What is the real place of surgery for infertile patients with endometriosis?

Dr Jim Tsaltas
Head of Gynaecological Endoscopy and Endometriosis Surgery
Monash Health
Monash University Dept of O&G
Melbourne IVF
AGES
* Nil To disclose relating to this lecture
* **Scope of my talk**
  * What evidence supports surgical intervention in the management of endometriosis-related infertility
  * I will try to avoid overlap with other speakers – however there will be much common ground

* **Topics considered in preparation**
  * Minimal to Mild Endometriosis
  * Endometriomas
  * DIE (deep infiltrating endometriosis)
    * Inclusive of rectovaginal and colorectal endometriosis
  * Surgical technique
  * Repeat Surgery
  * Surgery after failed IVF
I have taken the starting point that the patient has been diagnosed with endometriosis and they are infertile

* Diagnosis modality can include examination, ultrasound, laparoscopy

* The infertile population we review are couples with no significant male factor infertility, the female partner is ovulatory and has patent tubes

* Intervene at 12 mths of infertility if under age of 35 or at 6 months if 35 or over
The use of laparoscopic surgery in the treatment of subfertility related to minimal and mild endometriosis may improve future fertility.

Surgery involving ablation/excision (+/- adhesiolysis) is effective compared to diagnostic laparoscopy.

Evidence is high quality:
- 2 RCTs (Marcoux et al 1997, Gruppo Italiano 1999)
- Meta analysis of the two
  - Marcoux strong positive effect whereas Gruppo Italiano reported a small negative effect
  - Canadian study – Rx (50/172 – 29%), Non-Rx(29/169 – 17%) – 36W follow up
  - Italian Study – Rx (10/51 – 20%), Non-Rx – 10/145) – 12M follow up
- Jacobson et al – Cochrane review 2010
- Limitations of studies discussed by Cochrane and Vercellini etal (2009)

On the evidence; Laparoscopic surgery is recommended for minimal – mild endometriosis to enhance fertility.

Importance of ongoing laparoscopic skills training
- Surgery must remain an option – Barri etal 2010
Left pelvic side wall
* IVF is unfortunately not the answer for all
* It is expensive and can be emotionally taxing

* Surgery to investigate the infertile couple is a vital component and tool
  * It is diagnostic and often therapeutic

* Need to maintain these vital skills
* Will break down into endometriomas (ovarian disease) and also rectovaginal /DIE (including colorectal endometriosis)
* Must remember they are not separate entities and may co-exist and according to the literature endometriomas are often markers of more severe disease (Banerjee 2008, Chapron 2009)
* For this discussion I will separate the discussion into:
  * management of Ovarian disease (endometriomas)
  * management of rectovaginal endometriosis/DIE (including colorectal disease)
* Need to consider place of surgery, associated symptoms such as pain, access and costs of both surgery and IVF. Laparoscopic skill acquisition and training are vital.
Many studies have been produced to discuss this topic

Guidelines to date – ESHRE(2008), ASRM(2006), NHS(2010), WES (2012) – There may be a possible benefit

What is the Data?

Laparoscopic cystectomy by excisional surgery for endometriomata 4cm or greater improves fertility (spontaneous pregnancy rates) compared to drainage and coagulation (Beretta 1998, Alborzi 2004). Many other observational studies show an increased pregnancy rate after surgery for endometriomas with a weighted mean of 50% - summarized in Vercellini 2009

As well as improved fertility rates excision has lower recurrence of endometriomas and symptoms (Hart 2008 and updated 2011 – cochrane review) as compared to drainage and coagulation

High quality as are RCT – limitation not including expectant arm in trial – therefore we do not know true rate of pregnancy with no surgery

Issue with waiting is often the age of the female partner at presentation.
Abnormal anatomy: Ovary

- Ground glass appearance
- Thick walled
- Uni- or multilocular
- Multiple lesions
- Kissing ovaries
- Hyperechogenic wall foci
- Wall nodularities
- Acoustic enhancement
- Absence of internal vascularity
- ‘shifting’ content
- (No acoustic streaming)
- Do not regress
* Based on the above evidence
* Weight of other studies
* Other symptoms attributed to the endometriosis – significant pain, impact on patients QOL, histological diagnosis, reduce risk of cyst complications, improve access for IVF if required and reduce risk of post IVF abscess formation. (Garcia-Velasco 2009)
* Tubal and Male factor infertility
* Access to trained surgeons and IVF
* Must no look at surgery and IVF as competing interests but rather as complementary therapeutic strategies (Barri 2010, Littman 2005, Adamson 2005)
Evidence of moderate to high grade exists to recommend excisional surgery for endometriomas 4cm or more to improve fertility. Appropriate skill and training is required for safe and complete excision. It is important to minimize ovarian damage and further studies are required to ascertain if suturing for haemostasis is superior. (Data from new Plasma-Jet technology is awaited with interest)

Surgeons should consider measurements of ovarian reserve pre and post operative to help counsel patients.
There has been much discussion re the benefits and risks of endometrioma surgery in the recent literature. I believe this has led to the avoidance of surgery even in cases where it is clear cut that patients need surgery based on their symptoms. Pain, infertility, pressure, access for IVF.

