ESHRE Campus workshop

Adenomyosis
A Reproductive Disorder

Leuven, Belgium

19 & 20 April 2007

Contents

Organisation

Course Coordinators

- S. Gordts (B) - Special Interest Group “Reproductive Surgery”
- Th. D’Hooghe (B) & A. Bergqvist (S) - Special Interest Group “Endometriosis & Endometrium”

Invited Speakers, Chairpersons and Discussants

- M. Bazot (F)
- A. Bergqvist (S)
- V. Blomlie (S)
- I. Brosens (B)
- J. Brosens Jr. (UK)
- R. Campo (B)
- P.G. Crosignani (I)
- Th. D’Hooghe(B)
- J. Donnez (B)
- S. Gordts (B)
- Sy Gordts (B)
- P. Greaves (UK)
- A. Herrler (D)
- J. Keckstein (A)
- Ph. Koninckx (B)
- G. Kunz (D)
- M. Nisolle (B)
- A. Pellicer (E)
- R. Pijnenborg (B)
- P. Puttemans (B)
- J. Rabinovici (IL)
- J. Spies (USA)
- D. Timmerman (B)
- P. Vercellini (I)

Aim of the Symposium

- Course will concentrate upon the influence of adenomyosis on implantation and reproduction. The course will deal with epidemiology and pathophysiology, influence of adenomyosis on uterine environment, possibilities of imaging and different treatment modalities will critically be evaluated.

Course objectives

- Recently more evidence is gained of a negative impact of adenomyosis on reproductive performance. The course intends to elucidate on these problems and when possible to put forwards some recommendations.

Target audience

- All those with interest in reproductive medicine, imaging and endometriosis: gynaecologists, reproductive surgeons and radiologists

Scientific organisation

S. Gordts
Leuven Institute for Fertility and Embryology (L.I.F.E.)
Tiensevest 168
3000 Leuven
Belgium
E-mail: lifeleuven@lifeleuven.be

19 April 2007

MORNING PROGRAM

08.00-08.45 Registration

08.45-09.00 Welcome

S. Gordts (B)

Session 1: Epidemiology and pathophysiology

Chairmen: I. Brosens (B) – P. Puttemans (B)

09.00-09.30 Epidemiological factors and symptomatology of adenomyosis

P. Vercellini (I)

09.30-10.00 Adenomyosis: a cause of infertility and pelvic pain?

Th. D'Hooghe (B)

10.00-10.30 Experimental and comparative data

P. Greaves (UK)

10.30-10.45 Discussion

10.45-11.15 Coffee

Chairmen: T. D' Hooghe (B) – J.Brosens Jr. (B)

11.15-11.45 Immunological, hormonal and growth regulating factors in adenomyotic tissue.

A. Bergqvist (S)

11.45-12.15 Angiogenesis in adenomyosis

M. Nisolle (B)

12.15-12.30 Discussion

12.30-14.00 Lunch

19 April 2007

AFTERNOON PROGRAM

Session 2: Adenomyosis and uterine environment

Chairmen: A. Bergqvist (S) – P. Vercellini (I)

14.00-14.30 Control of deep placentation?
R. Pijnenborg (B)

14.30-15.00 Impaired embryo-maternal signalling in adenomyosis
A. Herrler (D)

15.00-15.30 Adenomyosis and pregnancy outcome after IVF
A. Pellicer (E)

15.30-15.45 Discussion

15.45-16.15 Coffee

Chairmen: S. Gordts (B) – A. Pellicer (E)

16.15-16.45 Link with endometriosis
G. Kunz (D)

16.45-17.15 Hormone response of the endo-myometrial junctional zone
J. Brosens (UK)

17.15-17.30 Discussion

20 April 2007

MORNING PROGRAM

Session 3: Imaging and adenomyosis

Chairmen: P.G. Crosignani (I) - J. Donnez (B)

