Infertility treatment for endometriosis: Laparoscopic Surgery and/or Assisted Reproduction

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TEACHING OBJECTIVES
Role of endoscopy in subfertile women
- Diagnostic phase
- Before IUI
- Before IVF
- After IVF
Need for integration Repro Surgery+ART
LUFC protocol

Prevalence of endo in subfertile women
The overall prevalence of endometriosis in subfertile women is:
• 10%
• 30%
• 50%

The prevalence of endometriosis in subfertile women with a regular menstrual cycle whose husband has normal sperm is:
• 10%
• 30%
• 50%
Prevalence of endo in subfertile women

The overall prevalence of endometriosis in subfertile women is:
• 10%
• 30% CORRECT (3% in controls with tubal sterilization)
• 50%

The prevalence of endometriosis in subfertile women with a regular menstrual cycle whose husband has normal sperm is:
• 10%
• 30%
• 50% CORRECT (Meuleman et al, in press)
Increased endo prevalence in infertile vs fertile women

<table>
<thead>
<tr>
<th>Ref (year)</th>
<th>N pat</th>
<th>Endo</th>
<th>St I-II</th>
<th>St III-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lap stereotypes</td>
<td>7953</td>
<td>4%</td>
<td>91%</td>
<td>9%</td>
</tr>
<tr>
<td>Infertile</td>
<td>2372</td>
<td>33%</td>
<td>68%</td>
<td>32%</td>
</tr>
<tr>
<td>P value</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
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</tbody>
</table>

50% prevalence of endometriosis in women with reg cycle/nl male factor

- Meuleman et al, 2008 FS in press

Prevalence endo:

- 47% (104/221) (2/3 Stage I-II, 1/3 Stage III-IV)
- 54% (61/113) in patients with pain
- 40% (43/108) in patients w/o pain.

In patients without anatomical abnormalities (hyper-echogenic cysts or nodules) suggestive of endometriosis at pre-operative TVU, the prevalence of endometriosis was 46% (58/127).

Multivariate logistic regression model including pain, ultrasound data, age, duration of infertility and type of fertility: no prediction of endo

29% prevalence non-endo pathology in women with reg cycle/nl male factor

- 29% patients had non-endometriotic pathology
  (5% of endo; 40% of controls)

9% uterine pathology: SM myoma, polyp, endometritis, uterine septum, Diethylstilbestrol (DES) malformation
19% non-endometriotic tubal pathology: hydrosalpinx, adnexal adhesions
1% combined uterine/non-endometriotic tubal pathology (Meuleman et al, 2008)

!! surgical risk or cost-effectiveness assessment is needed
Laparoscopic excision of minimal-mild endometriosis

1. Is effective to treat infertility and pain
2. Is only effective to treat infertility, not pain
3. Is only effective to treat pain, not infertility

ESHRE guideline for the diagnosis and treatment of endometriosis

Stephen Knowles, Agneta Bergqvist, Charles Chang, Thomas D’Hooghe, Gerard Vanholder, Robert Cramer, Lieve Hummelen, Andrew Prentice, and Erwin Seidler on behalf of the ESHRE Special Interest Group for Endometriosis and Endometriosis CellLine Development Group

The objective was to develop recommendations for the diagnosis and treatment of endometriosis and its associated symptoms. A working group was convened comprising of practicing gynaecologists and experts in evidence-based medicine to prepare clinical practice guidelines and to make reviews, the report provides an overview of the evidence required to make evidence-based recommendations and clinical guidelines. As much as possible, the entire ESHRE Special Interest Group for Endometriosis and Endometriosis was given the opportunity to comment on the draft guidelines, after which it was reviewed by the ESHRE Scientific Committee.
Role of ESHRE Special Interest Group for Endometriosis (SIGEE)

- Education and training
- ESHRE Guidelines for endometriosis: Annual update via Working Group
- ESHRE endometriosis cost working group: 2007-10

Ablation of endometriotic lesions plus adhesiolysis to improve fertility in minimal-mild endometriosis is effective compared to diagnostic laparoscopy alone (Jacobson et al, 2004b).

