The Optimal Treatment of Recurrent Endometriosis in Infertile Patients

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Women with endometriosis are confronted with one or both of two major problems: pain, infertility or both. It affects an estimated 176 million women of reproductive age group worldwide (Adamson et al., 2010). By far the most frequent cause of pelvic pain in women of reproductive age group (Vercellini 1997). Symptomatic disease may cause prolonged suffering and disability, affecting negatively health-related QOL (Gao et al., 2006a; Bianconi et al., 2007). Economic and social costs of endometriosis impact unfavourably on national health systems and working ability (Gao et al., 2006b; Simoens et al., 2007).
INFERTILITY

- Affects approximately 10% of the female population in their fertile years and 10-25% requiring ART.
- Classic studies suggest that 25-50% of infertile women have endometriosis and 30-50% of women with endometriosis are infertile.
- Distorted pelvic anatomy, impaired oocyte release, inhibit ovum pickup and transport, Altered peritoneal function, Endocrine and anovulatory disorders, Impaired implantation, Progesterone resistance, Decreased levels of cellular immunity.
- Despite of reasonable evidence confirming an association between Endometriosis and infertility, a causal relationship has not yet been established (The Practice Committee of the American Society for Reproductive Medicine, 2004).
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.
Endometrioma and Ovarian responsiveness

- A primary or secondary event?
- Quantitative or qualitative or BOTH!
- 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.
- 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 complications of cyst removal prior to ART (Somigliana et al., 2006a; Garcia-Velasco 2008).
Ovarian responsiveness is damaged after the presence and excision of ovarian endometriomas (Gupta et al., 2006; Somigliana et al., 2006a).

Reported prevalence of post-surgical ovarian failure as high as 2.4%.

Surgery-mediated damage causes:
- accidental removal of a healthy ovarian tissue during cystectomy
- local inflammation or vascular compromise following electrosurgical coagulation.
Electrosurgical coagulation during hemostasis could play an important role in damage to ovarian stroma and vascularization.

Particular attention in case of bilateral endometriotic cysts. Increased rates of ovarian failure in such cases treated surgically.
Endometrioma-mediated damage leads to reduced follicular numbers and activity antecedent to surgery. The number of developing follicles and the retrieved oocytes are lower in affected women when compared with unaffected controls. (Gupta et al., 2006; Esinler et al., 2006; Somigliana et al., 2006b; Yazbeck et al., 2006; Cirpan et al., 2007; Matalliotakis et al., 2007; Kumbak et al., 2008).

Conversely, the potential impact of this endometrioma-related reduced responsiveness on the success rate of IVF is less recognized. At least two main hypotheses to explain this contrasting result: 

the damage could be quantitative rather than qualitative.
Surgery for endometriosis-associated infertility: a pragmatic approach

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Re-operations are technically more demanding and potentially more risky!

Fedele et al., (2006) compared the post-operative results after laparoscopic excision of primary vs. recurrent endometrioma and found the effect of repetitive laparoscopic surgery is similar to that observed after first-line surgery.

Garcia-Velasco et al. (2004a) and Wong et al. (2004) did not find a significant difference in the pregnancy rates for the women who underwent surgery for endometriosis prior to IVF.

Demirol et al. (2006), who reported the results of the first available RCT on this issue were similar to above. For infertile women with recurrent endometriosis and prior one or more fertility surgeries done, IVF-ET is a better therapeutic option. (ASRM 2004)
Surgery before or after IVF?

- 2 questions should be answered
  - does the presence of endometrioma impair the results of IVF?
  - Is IVF outcome affected after removal of endometrioma?

- Studies have shown no significant difference between the pregnancy rate of women who had surgery before IVF and those who went directly for IVF. (*Velasco et al.*, 2004; *Wong et al.*, 2004; *Demirol et al.*, 2006).

- Studies have shown that presence of small endometrioma <4cm does not impair IVF outcomes and a general agreement that >4cm may create difficulty during oocyte retrieval (*Somigliana et al.*, 2006).

However, very few studies show that laparoscopy should be considered for the treatment of endometriosis-associated infertility even after multiple IVF failures.
Objective is the baby...

WHY NOT IVF?
Surgery Vs IVF for recurrent endometriosis

- Perplexities arise during counselling of infertile women with recurrent endometriosis when they have failed to conceive after a first surgical procedure.
- In case with small endometriomas (<4cm), the choice is generally between repeat surgery or IVF-ET.
- Studies from Pagidas et al. (1996) and Cheewadhanaraks et al. (2004) do not suggest surgery is better than IVF.
- Infertile women with moderate to severe endometriosis and previous one or more infertility operations, IVF-ET is often a better therapeutic option than another infertility operation (The American Society for Reproductive Medicine, 2004).
Surgery for infertility is rendered obsolete by advanced reproductive technologies (DeCherney 2006).

Feinberg et al. (2008) claimed that ART has superseded surgery as first-line therapy for endometriosis associated infertility, as the latter carries more risk and less proven benefits than IVF.

IVF treats multiple co-existing fertility problems and can be performed without delay thus making it more beneficial for older patients (Adamson 2005).
Treatment of Recurrent Endometrioma

- Risk of pelvic abscess – ruptured endometrioma
- Risk of occult malignancy
- Retrieval difficulties
- Contamination with endometrioma content
- Endometriosis progression

- Surgical-related damage
- Minor and major surgical complications
- Economic costs
- Lack of evidence that surgery improves IVF pregnancy rates

Favours SURGERY

Favours Expectant Management
Endometrioma responds poorly.

No evidence that medical treatment improves fertility.

In reality, fertility is essentially eliminated during treatment as all medical treatment for endometriosis inhibit ovulation.