09.00-09.30	Adenomyosis: a difficult sonographic diagnosis
	D. Timmerman (B)
09.30-10.00	Importance of MRI in the diagnosis of adenomyosis
	M. Bazot (F)
10.00-10.30	MRI: Scandinavian experience
	V. Blomlie (S)
10.30-10.45	Discussion
10.45-11.15	*Coffee*

Chairmen: Ph. Koninckx (B) – Sy.Gordts (B)

11.15-11.45	Adenomyosis and diagnostic endoscopy
	R. Campo (B)
11.45-12.15	Adenomyosis and operative endoscopy
	J. Keckstein (A)
12.15-12.30	Discussion
12.30-14.00	*Lunch*

20 April 2007

AFTERNOON PROGRAM

Session 4: Treatment modalities

Chairmen: R. Campo (B) - J. Rabinovici (IL)

14.00-14.30	Is surgery of any benefit: prevention and treatment ***S. Gordts (B)***
14.30-15.15	Value of uterine artery embolisation ***J. Spies (USA)***
15.15-15.30	Discussion
15.30-16.00	*Coffee*

Chairmen: V. Blomlie (S) – D. Timmerman (B)

16.00-16.30	Possibilities of MRI focused ultrasound ***J. Rabinovici (IL)***
16.30-17.00	Place of medical treatment ***P.G. Crosignani (I)***
17.00-17.15	Epidemiologic data on adenomyosis and cancer ***A. Bergqvist (S)***
17.15-18.00	Round table: Adenomyosis and infertility: to be treated? ***Moderator:*** I. Brosens (B) - J. Donnez (B)
18.00	Closure

Adenomyosis: experimental and comparative data

Peter Greaves
Department of Cancer Studies & Molecular Medicine, University of Leicester, United Kingdom

Overview

- Comparative pathology
- Experimental models
  - Mice
  - Rats
  - Rabbits
- Own data in a mouse model

Adenomyosis in animals

- Not well studied
  - Histological examination of uterus not widely or systematically practiced
- Develops spontaneously in laboratory animal species
  - Rodents, dogs, cats, rabbits, primates
  - Some strains of mice predisposed
- Unequivocal endometriosis only in monkeys
    - Adenomyosis not reported in mouse model of endometriosis expressing activated mutant *K-ras* (Dinulescu et al. *Nature Med* **11** 63-70 2005)

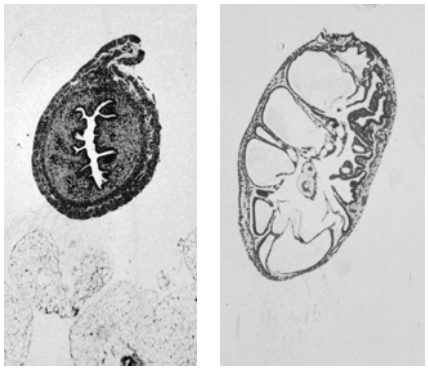
Clinico-pathologic study in baboons

Southwest Foundation fro Biomedical Research, San Antonio
(Barrier et al. *Fertility and Sterility* **82** suppl 3, 2004)

- 3827 autopsies and surgical specimens
- 3 sections/uterus examined by same pathologist over 16 years
- Definition » endometrial tissue separate from normal endometrium
- 37 animals with adenomyosis
- Parity in those with adenomyosis = 3
- Parity in those without = 7.8 (difference $p<0.001$)
- Significant difference maintained if cases of endometriosis excluded