**Evidence Level 1a**

INFERTILITY – surgical Tx

<table>
<thead>
<tr>
<th></th>
<th>Endocan 1997*</th>
<th>GISE Italy 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>341 (power calc)</td>
<td>91 (54surg, 47 diagn)</td>
</tr>
<tr>
<td>Dur Inf</td>
<td>2 yrs</td>
<td>4 yrs</td>
</tr>
<tr>
<td>GnRH</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>MFR</td>
<td>Diagn 2.4%</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td>Surg 4.7%</td>
<td>No data</td>
</tr>
<tr>
<td>Rate Ratio</td>
<td>1.9 (95% CI:1.2-3.1)</td>
<td></td>
</tr>
<tr>
<td>CPR</td>
<td>Diagn 18%</td>
<td>No data</td>
</tr>
<tr>
<td>36wks Surg</td>
<td>31%</td>
<td>No data</td>
</tr>
<tr>
<td>L/Bp</td>
<td>Diagn No data</td>
<td>22%</td>
</tr>
<tr>
<td>1 yr</td>
<td>Surg No data</td>
<td>20%</td>
</tr>
</tbody>
</table>

* Pts informed about type of surgery postoperatively

http://guidelines.endometriosis.org
Rationale for operative laparoscopy in women with minimal/mild endometriosis

1. Complete diagnosis

2. 50% will have endometriosis (Meuleman et al., 2008) and surgery will increase spontaneous MFR and reduce pain (ESHRE Guidelines, 2005)

3. 40% of those without endometriosis have other fertility-reducing pelvic pathology which may benefit from surgery (Meuleman et al, 2008)

Treatment with intrauterine insemination (IUI) improves fertility in minimal–mild endometriosis. Evidence Level 1b

A INFERTILITY – ART: IUI

Treatment with intrauterine insemination (IUI) improves fertility in minimal–mild endometriosis. IUI with ovarian stimulation is effective but the role of unstimulated IUI is uncertain (Tummon et al., 1997).

Surgically untreated endometriosis:
lower fecundity after COH and IUI

-Hughes et al, 1997, Meta-analysis 5214 cycles

Stepwise logistic regression:

OR for pregnancy assoc with

Endo 0.45 (95%CI 0.27-0.76)

Male factor 0.48 (95%CI 0.37-0.61)

- MFR Endo Unexplained P
  Omland 99 16% 34% <0.05
  Nuojua 98 6% 15% 0.05
Does surgery for min/mild endo increase pregnancy rate after IUI?

- May increase the pregnancy rate during IUI (correct)
- Does not increase the pregnancy rate during IUI
- Reduces the pregnancy rate during IUI

No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination

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Declaration: The authors have declared that no conflicts of interest exist in relation to this paper.
Reproductive outcome after COH and IUI

Unexplained infertility = Min/Mild Endo RECENTLY SURGICALLY TREATED

SIMILAR
- Pregnancy rate per cycle (20%)
- Cumulative live birth rate (67%) after 4 cycles
- MPR < 10%

Does surgery for min/mild endo increase pregnancy rate after IUI? Need for more RCTs
Tanahatoe et al, 2006:
RCT reallocation study (role laparoscopy in patients for IUI): at random allocation of patients with unexplained, cervical or mild male subfertility to IUI or to laparoscopy: NO difference in pregnancy rates or pelvic pathology with therapeutic implications.

 Needed: RCT to test the hypothesis that surgical excision of endometriosis before IUI increases the pregnancy rate during IUI treatment when compared to diagnostic laparoscopy alone (ENDOCAN STUDY FOR IUI).

