. | | | |
|---|---------------|----------------|---------|
| | + Laparoscopy | No laparoscopy | P value |
| Number of patients (n) | 29 | 35 | |
| Average age (y) | 34 | 37 | .613 |
| Average FSH | 8.0 | 8.1 | NS |
| Average no. of failed IVF cycles | 2 | 2 | NS |
| Pregnancy rate | 22/29 | 13/35 | <.01 |
| Spontaneous pregnancy rate | 13/29 | 2/35 | <.01 |

The study compared the response of the affected ovary to the contralateral, unaffected ovary, as well as the quality of the retrieved oocytes. The authors concluded that the presence of a unilateral endometrioma does not affect the ovarian response to stimulation. Both the European Society for Human Reproduction and Embryology (ESHRE) in 2005 and the Royal College of Obstetricians and Gynecologists (RCOG) in 2006 recommend surgery if ovarian endometriomas are equal to or larger than 3 cm (ESHRE, 2013).

Surgery after failed IVF

One of the clinical situations that frequently arise is what to do next after a failed IVF cycle due to endometriosis. Not surprisingly, there are no RCTs available to answer that important question. A study from Stanford, California sheds some light with a series of 29 patients with several failed IVF cycles and endometriosis (Littman et al., 2005). An experienced laparoscopic surgeon performed laparoscopic treatment of endometriosis. Following the surgery, 22 patients (76%) conceived, compared with 13 of the 35 (37%) who elected not to undergo surgery (Table IV). It is important to highlight that no distinction was made between treatment dependent and treatment independent pregnancy (Vercellini et al., 2009a). Diamond (2005) commented that some patients only had one IVF cycle before entering the study and there was no control for other fertility factors between the two groups.

Adamson (2005) also highlighted that the proportion of patients who conceived spontaneously after laparoscopic surgery without further IVF is not statistically different from that observed in the non-laparoscopic surgery group. Hershlag and Markovitz (2005) criticized the study regarding the unusual 100% prevalence of endometriosis in the surgery group, in addition to the matching of controls in terms of disease state and endometriomas.

We agree with Diamond (2005) that value of this study is challenging the conclusion that IVF is the final treatment for endometriosis-associated infertility before oocyte donation.

Surgery or IVF after failed surgery

The ideal conservative laparoscopic approach of endometriosis is still controversial. An interesting situation arises when patients with moderate or severe endometriosis fail to conceive after the first surgical procedure. Vercellini et al (2009a/b) study observed a lower pregnancy rate in patients who had a second operation (22%) for recurrent endometriosis compared with patients who had primary surgery (40%) for endometriosis. The choice in this situation is between either a second surgery or IVF. These options have been compared elegantly in two retrospective studies. Pagidas et al. (1996) reported a nine-month cumulative pregnancy rate of 24.4% in 18 women undergoing second surgery for moderate or severe endometriosis (Stage III or IV) and a pregnancy rate of 33.3% and 69.6% in 23 women undergoing one or two IVF cycles, respectively. Cheewadhanaraks et al. (2004) observed a 12-month cumulative pregnancy rate of 20.5% in 32 patients who underwent repeat laparotomy versus a clinical pregnancy rate of 12.5% in 24 patients who had one IVF cycle. The odds ratio is 1.70 (95% CI 0.67-4.32), which does not suggest that surgery is better than IVF.

Adamson (2005) emphasized that the benefits and costs of different treatment alternatives need to be explained to the patient. An individualized treatment plan should be developed, taking into account the age and duration of infertility. The major advantages of surgery are effectiveness compared with one IVF cycle, without increased risk of multiple pregnancies and the possibility of achieving subsequent pregnancies. In addition, pain symptoms could be significantly alleviated and diagnosis histologically confirmed. Major

disadvantages of surgery are cost, morbidity, and longer time to conception. IVF treatment is definitely a suitable option for older patients. In addition, it addresses other factors, such as male infertility or ovulatory disorders, and there is no delay. We believe that IVF is a more effective option when patients with moderate or severe endometriosis who fail to conceive after primary surgery.

Is the incidence of endometriosis increased after ovarian stimulation for ART?

One of the concerns of having IVF after surgery is an increased endometriosis recurrence rate in women exposed to high estradiol levels during ovarian stimulation for IVF when compared to less high estradiol levels (Rizk et al., 2014). Renier et al. (1995) reported a rare case with a rare coincidence of ureteral endometriosis presented by acute renal colic after ovarian stimulation. Anaf et al. (2000) reported four cases of severe digestive complications due to rapid growth of sigmoid endometriosis after ovarian stimulation. Prior to stimulation patients had no digestive symptoms and after the ovarian stimulation the digestive symptoms developed.

In a retrospective cohort study D'Hooghe (2006) did not observe an increased cumulative recurrence of endometriosis after ovarian stimulation for IVF when compared to ovarian stimulation for IUI despite the higher estradiol levels associated with IVF ovarian stimulation. Interestingly a study from Leuven suggested the estradiol level is not the determining factor for endometriosis recurrence.

Conclusion

Laparoscopic surgery for excision or ablation of mild endometriosis almost doubles the spontaneous pregnancy rate based on prospective randomized controlled trials. In women with moderate to severe endometriosis, operative laparoscopy increases the spontaneous pregnancy rates based on controlled trials. Excision of ovarian endometriomas larger than 4 cm increases the pregnancy rate and decreases the recurrence rate, but may negatively impact the ovarian reserve as measured by AMH. The decrease in AMH may recover in some patients after one year. The antral follicle count is not significantly affected after excision of endometriomas. IVF is the best option for patients after failed primary surgery. Repeat surgery is associated with significantly lower pregnancy rate. The pregnancy rate after intrauterine insemination IUI may be increased after surgery for mild endometriosis. The place of IUI is limited in patients with moderate or severe endometriosis and in older women. The incidence

of recurrence of endometriosis is not increased after controlled ovarian stimulation for IVF.

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