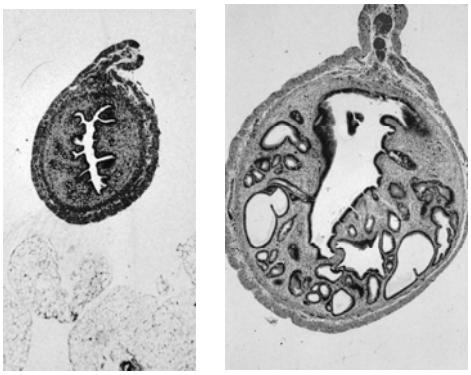
Experimental models of adenomyosis

- Mouse
  - Implantation of anterior pituitary gland in uterus or under renal capsule (Mori et al. *Acta Anat* **116**, 46-54 1983)
    - » 'Hormonal disturbance' or prolactin implicated by authors
  - 12-18 months exposure to progesterone
- Rats
  - Pituitary implantation
  - Fluoxetine (serotonin uptake inhibitor) treatment for 14 weeks
    - » Associated with prolactin increase
- Rabbits
  - Oestrogen treatment



Control mouse

Tamoxifen



Control mouse (1 year) Ethynyloestradiol

Neonate CD-1 mouse models (dosing days 1-5, sc)

Newbold et al. *Cancer Research* **50**, 7677-7681 1990

	Dose (mg/pup)	Endometrial carcinomas at 18 months (%)
Diethylstilboestrol	1	90
Tamoxifen	1 2 10 (5mg/kg) 25 50	19 90 50 9 0
Genestein	100	35

CD1 mouse studies with SERMS

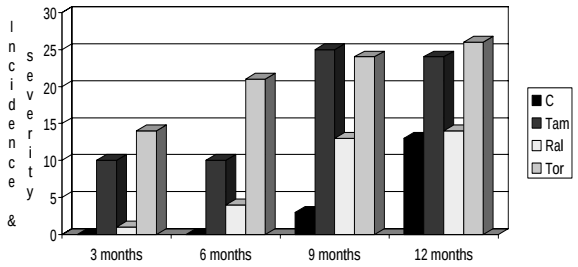
Control	Tamoxifen (base)	Raloxifene hydrochloride	Toremifene citrate
0	1 mg/kg 2.7 μmol/kg	1.37 mg/kg 2.7 μmol/kg	1.6 mg/kg 2.7 μmol/kg

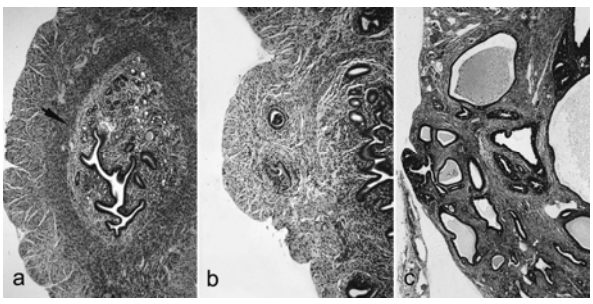
➢***Neonatal oral dosing, sacrifices at 6 days, 3, 6, 9, 12 months and 'life time'***

Adenomyosis at 3 months

Control 1	Tamoxifen	Raloxifene	Toremifene
0/30	*10/10*	*1/10*	*9/10*

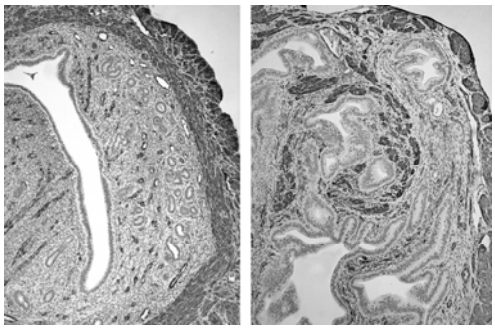
Adenomyosis: Incidence/severity score





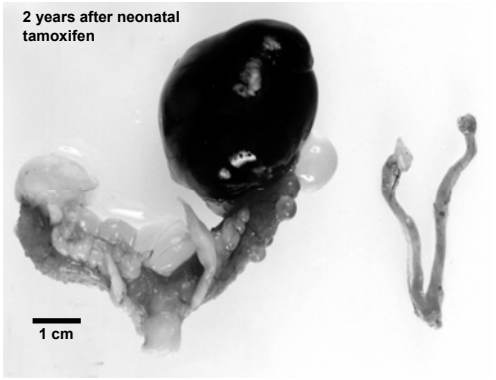
From: Greaves and White, *Best Practice & Research Clinical Obstetrics and Gynaecology*, **20**, 510, 2006

