Surgical measures for endometriosis-related infertility: A plea for research

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ABSTRACT

The precise relationship between endometriosis and infertility is debated. Surgery is considered to play a role within the framework of the therapeutic options to cure infertile women with the disease even though its effectiveness is generally modest. In fact, there is unquestionably the need to improve surgical techniques in this area. Specifically, two main aspects require optimization: 1) preventing the injury to the follicular reserve that follows surgical excision of ovarian endometriomas and 2) preventing post-surgical formation and re-formation of adhesions. The comparison between the excision/stripping and the vaporization/coagulation techniques represents the main point of debate on what is the best procedure to remove ovarian endometrioma. Randomized controlled trials showed that the excision technique is associated with a higher pregnancy rate and a lower rate of recurrence although it may determine severe injury to the ovarian reserve. Improvements to this latter aspect may be represented by a combined excisional-vaporization technique or by replacing diathermy coagulation with surgical ovarian suture. Barrier agents reduce but not eliminate the post-surgical adhesion formation in women with endometriosis. Encouraging evidence has been reported with Interceed, Oxiplex/AP gel and Adept solution. However, available studies are mainly based on II look laparoscopies performed few weeks after the intervention and data on fertility is lacking. Clinical trials including pregnancy rate as a specific outcome are warranted.

1. Introduction

The relationship between endometriosis and infertility remains unclear [1,2]. Although there is clear evidence supporting an association between the two conditions, a substantial proportion of affected women conceive spontaneously. Moreover, even when causality appears likely, surgical removal may be ineffective. In fact, surgery may not surmount all the bio-molecular alterations associated with the endometriosis-related chronic inflammation and it may not adequately repair some of the detrimental effects of the disease. Moreover, it does not remove the causes of endometriosis and thus it does not prevent recurrences. Importantly, the advent of valid alternatives to operation such as IVF has further complicated this scenario. In line with this complexity, the role of surgery in the management of infertile women with endometriosis is currently a matter of debate [1–3].

Regardless of the precise role surgery in this context, there is unquestionably the need to improve the current surgical techniques. The enthusiasm surrounding the advent and wide-spread diffusion of endoscopic techniques is now over and efforts to modify and improve the surgical techniques are presently scanty. We conversely do believe that progresses in this area are warranted and possible and to support this idea, we herein review current knowledge in this field. The treatment options for the different forms of the disease, i.e. peritoneal implants, endometriomas and adhesions will be discussed separately. Particular emphasis will be paid to the innovative interventions that have been proposed.

2. Peritoneal implants

Two main techniques have been suggested to remove the superficial peritoneal deposits of endometriosis, the excision and the laser or diathermy ablation. At present, there is no scientific evidence supporting one method respect to the other [4]. Not surprisingly, gynecologists currently tend to be divided into those who ablate and those who excise. The most common thought is that the two may be equally effective, with ablation being easier to perform. In line with this view, a recent Randomized Controlled Trial (RCT) compared the two techniques in women with

endometriosis and pelvic pain and failed to detect any difference in pain recurrence at 12 months follow-up [5]. The impact on fertility was investigated in a small retrospective study using historical controls [6]. These authors also showed comparable results with the two techniques.

The scenario is even more vague when considering deep invasive peritoneal implants. Currently, the debate refers to the most appropriate management for this form of the disease, in particular when located in the posterior vaginal and anterior rectal wall [7,8]. Four different approaches have been proposed: long-term medical treatment with progestins or estroprogestins, nodule dissection either without opening the rectum (shaving) or removing the nodule along with the surrounding rectal wall (full thickness or disk excision) and colorectal resection. However, as a relationship between deep invasive endometriosis and infertility has not yet been definitively demonstrated, this problem is speculative in this context. The concomitant presence of other forms of endometriosis such as superficial implants, ovarian endometriomas and pelvic adhesions, and not the deep form itself, might be actually involved in determining the infertility condition [1,9]. Noteworthy, a recent paper comparing the effects of surgery and expectant management in infertile women with rectovaginal endometriosis failed to document any benefit from the intervention [10]. In contrast, Bianchi et al. recently reported improvement of IVF success in women who were removed deep invasive endometriosis when compared to those who were not [11]. Discrepancies on this point are difficult to explain and clarification is warranted, especially considering that surgery for rectovaginal endometriosis is a demanding intervention that can cause severe complications [1]. In these cases, surgery for infertility problems should be indicated only if very well supported by clinical evidence.

