

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

Thomas M.D'Hooghe, MD, PhD and  
Christel Meuleman, MD  
Leuven, Belgium

ESHRE Campus Course  
May 29-30, 2009

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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




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**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%




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**Endometriosis and assisted reproduction: the role for reproductive surgery?**  
 Annemeke De Hondt, Christel Meuleman, Carla Tomassetti, Karen Peeraer and Thomas M. D'Hooghe

Endometriosis and Subfertility: Is the Relationship Resolved?  
 Current Opinion in Obstetrics and Gynecology 2008; 18:374-378

Thomas M. D'Hooghe, M.D., Ph.D.,<sup>1</sup> Sophie Debrock, Ph.D.,<sup>1</sup> Joseph A. Hill, M.D.,<sup>2</sup> and Christel Meuleman, M.D.<sup>3</sup>

ARTICLE IN PRESS

**High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners**

Christel Meuleman, M.D.,<sup>4</sup> Birgit Vandenberghe, M.D.,<sup>5</sup> Steffen Finess, Ph.D.,<sup>6</sup> Carl Splitters, Ph.D.,<sup>7</sup> Dirk Timmerman, M.D., Ph.D.,<sup>8</sup> and Thomas D'Hooghe, M.D., Ph.D.<sup>9</sup>

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Article

Outcome after multidisciplinary CO<sub>2</sub> laser laparoscopic excision of deep infiltrating colorectal endometriosis



Dr. Christel Meuleman MD has been trained in reproductive medicine and reproductive surgery at the University Hospital Leuven, Belgium. As Clinical Head she coordinates the program Endometriosis and Fertility Surgery at the Leuven University Fertility Centre of the department of Obstetrics and Gynecology of the University Hospital Leuven. At present she is completing a PhD on quality control in the surgical diagnosis and treatment of endometriosis.

Dr Christel Meuleman  
 Christel Meuleman<sup>1</sup>, Anneli D'Hoore<sup>2</sup>, Gen Van Clayenbeurghe<sup>3</sup>, Helle Bales<sup>4</sup>, Thomas D'Hooghe<sup>1</sup>  
<sup>1</sup>Leuven University Fertility Centre, Department of Obstetrics and Gynecology; <sup>2</sup>Department of Abdominal Surgery; <sup>3</sup>Department of Urology, University Hospital Leuven; <sup>4</sup>Biomedical Science, University of Leuven, Belgium  
 \*Correspondence: e-mail: thomas.dhooghe@uz.leuven.ac.be


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**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)**


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### Increased endo prevalence in infertile vs fertile women

! Surgeon, histo, subtle, time since last pregnancy

Ref (88-2000)	N pat	Endo	StI-II	StIII-IV
LapSter 8 prs	7953	4 %	91 %	9 %
Infertile 6 prs	2372	33 %	68 %	32 %
P value		P < 0.0001		P < 0.0001




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### 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




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### 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




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**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




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**Laparoscopic excision of minimal-mild endometriosis**

- 1. Is effective to treat infertility and pain (correct)**
- 2. Is only effective to treat infertility, not pain
- 3. Is only effective to treat pain, not infertility




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<http://guidelines.endometriosis.org>

**ESHRE guideline for the diagnosis and treatment of endometriosis**

Stephen Kennedy<sup>1,10</sup>, Agneta Bergqvist<sup>2</sup>, Charles Chapron<sup>3</sup>, Thomas D'Hooghe<sup>4</sup>, Gerard Dunselman<sup>5</sup>, Robert Greb<sup>6</sup>, Lone Hummelshoj<sup>7</sup>, Andrew Prentice<sup>8</sup> and Ertan Saridogan<sup>9</sup> on behalf of the ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group\*

<sup>1</sup>University of Oxford, Oxford, UK, <sup>2</sup>Karolinska Institutet, Stockholm, Sweden, <sup>3</sup>Clinique Universitaire Baudelocque, Paris, France, <sup>4</sup>Leuven University, Leuven, Belgium, <sup>5</sup>Maastricht University, Maastricht, The Netherlands, <sup>6</sup>Maastricht University Hospital, Maastricht, Germany, <sup>7</sup>Endometriose Foreningen, Denmark, <sup>8</sup>University of Cambridge, Cambridge, UK and <sup>9</sup>University College Hospital, London, UK  
<sup>10</sup>To whom correspondence should be addressed at: Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK. E-mail: Stephen.kennedy@obs-gyn.ox.ac.uk

The objective was to develop recommendations for the diagnosis and treatment of endometriosis and its associated symptoms. A working group was convened comprised of practising gynaecologists and experts in evidence-based medicine from Europe, as well as an endometriosis self-help group representative. After reviewing existing evidence-based guidelines and systematic reviews, the expert panel met on three occasions for a day during which the guideline was developed and refined. Recommendations based solely on the clinical experience of the panel were avoided as much as possible. The entire ESHRE Special Interest Group for Endometriosis and Endometrium was given the opportunity to comment on the draft guideline, after which it was available for comment on the ESHRE website for 30 x 10.99 h.