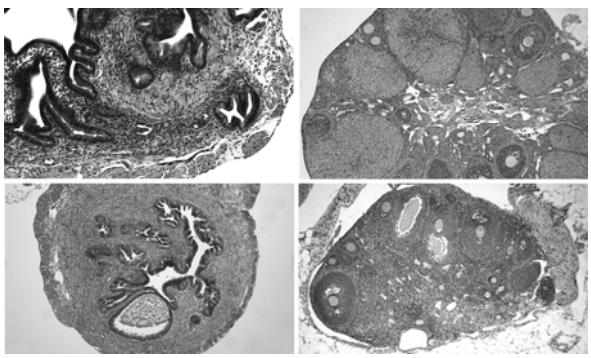
α-smooth muscle actin stain



Control mouse uterus

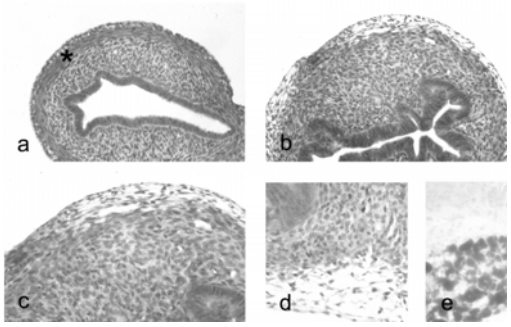
Neonatal tamoxifen dosed





Oral neonatal tamoxifen compared with neonatal 4-hydroxyoestradiol

Histopathology at 6 days

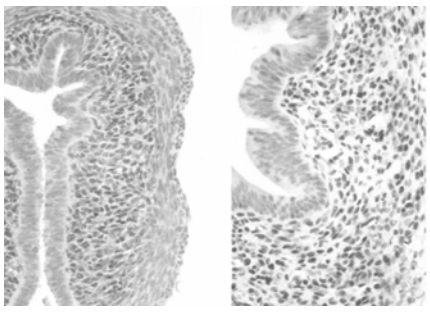


*Parrott et al. Am J Pathol, **159**, 623, 2001*

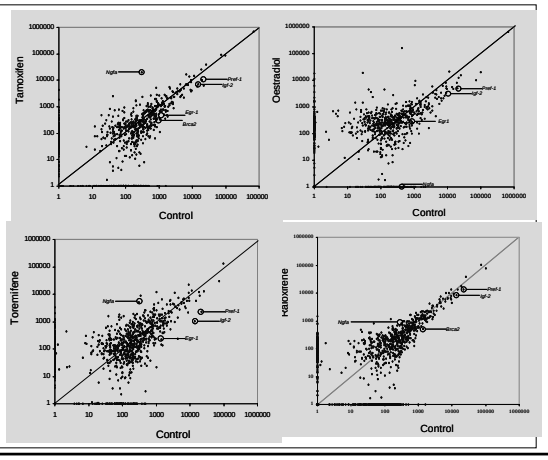
Dysplasia of uterine mesenchyme at 6 days