3. Ovarian endometriomas

No RCTs are available in relation to the improvement of pregnancy rates following the surgical treatment of moderate-severe endometriosis. Nonetheless, there is a general agreement that surgery for ovarian endometriomas may be beneficial. A recent review of the case series on this topic documented pregnancy rates following excision of ovarian endometriomas varying from 30% to 67%, with an overall weighted mean of about 50% [1]. However, due to the intrinsic limitations of this kind of studies, this success rate has to be viewed as an overestimation of the true effectiveness of surgery [1].

Presently, the comparison between the excision/stripping and the vaporization/coagulation techniques represents the main point of discussion. Data derived from the two RCTs specifically conducted on this issue [12,13] confirmed a substantial advantage of the excision technique with an Odds Ratio (OR) of pregnancy of 5.1 (95% CI: 2.0–12.8) [1,14]. Moreover, an increased risk of endometrioma recurrence has been repeatedly associated with the vaporization/coagulation technique [1]. On the other hand, a significant damage to the ovarian reserve has been described in association with the excision technique and some cases of post-surgical ovarian failure after laparoscopic stripping of bilateral endometriomas have been reported [15,16]. More specifically, the rate of ovaries whose follicular reserve is definitely impaired following the excision technique has been estimated to be about 13% [17]. Unfortunately, due to the lack of a reliable method to monitor the ovarian reserve before and after surgery, awareness about this risk is surprisingly recent [18]. Serum dosages such as day 3 serum FSH or AMH do not discriminate between the two gonads and they are useful only in women with bilateral disease. Antral Follicle count (AFC) consents independent evaluation of the ovaries but its accuracy in estimating ovarian reserve in affected gonads has yet to be demonstrated. Conversely, ovarian responsiveness to hyper-stimulation is considered more informative, especially in women with monolateral disease since the contralateral unaffected gonad represents an optimal control [19]. Results from several recent studies in this context are summarized in Table 1 [17,20–29]. Overall, despite some inconsistencies, the following conclusions can be drawn: 1) ovarian responsiveness is not affected in unoperated ovaries thus suggesting that the presence of an endometriomas *per se* does not markedly affect the ovarian reserve; 2) ovarian responsiveness is reduced in ovaries that underwent excision of the cyst with an overall mean reduction of about 50%; 3) laser-vaporization of the cyst wall may be less harmful to the follicular reserve. In line with these conclusions, in an RCT comparing the two techniques, Tsolakidis et al. documented a less severe reduction of AMH and AFC in women who were operated using laser-vaporization [30]. Interestingly, Donnez et al. recently proposed a mixed technique that combines excisional and ablative surgery with an initial excision of a large part (80–90%) of the cyst with the stripping technique and subsequently, when approaching the hilus where the ovarian tissue is more functional and the plane of cleavage less visible, a resection of the dissected tissue (partial cystectomy) [31]. CO_2 laser is then used to vaporize the remaining 10–20% of the cyst wall close to the hilus. These authors reported on 52 treated women and showed a cumulative pregnancy and recurrence rates at 6 months of 32% and 2%, respectively. Post-surgical AFC resulted similar in the operated and non-operated gonads. More robust evidence and external validation are however warranted.

Table 1
Studies comparing ovarian responsiveness during IVF in affected and contralateral intact gonads in different clinical conditions.