Laparoscopic surgery for women with mod/sev endometriosis or direct IVF?
We do not know
International multicenter study
World Endometriosis Research Foundation (WERF)
No RCT or meta-analyses are available to answer the question whether surgical excision of moderate–severe endometriosis enhances pregnancy rates. Based upon three studies (Adamson et al., 1993; Guzick et al., 1997; Osuga et al., 2002) there seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis, but statistical significance was only reached in one study (Osuga et al., 2002).

| Stage | CPR 1yr | CPR 1y | CPR 1.5yr | Stat  
|-------|---------|---------|-----------|---
| I     | 39%     | 45%     | 45%       | NS, Guzick 1997  
| II    | 31%     | 32%     | 28%       | NS, Adamson, '93  
| III   | 30%     |         |           | P<0.05, Osuga, 02  
| IV    | 25%     |         |           |  

Importance of tubal status (Osuga, 02)

IVF is appropriate treatment especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed.

The recommendation above is based on a systematic review but the working group noted that endometriosis does not adversely affect pregnancy rates in some large databases (e.g. SART and HFEA).
COH for IVF/ICSI is equally effective with both GnRH-a and GnRH antagonist protocols in terms of implantation and clinical pregnancy rates, but COH with GnRHa may be preferred because of the availability of more MII oocytes and embryos (Pabuccu et al, 2007).

**Evidence Level 1b**

**INFERTILITY – ART: COH for IVF**

**IVF outcome impaired in endo pts**
- Barnhart et al, 2002:
  - 54% reduction in PR > tubal infertility
  - Also for minimal/mild endo
  - Negative correlation with ASRM stage
  - Most likely effect on oocyte/embryo (not EM; egg donor studies Valencia IVI)

**Does endo surgery before IVF improve reproductive outcome?**
- No RCTs
- Surrey et al, 2003: retrospective analysis women w/o endometriomata: no difference

! We do not know
Does surgery of endometrioma before IVF improve reprod outcome?
Garcia-Velasco, 2004 (nonrandomized study):
- higher gonadotropin requirements but similar number of retrieved oocytes
  and similar pregnancy rates (surgery versus no surgery)
Somigliana et al, 2006: meta-analysis of 6 other retrospective studies
- effect of PR after IVF non conclusive
  - possibility of reduced ovarian response during OS: ? Role of previous
    presence of the cyst versus damage caused by surgery
Demirol et al, 2006: RCT
  US diagnosed ovarian endometriotic cysts (>= 3 cm <= 6 cm)
  ICSI directly versus ovarian cystectomy followed by ICSI
  PR comparable, but surgical group higher dose of gonadotrophins,
  longer duration of stimulation, and lower N oocytes.

Laparoscopic surgery prior to IVF?
Laparoscopic excision of an endometriotic ovarian cyst before IVF is justified if the cyst has the following size on preoperative US:
- 1-2 cm
- 2-3 cm
- 3 cm or more
- never justified
Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma ≥4 cm in diameter is present to confirm the diagnosis histologically; reduce the risk of infection; improve access to follicles and possibly improve ovarian response. The woman should be counselled regarding the risks of reduced ovarian function after surgery and the loss of the ovary. The decision should be reconsidered if she has had previous ovarian surgery.

Evidence Level 1b

Coagulation or laser vaporization of endometriomas without excision of the pseudo-capsule is associated with a significantly increased risk of cyst recurrence (Vercellini et al, 2003; Hart et al, 2005).

Laparoscopic surgery after failed IVF?

- Littman et al, 2005
  29 pts with at least 1 failed IVF cycle
  Radical laposcopic surgery senior surgeon
  22 pts conceived (13 spt, 3 IUI, 7 IVF)

Criticism: retrospective, not blinded, symptomatic pts only, not uniform
Does IVF increase the cumulative recurrence rate of endometriosis?

- No evidence

Risk for recurrence is no reason to withhold IVF therapy after surgery for endometriosis stage III or IV since cumulative endometriosis recurrence rates are not increased after ovarian hyperstimulation for IVF (D’Hooghe et al, 2006).