Medical treatment by itself should not be considered in infertile women with endometrioma.

USG guided aspiration +/- sclerosant ?? – risk of recurrence.

Combined medical (pre/post op) and surgical treatment - No evidence in literature and it may delay fertility further!
What experts say ...

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

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Recommendation</th>
<th>ASRM 2006</th>
<th>RCOG 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal-mild endometriosis (stage I–II disease)</td>
<td>Limited benefit: surgery recommended</td>
<td>Small benefit: surgery recommended</td>
<td>Demonstrated benefit: surgery recommended</td>
</tr>
<tr>
<td>Moderate–severe endometriosis (stage III-IV disease)</td>
<td>Possible but unproven benefit: surgery recommended</td>
<td>Possible benefit: surgery recommended</td>
<td>Possible benefit: recommendation uncertain</td>
</tr>
<tr>
<td>Post-operative adjuvant treatment</td>
<td>No benefit: not recommended</td>
<td>No benefit: not recommended</td>
<td>No benefit: not recommended</td>
</tr>
<tr>
<td>Surgery before IVF</td>
<td>Recommended if endometrioma ≥ 4 cm</td>
<td>Doubtful benefit: no recommendation</td>
<td>Recommended if endometrioma ≥ 4 cm</td>
</tr>
<tr>
<td>Recurrent endometriosis</td>
<td>No recommendation</td>
<td>Second-line surgery not recommended</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>
Management of women with endometriosis

Guideline of the European Society of Human Reproduction and Embryology

ESHRE Endometriosis Guideline Development Group

September 2013
Hormonal therapies for treatment of endometriosis-associated infertility

Key question: Are hormonal therapies effective for infertility associated with endometriosis?

Recommendation

In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility (Hughes, et al., 2007).

References
Surgery for treatment of endometriosis-associated infertility

- Key question: Is surgery effective for infertility associated with endometriosis?

**Recommendations**

<table>
<thead>
<tr>
<th>In infertile women with AFS/ASRM stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates (Jacobson, et al., 2010, Nowroozi, et al., 1987).</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may consider CO2 laser vaporization of endometriosis, instead of monopolar electrocoagulation, since laser vaporisation is associated with higher cumulative spontaneous pregnancy rates (Chang, et al., 1997).</td>
<td>C</td>
</tr>
<tr>
<td>A</td>
<td>In infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Hart, et al., 2008).</td>
</tr>
<tr>
<td>---</td>
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<tr>
<td>B</td>
<td>The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.</td>
</tr>
<tr>
<td>B</td>
<td>In infertile women with AFS/ASRM stage III/IV endometriosis, clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates (Nezhat, et al., 1989, Vercellini, et al., 2006a).</td>
</tr>
</tbody>
</table>
Surgical therapies as an adjunct to treatment with ART

- Key question: Should surgery be performed prior to treatment with ART to improve reproductive outcomes?

**Recommendations**

| A | In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with assisted reproductive technologies improves pregnancy rates. (Benschop, et al., 2010, Donnez, et al., 2001, Hart, et al., 2008). |

| GPP | In women with endometrioma larger than 3 cm, the GDG recommends clinicians only to consider cystectomy prior to assisted reproductive technologies to improve endometriosis-associated pain or the accessibility of follicles. |

| GPP | The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery. |
**Hormonal therapies**

- **Key question:** Are hormonal therapies effective as an adjunct to surgical therapy for treatment of infertility?

**Recommendations**

<table>
<thead>
<tr>
<th>In infertile women with endometriosis, the GDG recommends clinicians not to prescribe adjunctive hormonal treatment before surgery to improve spontaneous pregnancy rates, as suitable evidence is lacking.</th>
<th>GPP</th>
</tr>
</thead>
</table>

| In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates (Furness, et al., 2004). | A |

**References**

Endometriosis and infertility: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

Women with endometriosis typically present with pelvic pain, infertility, or an adnexal mass, and may require surgery. Treatment of endometriosis in the setting of infertility raises a number of complex clinical questions that do not have simple answers. This document replaces the 2006 ASRM Practice Committee document of the same name. (Fertil Steril® 2012;98:591–8. ©2012 by American Society for Reproductive Medicine.)

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Advances in reproductive technology have made fertility preservation techniques a real possibility.

Three possibilities for preserving their fertility: cryopreservation of their oocytes, embryos, and, most recently, ovarian tissue.

There have been various reports of successful pregnancy with cryopreserved oocytes/ ovarian tissue.
A number of questions remain unanswered to bring this technique into mainstream use. For example:

- How long can the tissue remain frozen and still function after thawing?
- Where is the best location to transplant the tissue strips?
- How much ovarian tissue is required to provide enough oocytes for successful pregnancy?
- How long will the tissue function after transplantation?

Ethical issues
PATIENT’S ROLE..

- Need for Unbiased and Informative Counselling.

- Both surgery and ART should be offered to infertile patients.

- Complete and detailed information on risks and benefits of treatment alternatives must be offered to patients, giving a realistic estimate of chances of success of repetitive surgery and of multiple IVF cycles in order to allow unbiased choices between different possible options.

- Uncertainties deriving from lack of reliable evidence should be discussed.
DILEMMA Continues !!
THE FINAL REMARKS....

- Still an open problem not only for the patient but also for the surgeon who must deal with it!
- No consensus exists for most suitable treatment!
- Comprehensive and personalized patient management.
- At least five points have to be considered; the age of the woman, the presence/absence of pain, the number of previous interventions, ovarian reserve and the possibility of occult malignancy.
- Need of RCTs to elucidate whether or not ovarian endometriomas should be treated before undergoing an IVF–ICSI cycle and which treatment is more suitable.