Conditions and studies	N. cases	Affected gonad	Intact gonad	*p*
Unoperated gonad				
Almog et al., 2011 [20]	81	6.0 ± 0.4	6.1 ± 0.5	n.s.
Benaglia et al., 2011 [21]	84	5.3 ± 2.8	5.6 ± 3.5	n.s.
Operated gonad (stripping)				
Loh et al., 1999 [22]	12	4.6	3.6	n.s.
Ho et al., 2002 [23]	38	1.9 ± 1.5	3.3 ± 2.1	<0.001
Somigliana et al., 2003 [24]	46	2.0 ± 1.5	4.2 ± 2.5	<0.001
Ragni et al., 2005 [25]	38	1.8 ± 1.8	4.5 ± 2.0	<0.001
Duru et al., 2007 [26]	28	3.1 ± 1.8	4.4 ± 1.4	<0.05
Alborzi et al., 2007 [27]	70	3.2 ± 1.1	3.2 ± 1.7	n.s.
Almog et al., 2010 [28]	81	4.7 ± 3.9	7.5 ± 4.7	<0.001
Benaglia et al., 2010 [17]	93	3.4 ± 2.4	5.7 ± 3.0	<0.001
Operated ovary (Laser-vaporization)				
Donnez et al., 2001 [29]	87	5.2 ± 3.0	6.6 ± 3.5	n.s.
Alborzi et al., 2007 [27]	40	2.6 ± 1.6	2.8 ± 1.6	n.s.

Data refers to the number of follicles at the time of hCG administration. n.s.: not significant.

Research in this field is mainly broken down by our ignorance regarding the causes of the surgical-mediated damage. Several pathogenetic insults have been hypothesized and include: (i) accidental removal of a consistent amount of ovarian tissue during cystectomy, (ii) follicular depletion consequent to the use of electrosurgical coagulation to achieve hemostasis, (iii) damage to ovarian vascularization and ovarian fibrosis secondary to a local inflammatory reaction [3]. It is critical to disentangle this aspect. For instance, if the damage is mainly mediated through electrosurgical coagulation, one may abstain from the use of this tool. In line with this hypothesis, Fedele et al. suggested to refrain from bipolar electrocoagulation following the stripping of the endometrioma and proposed to achieve haemosthasis by suturing the residual ovarian parenchyma [32]. In a comparative study on 47 women with a single ovary with an endometrioma, they documented lower levels of day 3 serum FSH in the 26 women whose ovary was sutured when compared to the 21 who were treated with electrocoagulation. Noteworthy, ovarian suture would also reduce adhesions formation [33]. In an RCT involving 44 women, Benassi et al. documented less bleeding and a shorter operating time when the laparoscopic excision of the endometrioma was done with the aid of a mucolytic substance, Mesna [34]. Data on the ovarian reserve is however lacking. Again, more robust evidence and external confirmation are required to validate these approaches.

4. Adhesions

Prevention of adhesions, whether *de novo* or by re-formation, is one of the most important and surprisingly neglected aspect of the surgery for endometriosis. Adhesions may cause infertility by determining anatomical distortion, thus impeding the tubes to properly display their complex function [35]. Noteworthy, they can also cause dyspareunia, chronic pelvic pain, intestinal obstruction and complications at subsequent surgery [35,36].