Treatment with a GnRH agonist for 3-6 months before IVF or ICSI should be considered in women with endometriosis as it increases the odds of clinical pregnancy fourfold. However, the authors of the Cochrane review stressed that the recommendation is based on only one properly randomized study and called for further research, particularly on the mechanism of action (Sallam, Garcia-Velasco et al., 2006).

http://guidelines.endometriosis.org
Meuleman et al, RBM Online, 2009

- Outcome after Multidisciplinary CO₂ Laser Laparoscopic Excision of Deep Infiltrating Colorectal Endometriosis (Moderate-Severe endometriosis)
- Post-operative complications
- Pain
- Quality of life
- Sexual satisfaction
- Cumulative pregnancy rate
- Cumulative recurrence rate of endometriosis

Cumulative Pregnancy rate
- Population: 16/33 patients (7 spontaneous, 8 IVF, 1 IUI)

- Cumulative pregnancy rate
  - 1 year 31%
  - 2 years 49%
  - 3 years 55%
  - 4 years 70%

Cumulative Recurrence rate

Histologically proven endometriosis
Recurrence in 3/56 (5%) patients
Cumulative recurrence rate:
  - 1 year 2%
  - 2-3-4 years 7%

No recurrences of colorectal endometriosis!
Comparison literature
Fedele et al, 2004: 34% cumulative clinical or sonographic recurrence rate within 3 years after conservative surgery for rectovaginal endometriosis in patients with AFS III or AFS IV disease

DOES OS during IVF RESULT IN AN INCREASED ENDOMETRIOSIS RECURRENCE RATE?
• Selected complex Endo Stage III-IV patients scheduled for treatment with ART (D’Hooghe et al, Fertil Steril 2006)
• Mostly referred patients, often more than 1 surgery for endo in the past

Background
• Endometriosis is estrogen-dependent disease: rarely before menarche
• Is exposure to increased E2 levels related to recurrence?
  >2 case-reports
  – Renier et al. 1995: ureteral endometriosis after ovarian stimulation in patient with history of endometriotic cyst
  – Anaf et al. 2000: 4 cases of rapid growth of sigmoid endometriosis during ovarian hyperstimulation
• Hypothesis: Cumulative endometriosis recurrence rate (CERR) after fertility surgery for rAFS III and rAFS IV endometriosis is INCREASED in women exposed to high E2 levels during IVF when compared to women exposed to lower E2 levels during IUI
DEFINITION OF RECURRENCE OF ENDOMETRIOSIS

- Clinical and/or biopsy-proven endometriosis at laparoscopy, or the presence of an endometriotic cyst on ultrasound, confirmed by cytological examination
- NOT: Suspected recurrence based only on ultrasound criteria (ovarian endometriotic cysts)

Cumulative Recurrence Rate of Endometriosis within 2 years: 55% pre-ART and 30% post-ART
DISCUSSION

- Endo recurrence IVF versus IUI
  - first report in literature
  - Hypothesis not confirmed
  - Possible role of pituitary downregulation with LHRH analogues (buserelin acetate) in long protocol for IVF?
  - Possible role of open Fallopian tubes as risk factor for recurrent retrograde menstruation in the IUI group as opposed to the IVF group?

Does OS during IVF increase endo recurrence risk? Overall conclusion

- At present: no evidence that hormonal stimulation for ART results in a higher endometriosis recurrence rate after surgery for AFS Stage III to Stage IV endometriosis
- Need for clear definition of recurrence
- Need to control for postoperative hormonal suppression therapy
- Need for more prospective cohort studies and for prospective RCTs to determine the role of hormonal stimulation for ART and the role of hormonal suppression as risk factors or protective factors in the recurrence of endometriosis