Control	Oestradiol	Tamoxifen	Raloxifene	Toremifene
0/5	0/6	6/6	0/5	6/6

Expression of ERα protein at 6 days



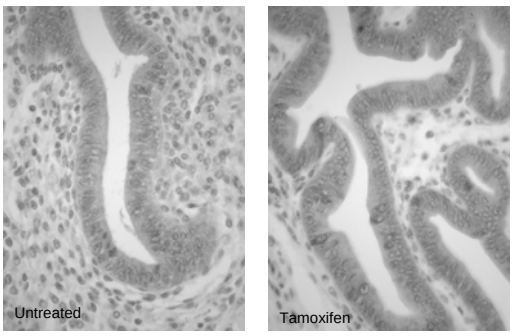
Control Tamoxifen



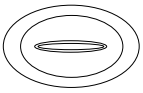
Altered Gene Expression

Gene	Putative function
***Igf-2* precursor**	Stimulates mitogenic activity in human endometrial stromal cells Involved in the growth of uterine smooth muscle tumours Modulate steroid hormone actions in the endometrium
Pref-1	Inhibits the differentiation of preadipocytes into adipocytes Down regulated during their differentiation
Ngfa	Role in myogenic differentiation Receptor highly expressed in uterine smooth muscle cells Repressed at the onset of myogenic differentiation

NGF immunocytochemistry



Laser Capture Microscopy & RT-PCR



Mouse uterus

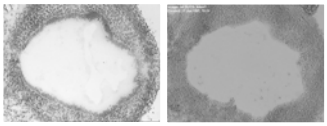
LCM

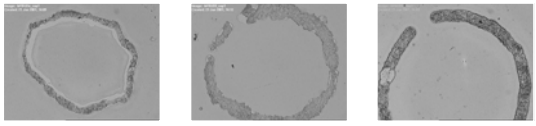
RNA extraction

Semi-quantitative RT-PCR

Expression levels of genes

Mouse uterus at day 6



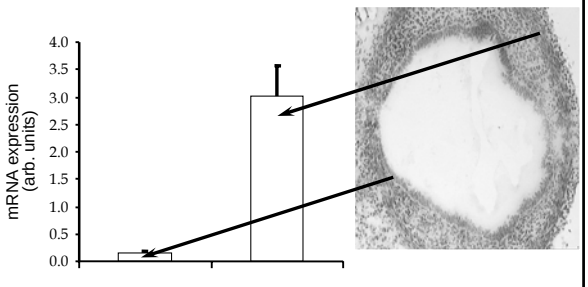


Luminal Epithelium

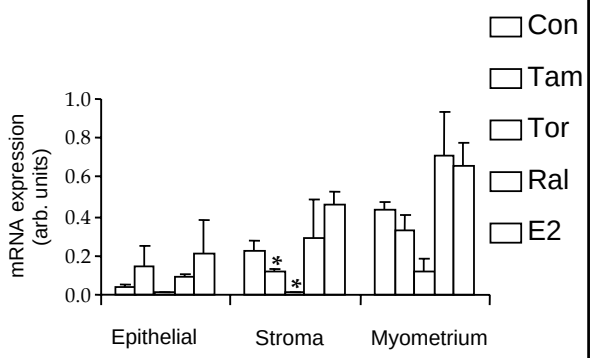
Stroma

Myometrium

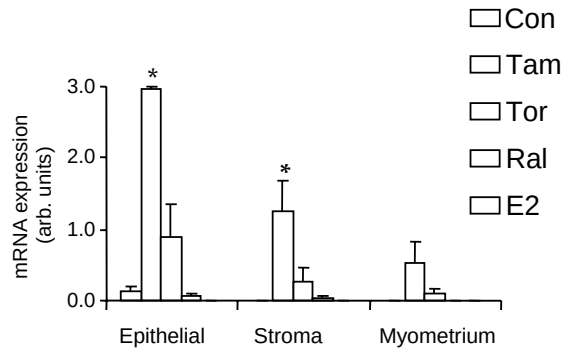
acta gene expression at day 6



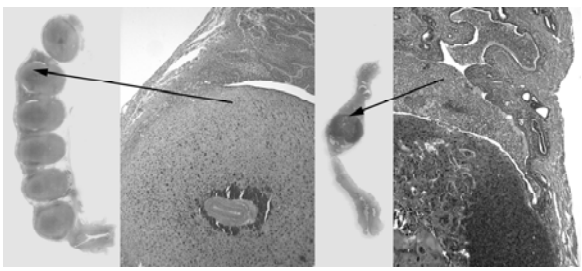
Effect of SERMs: *pref1* gene expression at day 6