I was impressed with the recent article by our colleagues from Italy about the benefits of surgery. It resonated with many of the thoughts I had been having.

“Effect of surgery for Endometrioma on Ovarian function: A different point of view”

Muzii L, Luciano A, Zupi E and Panici P

JMIG Vol 21, No 4 (July/Aug 2014)
* Current evidence of possible damage to ovarian reserve is not strong enough to recommend against surgery

* Surgery yields postoperative pregnancy rates of 50% and treats associated pain

* Some evidence exists for the possibility that the damage to the ovary may be due to the endometrioma

* Damage to the ovary is significantly less when surgery is performed by experienced operators
Planning Surgery

* Careful pre op assessment
* Indication for surgery
  * Confirm diagnosis
  * Pain
  * Infertility
  * Facilitate access to oocytes at IVF OPU
* Assessment of ovarian reserve – will become more critical
  * Ultrasound to include – AFC
  * AMH (Anti-Mullerian hormone)
    * AMH is produced by the follicles, it corresponds well with AFC and ovarian response to hyperstimulation in IVF, it is the only marker that is menstrual cycle independent and easily measurable (Chang HJ et al – 2010)
Reducing Risks

- Care with surgical technique
  - Excision is preferred method
  - Care with identification of planes (Canis Principle)
  - Minimize diathermy and conserve all ovarian tissue possible
    - Recent small randomized clinical trial – shows potential less reduction in ovarian reserve when suturing is used for haemostasis – AFC outcome measure (Coric 2011)
    - Minimize the amount of coagulation used – be very precise in its application
    - Combined technique – excisional surgery and also ablative surgery for 10 – 20% of endometrioma wall next to hilus (Donnez 2010)
    - I await with interest more data re Plasmajet technology (Roman 2015)
  - Small study looked at reduction of post operative adhesions by suture to close the ovary for haemostasis compared to traditional diathermy (endometriomas) RCT – favored suturing – Pellicano 2008, Litta et al 2013
    - This is now our practice
  - Haemostatic Aids in the ovary – ie Floseal with or without suturing (Angioli R eta l – 2009)

- AMH excellent marker
  - should consider recommendation of routine AMH testing pre and 3 mths post endometrioma surgery
  - should consider egg freezing prior to recurrent endometrioma surgery in young patient with low AMH not trying to conceive
  - Should consider IVF if ovarian reserve is compromised but will depend on ability to access follicles – LDR protocol with 3 M GnRH analogue pre stimulation(Garcia-Velasco J, Somigliana E – 2009)
Due to implications of surgery on endometriomas we will hear and discuss more about the implications and potential place of fertility preservation (Oocyte freezing, single parenthood options).

Fertility preservation in women with endometriosis: for all, for some, for none?


Human reproduction

An excellent overview on the subject
AMH produced by small growing follicles

La Marca et al 2010
* Early studies suggested improvement in fertility rates after management of DIE (Chapron 1999)
* Since that time a number of articles have been published discussing this issue
* Severe endometriosis which infiltrates the posterior vaginal wall and anterior rectal wall is one of the most challenging surgical issues we face as gynaecologists.
* There have now been a number of studies on this topic. Studies are either retrospective, observational or prospective.
* Surgery may be challenging and the risks of intraoperative and post operative morbidity not negligible
* Surgery should only be performed with the appropriate multidisciplinary set up
* Pregnancy rates from studies quoted vary from 23 - 57% (recent review Meuleman 2011) These studies vary in quality and the grade of evidence are mostly low quality with occasional moderate quality studies
Recent Studies of interest

* **Ferrero 2009 Pregnancy after bowel resection**
  * Surgery: Laparoscopy – 57.6%, Laparotomy – 23.6%
  * Surgical technique based on the preference of the colorectal surgeon
  * Laparoscopy superior to laparotomy
  * No Spont Preg in women over 35 after surgery

* **Stepniewska A 2009**
  * 3 Groups
  * Greater than 1 year infertility (average – 2.5 years)
  * Retrospective cohort study with longitudinal evaluation of clinical outcomes
    * 60 – severe pain request bowel surgery – spont pregn 12/30, IUI 0/5, IVF – 5/13
    * 40 – no consent for bowel surgery(all other endo removed) - Spont Pregn 7/23, IUI 0/3, IVF – 1/13
    * 55 – Stage 3 -4 endo but no bowel endo - spont pregn 24/34, IUI – 4/6, IVF – 4/6
  * Best outcomes in patients who had stage 3 – 4 endometriosis without bowel involvement
* Vercellini 2006
  * 105 women – 44 chose surgery, 61 expectant management
  * Patients self selected
  * Surgery by laparotomy for severe rectovaginal endometriosis
  * 24 month follow up
  * Surgery – 44.9%
  * Expectant management – 46.8%
  * Bias as stated by authors – patients with more pain and potentially more aggressive disease chose surgery and this may influence pregnancy rates
Barri 2010
* Observational study
* 825 patients aged 20 – 40 years (mean age 35.3) with infertility and endometriosis – 2001 to 2008
* Mean length of infertility – 3.2+/− 2.3 years
* Diagnosed – stage 3 – 4 AFS Endometriosis
* Many with endometriomas
* 483 patients – surgery – 262 spont preg 54.2%
* 221 patients – no pregnancy – 144 IVF – 184 Oocyte retrieval and 56 pregnancies
* Syrgery then IVF if required – pregn rate 65.8%
* IVF chosen by 173 patients who chose no surgery – 68 pregnancies (patients matched) – 32.2%
* Again age is an issue in both groups (35 yoa)
* Surgery only - <35 – 229/372, >35 – 33/111
* Group 3 – no treatment – 20/69 – 11.8%
* Good study – favoring surgery
* If under 35 – Ivf at 12 months, if over 35 – Ivf at 6 months
Infertile patients with severe endometriosis including colorectal disease should consider surgery as an alternative to IVF. There are no RCT or meta-analyses to answer the question whether the surgical excision of severe endometriosis will enhance pregnancy rates. However recent studies of better quality and larger numbers suggest an improvement in pregnancy rates. Surgery should only be undertaken with appropriate consent and understanding of the risks. Women should be given a full understanding of all available options to help with conception. Surgery for this major disease should be managed by the appropriate multidisciplinary team.
Conclusion – Severe disease