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### 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

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### INFERTILITY – surgical Tx

<b>A</b>	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
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30 June 2007 <http://guidelines.endometriosis.org>

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	Endocan 1997*	GISE Italy 1999
<b>N</b>	341 (power calc)	91 (54surg, 47 diagn) !
<b>Dur Inf</b>	2 yrs	4 yrs !
<b>GnRH</b>	No	Yes! n=41(18surg,23 diagn)
<b>MFR</b> Diagn	<u>2.4%</u>	No data !
Surg	<u>4.7%</u>	No data !
	Rate Ratio 1.9 (95% CI:1.2-3.1)	
<b>CPR</b> Diagn	<u>18 %</u>	No data !
<b>36wks</b> Surg	<u>31%</u>	No data !
	P=0.006	
<b>LB/pt</b> Diagn	No data	22% !
<b>1 yr</b> Surg	No data	20% !

\* Pts informed about type of surgery postoperatively

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**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)




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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 <i>et al.</i> , 1997).	Evidence Level 1b
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30 June 2007

<http://guidelines.endometriosis.org>




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**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




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**Does surgery for min/mild endo increase pregnancy rate after IUI?**

- May increase the pregnancy rate during IUI
- Does not increase the pregnancy rate during IUI
- Reduces the pregnancy rate during IUI




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**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




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**CME** 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

*Eliza Werhouck, M.D., Carl Spiessens, Ph.D., Christel Meuleman, M.D., and Thomas D'Hooghe, M.D., Ph.D.*  
 Leuven University Family Centre, University Hospital Leuven, Leuven, Belgium

**Conclusion(s):** The data from our study suggest that COH and IUI shortly after laparoscopic excision of endometriosis is as effective as COH and IUI in patients with unexplained subfertility. (Fertil Steril® 2006;86: 966-71. ©2006 by American Society for Reproductive Medicine.)




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Werbrouck E, Spiessens C, Meuleman C, D'Hooghe TM.  
Fertil Steril 2006

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%



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**Does surgery for min/mild endo increase pregnancy rate after IUI? Need for more RCTs**

Tanahatoo 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).



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**Laparoscopic surgery for women with mod/sev endometriosis or direct IVF?**

We do not know

International multicenter study  
World Endometriosis Research  
Foundation (WERF)



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## INFERTILITY – surgical Tx

**B**

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).

Evidence Level 3

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### Neg correlation between ASRM stage endometriosis and CPR after surgery

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

? Importance of tubal status (Osuga, 02)

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## INFERTILITY – ART: IVF

**B**

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

Evidence Level 2b

**A**

IVF pregnancy rates are lower in patients with endometriosis than in those with tubal infertility (Barnhart *et al.*, 2002; Templeton A *et al.*, 1996).

Evidence Level 1a

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)

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### 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)




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### 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




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### 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 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
- Demirel 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.
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### 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




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### 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 (correct)
- never justified




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### INFERTILITY – ART: IVF

GPP

Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma  $\geq 4$  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.




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## INFERTILITY – surgical Tx

**A**

<p>Laparoscopic cystectomy for ovarian endometriomas &gt; 4 cm diameter improves fertility compared to drainage and coagulation (Chapron et al, 2002; Beretta et al, 1998). 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)</p>	<p>Evidence Level 1b</p>
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30 June 2007 <http://guidelines.endometriosis.org> 

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## Laparoscopic surgery after failed IVF?

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

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

- No evidence



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**Meuleman et al, RBM Online, 2009**

- Outcome after Multidisciplinary CO<sub>2</sub> 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



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**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%



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**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!