Effect of SERMs: *ngfa* gene expression at day 6



Implantation in control vs tamoxifen treated



Implantation in control vs tamoxifen treated

Treatment	Dose mg/kg	Gestation time	Embryos visible after 7 days	Litter size at term	Nº mice to term
Controls	0	19	***16***	***11***	12
Tamoxifen	0.25	20	***2***	***1***	6
4-hydroxy-estradiol	0.325	-	***0***	***0***	6
Estradiol	0.1	18	***15***	***17***	6

Down regulation of cell cycle genes only with tamoxifen

Summary: mouse model

- Adenomyosis produced by particular neonatal dose of tamoxifen or toremifene
- Not simple oestrogen agonism
- Presence of continued oestrus cycling
- Disturbance of endometrial stroma
  - Possibly linked to paracrine effect of NGF
- Adverse effect on implantation
  - Down-regulation of cell cycle genes
  - Inflammation?

Acknowledgements

- Richard Edwards
- Jennifer Edwards
- Andy Green
- Barbara Nolan
- Emma Parrot
- Ian White

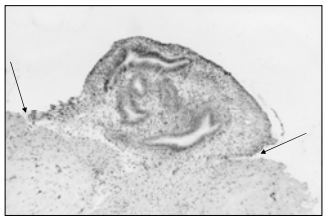
- Funding
  - Medical Research Council
  - AstraZeneca
  - Syngenta

Adenomyosis and Angiogenesis

19/4/2007 - Leuven
M Nisolle , P Nervo, G Bruyshant and JM Foidart

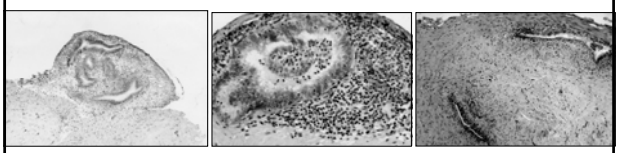
S. Blaccher, P. Gavitelli, S. Raver, A.Noel
Department of Obstetrics and Gynaecology
University of Liege - Belgium

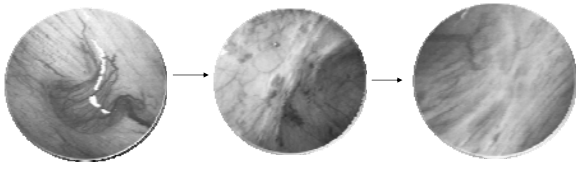
Transplantation Theory



Sampson 1927

Hypothesis of evolution





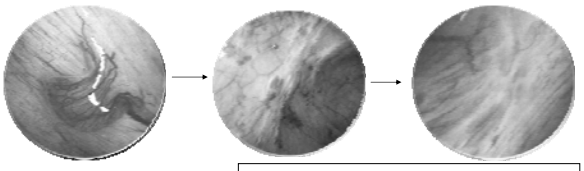
Nisolle et al Fertil Steril 1993

Hypothesis of evolution

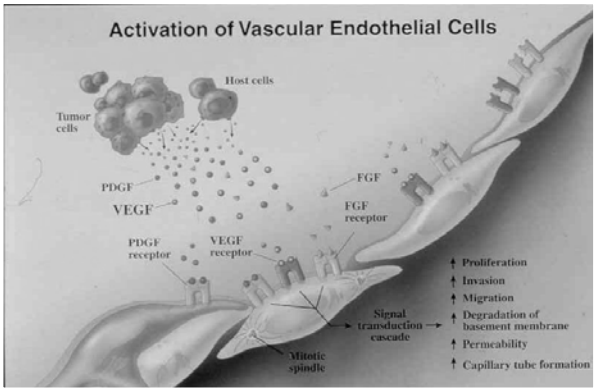
Immunohistochemical analysis of the role of angiogenic status of the vasculature of peritoneal endometriosis