Severe Endometriosis
Limited information is available on the effect of second line surgery for recurrent endometriosis in infertile women.

No RCT: repeat surgery vs expectant management; IVF vs repeat surgery

Studies

* Fedele 2006 – 1993 to 2002
  * 305 primary surgeries and 54 reoperations for recurrent endometrioma in the same ovary of the primary cyst
  * Pregnancy rate – Primary – 40.8%, Secondary – 32.4%
  * The surgical Procedure might be technically more challenging and involves a greater risk of further impairment of function.

* Vercellini 2009 – review article
  * Analysis of the literature – achieving a pregnancy after repetitive surgery was almost half that observed after primary surgery
  * 2 cycles of IVF better than repeat surgery

* Adamson 2005
  * Disadvantages of surgery – potential damage to ovarian reserve, morbidity, a potential longer time to conception compared to IVF and lack of trained surgeons

* ESHRE 2005
  * Final decision should consider presence of pain symptoms and large endometriomas. Pain and refusal to proceed to IVF still constitutes an indication for repeat surgery
* No evidence to recommend repeat surgery over IVF

* However should consider surgery if increasing pain, enlarging endometrioma and no desire for IVF. Surgery can be complex and appropriate consent needs to be obtained.

* Grade of Evidence is Low

* More studies required
Littman 2005
* Study in a tertiary IVF and Endoscopy centre
* Retrospective case series
* 29 patients with prior IVF failures – 22 conceived after laparoscopic treatment of endometriosis
  * 15 spontaneous conceptions
  * 7 IVF Pregnancies
* Authors believe that complete and thorough microsurgical eradication of endometriosis allows patients to conceive without further IVF therapy and may help optimize success for those who require subsequent IVF cycles

Prospective cohort study – Bianchi 2009 – Good study to read
Deep Infiltrating Endometriosis and IVF

<table>
<thead>
<tr>
<th></th>
<th>IVF only (n=105)</th>
<th>Surgery + IVF (n=64)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility duration (months)</td>
<td>29 ± 20</td>
<td>35 ± 18</td>
<td>.01</td>
</tr>
<tr>
<td>Total dose of FSH (IU)</td>
<td>2380 ± 911</td>
<td>2542 ± 1012</td>
<td>.01</td>
</tr>
<tr>
<td>Number of oocytes retrieved</td>
<td>10 ± 5</td>
<td>9 ± 5</td>
<td>.04</td>
</tr>
<tr>
<td>Fertilisation rate (%)</td>
<td>77.9</td>
<td>78</td>
<td>.76</td>
</tr>
<tr>
<td>No. of top quality embryos / patient</td>
<td>.59 ± 1</td>
<td>.57 ± 1</td>
<td>.48</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>1</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>19 ± 25.1</td>
<td>32.1 ± 30.6</td>
<td>.03</td>
</tr>
<tr>
<td>Pregnancy rate (%)</td>
<td>24</td>
<td>41</td>
<td>.004</td>
</tr>
</tbody>
</table>

(Bianchi et al J Min Invas Gyn 2009)
Failed IVF

* Pressing area of research need
* Continuing IVF in the place of DIE, which may be in fact progressing is probably not wise management- But we need the data
* Appropriate understanding of the surgical risks
* Appropriate consent
* Main concern pts have is bowel leak
* This surgery needs to be done by the team that is comfortable to deal with the risks
* Patient needs to feel secure and if a leak occurs it is not due to error
Surgery may play a role in patients who have failed IVF treatment and endometriosis. It may be inappropriate to continue with repeated IVF cycles without considering surgery to excise the endometriosis. Excision of endometriosis may enhance opportunity to conceive spontaneously and even enhance IVF outcomes.

Level of evidence - low
The information presented today will always create debate and discussion. However the evidence is clear regarding Minimal/Mild Endometriosis, Endometriomas. The area that will always create the most controversy will be DIE (this requires further studies and highly individualised care to manage this complex problem).