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**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
Budapest, February 26th 2010



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%



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



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



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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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Human Reproduction Vol.20, No.10 pp. 2098-2104, 2005
Advance Access publication June 24, 2005

<http://guidelines.endometriosis.org>

ESHRE guideline for the diagnosis and treatment of endometriosis

Stephen Kennedy^{1,10}, Agneta Bergqvist², Charles Chapron³, Thomas D'Hooghe⁴, Gerard Dunselman⁵, Robert Greb⁶, Lone Hummelshoj⁷, Andrew Prentice⁸ and Ertan Saridogan⁹ on behalf of the ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group*

¹University of Oxford, Oxford, UK, ²Karolinska Institutet, Stockholm, Sweden, ³Clinique Universitaire Baudelocque, Paris, France, ⁴Leuven University, Leuven, Belgium, ⁵Maastricht University, Maastricht, The Netherlands, ⁶Maastricht University Hospital, Maastricht, Germany, ⁷Endometriose Foreningen, Denmark, ⁸University of Cambridge, Cambridge, UK and ⁹University College Hospital, London, UK


¹⁰To 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

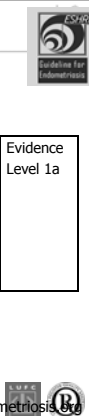


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INFERTILITY – surgical Tx

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

* Pts informed about type of surgery postoperatively



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)





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



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



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.)



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%



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).



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

We do not know

International multicenter study

World Endometriosis Research Foundation (WERF)



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

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)

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)

UZ LEUVEN **INFERTILITY – ART: COH for IVF** 


B	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 GnRH-a may be preferred because of the availability of more MII oocytes and embryos (Pabuccu et al, 2007).	Evidence Level 1b
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15 october 2009 

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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



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.



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 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



INFERTILITY – ART: IVF

GPP

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.

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<http://guidelines.endometriosis.be>



INFERTILITY – surgical Tx

A

Laparoscopic cystectomy for ovarian endometriomas > 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)

Evidence Level 1b

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<http://guidelines.endometriosis.be>



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



INFERTILITY – ART: IVF and recurrence risk of endo



B	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)	Evidence Level 2a
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<http://guidelines.endometriosis.org>



INFERTILITY – ART: IVF



A	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 <i>et al.</i> , 2006).	Evidence Level 1b
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<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



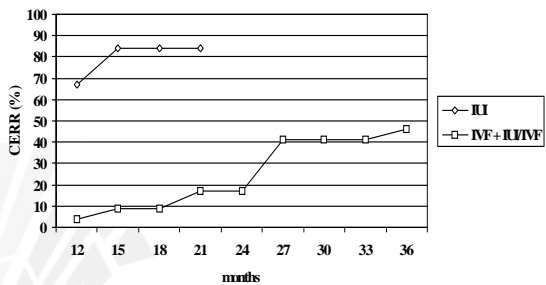
Background

- Endometriosis is estrogen-dependent disease: rarely before menarche
- Is exposure to increased E_2 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_2 levels during IVF when compared to women exposed to lower E_2 levels during IUI

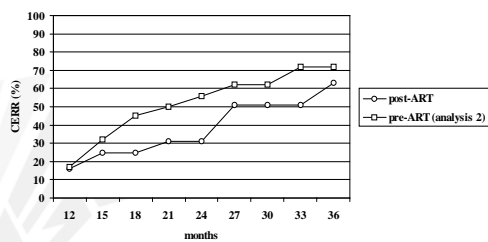


DEFINITION OF RECURRENCE OF ENDOMETRIOSIS

- 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



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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has been approved by Lloyd's Register Quality Assurance
to the following Quality Management System Standards:
ISO 9001 : 2000
The Quality Management System is applicable to:
**Multidisciplinary and evidence based management of couples
with fertility problems.**

Approval Certificate No: 453062	Original Approval: 30 November 2004
	Current Certificate: 30 November 2004
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INTERNATIONAL SYMPOSIUM
RADIOLOGIA UNIVERSITATIS LEUVENAE
November 20-21, 2004

9 YEARS OF REPRODUCTIVE
MEDICINE IN LEUVEN
THE INTEGRATION APPROACH OF
REPRODUCTIVE SURGERY AND IVF




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 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

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



Leuven University Fertility Center

Gynaecology	Psychology and Counselling	Paramedical staff	Fertility Lab	Research coördinator
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 Polckmans	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		



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



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

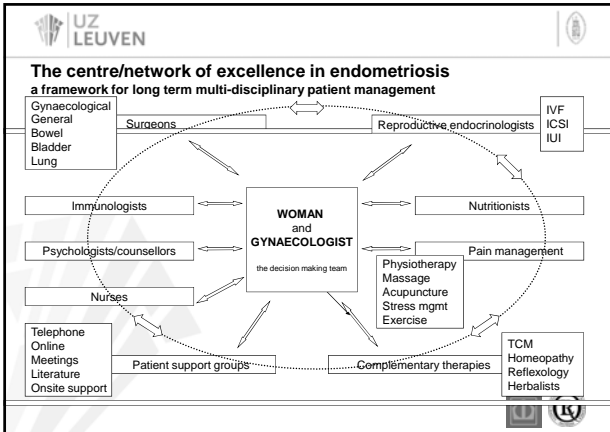


What about endometriosis centers of excellence?

Consistent, Evidence-based care

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





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- 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