- Studies with complete follow-up (clinical visits and questionnaires every 6 months) of all patients are ideal (PhD Dr Meuleman) but not always possible
- Life table analysis is the only reliable methodology for all recurrence studies to compensate for the variable duration of follow-up
- Patients who do not come back to their gynecologist after surgery for endometriosis are not necessarily cured, but may seek a second opinion elsewhere if endometriosis symptoms recur.
Outcome assessment
Repro Surgery
- Complications
- Recurrences
- Medicolegal cases
- Fertility
- Pain
- Quality of life
(PhD Dr Meuleman)

Surgery versus ART:
Integration Medical-Surgical aspects of Reproductive Medicine

1. Quality of patient care
2. Quality of training
3. Basis for research
4. Basis for attraction of young OB GYN
5. Part of larger multidisciplinary center
## Threats

**Problem 1: Infertility care = IVF only without proper diagnosis**
- Commercial interests
- Lack of surgical training/skills

## Threats

**Problem 2: Infertility care = General Gyne Endoscopy**
- Often no full female diagnosis
- Often no consideration for male/other factors
- Often no skills in reconstructive fertility-enhancing surgery
- Often no follow-up of infertility

## Integration Medical-Surgical Reproductive Medicine

1. Quality of patient care
2. Quality of training
3. Basis for research
4. Basis for attraction of young OB GYN
5. Part of larger multidisciplinary center
Q of training: international perspective

• ASRM Practice Committee
• UK situation
• EBCOG ESHRE Subspeciality training in Reproductive Medicine: both medical and surgical aspects (LUFC first EU center accredited)

Basis for research

• What is the place of Repro Surgery?
  - Endometriosis
  - Adhesiolysis
  - Tubal reconstruction/reanastomosis
  - Hysteroscopic surgery (septum, SM myoma, IU adhesions, …)

• Still many questions
Basis for research

- Endometriosis
  lower success after IUI or IVF
- Endometriosis Surgery before IUI or IVF?
  IUI (Werbrouck et al, 2006)
  IVF (no data)
- New challenges
  (ie ovarian transplantation)

LUFC protocol subfertile women

1. Investigation:
   - if pain: always endoscopy;
   - if persistent adnexal mass: always endoscopy
   - if no pain: endoscopy if reg cycle/nl sperm
2. Before IUI: always endoscopy (increased spont MFR, possibly increased MFR after IUI)
3. Before/during IVF: always endoscopy
   if ovarian endometriotic cyst >3cm
4. After failed IVF: no routine endoscopy if no pain or no persistent adnexal mass, endoscopy possible if not done during investigation
What about endometriosis centers of excellence?


Danish and German examples

Danish national guidelines

"cases of minimal and mild endometriosis should be referred to and treated centrally in each county"

and

"cases of moderate to severe endometriosis, patients with disseminated disease such as recto-vaginal endometriosis, retroperitoneal endometriosis or endometriosis on the bowels should be referred to one of two country centres of excellence: Copenhagen County Hospital Services (the County Hospital in Glostrup) and Aarhus University Hospital (Skejby Hospital)".

What about endometriosis centers of excellence?

Consistent, Evidence-based care
- excellence
- continuity of care
- multi-disciplinarity
- research
- training
- cost-effectiveness
The centre/network of excellence in endometriosis
a framework for long term multi-disciplinary patient management

Surgeons
Reproductive endocrinologists
Immunologists
Nutritionists

WOMAN
Gynaecological
General
Bowel
Bladder
Lung

IVF
ICSI
IUI

Psychologists/counsellors

Pain management

NURSE

Telephone
Online
Literature
Onsite support

Patient support groups

Complementary therapies

TCM
Homeopathy
Reflexology
Herbalists

Gynaecologist

Surgery

Reproductive endocrinologists

Funding

• Leuven University Research Council
• Belgian Fund for Scientific Research (FWO)
• Belgian Institute for Science/Technology (IWT)
• Endometriosis Association
• EU Public Health Grant
• Merck Serono Pharmaceuticals

Serono Chair Reproductive Medicine 2005-2010