Strategies aimed at preventing adhesion formation can be divided into those associated directly with the surgical procedure and those involving the use of specific therapies. For the former point, it is to note that cutting, surgical denudation, ischemia, dessication and abrasion can cause peritoneal trauma during surgery and that the subsequent healing process may result into adhesions between damaged serosal surfaces [35–37]. Surgical measures aimed to prevent these effects include reducing the extent of trauma through minimal tissue handling, avoidance of unnecessary dissection, prevention of dessication, meticulous hemostasis, minimizing the risk of infection, minimizing the number of interventions, ensuring optimal temperature of irrigating solutions and reducing the introduction of foreign material in the abdomen [35,36]. These measures have become accepted part of the normal surgical practice. In this regard, laparoscopy seems to fulfill many of these requirements and it has thus been viewed as a suitable approach to reduce adhesions. In fact, even if studies comparing potential risk of adhesions between laparoscopy and laparotomy have provided mixed results, it is now commonly accepted that, on balance, laparoscopy appears to be associated with lower adhesion formation [35,36]. Data on robotic surgery is lacking but it is unlikely that this innovation will radically modify the scenario [38]. Concerning the pharmacological treatments for adhesion prevention, two main approaches have been proposed: the use of systemic compounds and the local application of barrier agents, either liquid or solid. A tentative list of these options is reported in Table 2 [35–37,39]. Systemic drugs are currently abandoned because of the unsatisfactory results emerging from clinical trials [35,39]. More promising results have conversely derived from the use of barrier agents which is based on the rationale that, for an adhesion to form, there must be a prolonged contact between two areas of injury and

Table 2
Experimental drugs and proposed therapeutic schemes for adhesions prevention (literature review 1990–2010).

Groups	Compounds
Systemic agents	Nonsteroidal anti-inflammatory drugs
	Corticosteroids
	Heparin
	Fibrinolytics (streptokinase, recombinant tPA)
	Antibiotics
	Anti-histaminine
	Calcium channel blockers
	Chymase inhibitor
	VEGF inhibitors
	PAF inhibtors
	Collagen-α1 inhibitor
	IL-6 inhibitors
	Melatonin
	Progestogens
	GnRH analogs
Barrier agents: solutions	Dextran
	Icodextrin (Adept)
	Ferric hyaluronate gel (Intergel) [a]
	Hyaluronic acid in phosphate-buffered saline (Sepracoat)
	Auto-cross linked hyaluronic acid
	Polyethylene oxide/carboxymethylcellulose (Oxiples/AP)
	Spraygel
	Fibrin glue
	Heparin
	Noxytioline
Barrier agents: solid	Oxidated regenerate cellulose (Interceed)
	Expanded polytetrafluoroethylene (Gore-Tex)
	Hyaluronic acid/carboxymethylcellulose (Seprafilm)
	Fibrinogen/Thrombin/Aprotin/Collagen/Riboflavin (Fibrin sheet)
	Polylactic acid film

[a] Removed from the market in 2003 for side effects (pelvic pain and allergic reactions).

preventing this contact may also prevent adhesions [35,39]. Unfortunately, however, data on pain and pregnancy rate as relevant clinical outcomes is lacking. Based on the evaluation of adhesions at second look laparoscopy, the most convincing evidence for the group of solid barrier agents emerged for the placement of absorbable barriers of oxidized regenerated cellulose (Interceed) and expanded polytetrafluoroethylene (Gore-Tex) [37]. Considering liquid barrier agents, hyaluronic acid containing solutions such as ferric hyaluronate (Intergel), auto-crosslinked hyaluronic acid and hyaluronic acid in phosphate-buffered saline (Sepracoat) seem of benefit [39]. Collectively, available data supports the view that incidence and extent of adhesions can be reduced through the use of solid or liquid barrier agents but none of them completely eliminate adhesion formation.

Importantly, adhesiolysis is a critical preliminary step in the surgical procedures for endometriosis. It can facilitate further operative steps such as endometrioma or deep nodules removal and, as such, it is deemed mandatory. Nevertheless, the effectiveness of the procedure by itself is doubtful [35,40,41] and recurrence appears to be the rule. Evidence on the use of systemic or local agents in the specific group of women with endometriosis is scanty. To date, only three RCTs have been published [42–44]. Mais et al. recruited 32 women with severe endometriosis and a complete obliteration of the Douglas cul-de-sac [42]. After adhesiolysis and endometriosis treatment, Interceed was applied to the cul-de-sac serosa and the adnexa in 16 women while the remaining 16 women did not receive any adhesion prevention treatment and were used as controls. At second look laparoscopy performed 12–14 weeks later, 12 of the 16 women (75%) treated with Interceed were free of adhesions compared to two of the 16 controls