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## 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



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## 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



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## Background

- Endometriosis is estrogen-dependent disease: rarely before menarche
- Is exposure to increased E<sub>2</sub> 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 E<sub>2</sub> levels during IVF when compared to women exposed to lower E<sub>2</sub> levels during IUI



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## 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)

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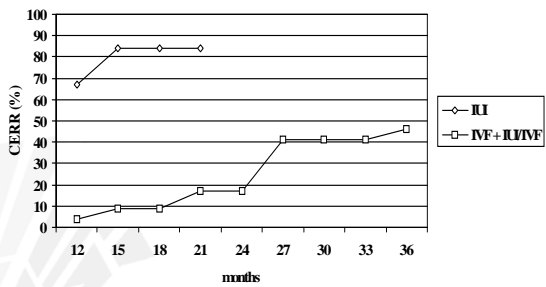
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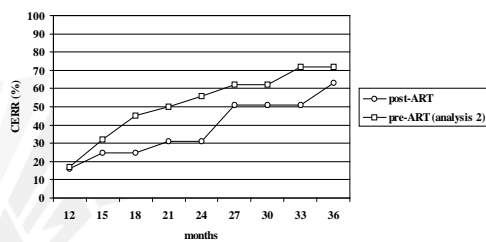
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### Cumulative Recurrence Rate of Endometriosis within 2 years: 55% pre-ART and 30% post-ART




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## 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?



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### 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



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### Does OS during IVF increase endo recurrence risk? Overall conclusion

- 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.



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**Outcome assessment  
Repro Surgery**

- Complications
- Recurrences
- Medicolegal cases
- Fertility
- Pain
- Quality of life

(PhD Dr Meuleman)




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**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




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### Threats

Problem 1: Infertility care =  
IVF only without proper diagnosis

- Commercial interests
- Lack of surgical training/skills



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### 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



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### 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



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**Q of training:  
international perspective**

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



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Recognition Committee

Prof. J. Garavito  
Chairman of ESHRE

B.C. Tarlatzis  
Chairman of the ESHRE  
Subspecialty Recognition  
Committee

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**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



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### 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)




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### 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




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### Leuven University Fertility Center

Gynaecology	Psychology and Counselling	Paramedical staff	Fertility Lab	Research coordinator
T D'Hooghe	K Demyttenaere	E Bakelants	C Spiessens	M Welckenhuysen
C Meuleman	P Enzlin	H De Bie	S Debrock	
L Meeuwis	U Vandenbroeck	E Dancet	G Bertin	
K Peeraer	M Vervaeke	K Dhondt	D Willemen	
C Tomassetti		J Gevaerts	H Devroe	
S Pelckmans	Center for Medical Genetics	V Gilissen	H Afschrift	
P De Loecker	JP Fryns	S Kurstjens	O De Maeght	
L Segal	E Legius	K Eelen	L Hollanders	
A Spaepen	T de Ravel de L'Argentière	L Magis	A Velaers	
I Thijs	Andrology	L Rijkers	F Vynckier	
Ph Albertyn	D Vanderschueren	S Schildermans	P Bols	
V. Vloeberghs	Ph Marcq	H Verbiest	E Vergison	
Gastro enterological surgery	Urology	S Verschuere	K Bullens	
A. D'Hoore	D Deridder	A Verlinden	B Quintens	
	G Bogaert	C Craenen	Ad Hoc Ethical Committee	
	B. Van Cleynenbreughel	C Grootaers	M. Hiele	
		C VandenBosch	P. Schotsmans	
		M Toeteneel	Faculty Ethical Committee	
		E Stuyckens		




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### What about endometriosis centers of excellence?

D'Hooghe TM and Hummelshoj L. (2006)  
*Multi-disciplinary centres/networks of excellence for endometriosis management and research: a proposal.*  
*Human Reprod*;21(11);2743-48.

→ Danish and German examples



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### 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, retro-peritoneal 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)".

Sundhedsstyrelsen (National Board of Health) Denmark:  
Guidelines for specialist treatment, February 2002



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### What about endometriosis centers of excellence?

Consistent, Evidence-based care

- excellence
- continuity of care
- multi-disciplinarity
- research
- training
- cost-effectiveness



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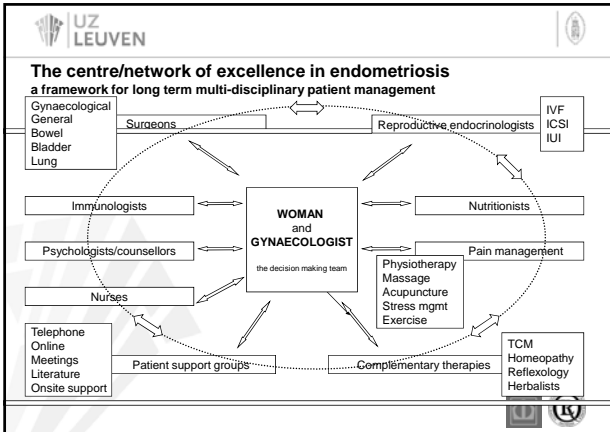
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