(12%) ($p < 0.05$). diZerega et al. investigated the benefits of the application of Oxiplex/AP gel [43] by recruiting 37 women operated for endometriosis. At the end of the intervention, 20 of them were applied Oxiplex/AP gel on the pelvic organs while the remaining 17 women did not receive any further treatment after surgery. At a second look laparoscopy performed 6–10 weeks later, the mean ± SEM AFS score dropped in the treated group from 8 ± 3 to 6 ± 2 whereas it was found to increase in the control group from 10 ± 2 to 14 ± 3 ($p < 0.01$). Finally, Brown et al. recruited 402 women who underwent gynecologic laparoscopy that included adhesiolysis and allocated them to either icodextrin 4% solution (Adept) versus lactate Ringer's solution (controls) administration [44]. The authors scored adhesions in 23 separate anatomical sites at both initial laparoscopy and at the second look laparoscopy performed 4–8 weeks later. Data was presented separately for the 241 women with endometriosis and documented a statistically significant benefit exclusively in women with more advanced disease (i.e., those with >6 sites of adhesions at initial laparoscopy). The number of sites with adhesions decreased by at least 3 or 30% in 14 out of the 36 (39%) women receiving Adept and in 4 out of the 27 (15%) controls ($p = 0.036$).

Although, overall, these three trials support some benefits of the barrier agents, it has to be pointed out that these effects were always evaluated at second look laparoscopy performed some weeks after the treatment and that data on clinical outcome such as pelvic pain and fertility is completely missing. It is also noteworthy that results from studies focusing on post-surgical adhesions in general should be inferred to the endometriosis condition with much caution. Adhesion prevention in endometriosis may represent a distinct challenge. In fact, the origin of adhesions in affected women remains poorly clarified but since surgery does not remove the causes of the disease, the original insult is expected to persist. As such, in the field of adhesion prevention following surgery, endometriosis should not be joined to other conditions such as fibroids or PID. In these two latter situations, preventing adhesion formation or re-formation after surgery may be expected to have definitive effects. For endometriosis, one should assume that, since the causes of the disease have not been removed, preventing adhesion formation exclusively using some agents at the time of surgery may be insufficient. Studies specifically aimed to evaluate fertility as an outcome are thus mandatory.

5. Comment and conclusions

Endometriosis has a distinctive tendency to recur after conservative surgery [45,46]. In a recent review, Guo estimated a disease relapse rate up to 20% at 2 years and to 40–50% at 5 years [45] and this is not surprising as surgery does not act on the underlying causes of the disease. Thus, two consequences derive: (i) recurrences should not be viewed as a hallmark of surgical clumsiness [47] and (ii) progresses in the efficacy of surgery have to pass through a better understanding of the disease. Of further relevance here is that one may not expect outstanding results by exclusively improving surgical measures. It is plausible that prolonged periods of adjuvant post-surgical treatments aimed at disrupting the pathogenetic mechanisms will be necessary. The objective should be to develop combined management strategies taking clearly into consideration that endometriosis is a chronic disease and that surgery should not be intended as definite but, conversely, as one of the tool of our armamentarium to counteract the disease [46]. The recent acquisition that prolonged post-surgical oral contraceptive use markedly prevent endometrioma recurrences is an illuminating example of this kind of approach [48]. Indeed, this management strategy has been moved forwards by the idea that endometriomas develop from ovulatory events.

Improvement of surgical techniques for endometriosis-related infertility is crucial. The scientific community should invest more on this issue. Well-designed studies are warranted on several controversial aspects. In our view, the two current most critical points in the research agenda are the following: 1) developing surgical techniques for ovarian endometriomas that do not impair ovarian reserve, 2) identifying management strategies (either surgical or through adjuvant treatments) to prevent adhesions formation or re-formation.

Contributors

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Conflict of interest statement

The authors state that they have no conflict of interest.

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