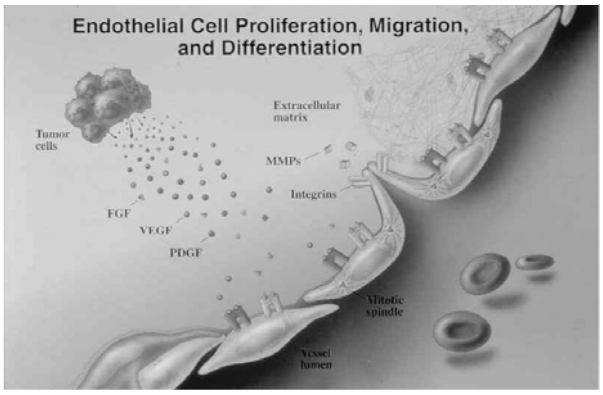
METHOD: Vessel maturation index : % of microvessels showing colocalization of CD 34 and alpha – SMA – positive staining

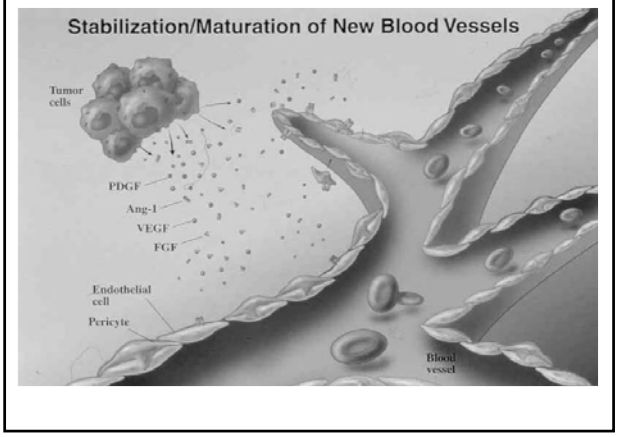
RESULTS: Higher fraction of immature vessels



Matsuzaki et al Fertil Steril 2001

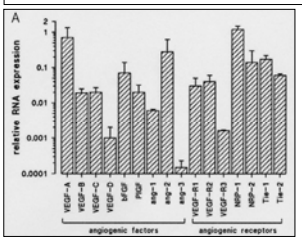


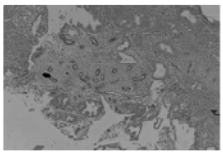




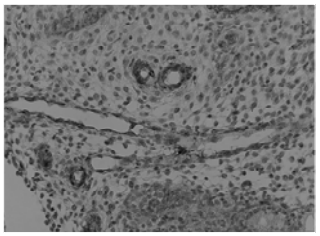
Eutopic Endometrium

Highly angiogenic
VEGF-A
bFGF
Angiopoietin-2





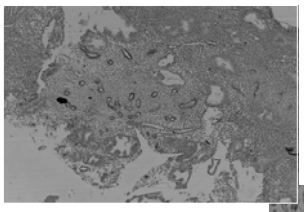
Nap et al JCEM 2004



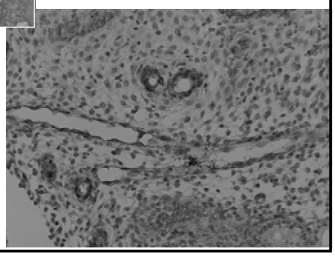
Eutopic Endometrium

VEGF-A
VEGF-R2: proliferation of endothelial cells
VEGF-R1: migration of endothelial cells

Ang-1: recruitment of pericytes



Mature vessels
a-SMA+
vWF +
(RED)

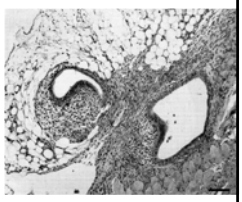


Immature vessels
vWF +
a-SMA –
(brown)

Transplantation of menstrual endometrium in nude mice

Morphological and immunohistochemical results of the implants removed on days 1, 3, and 5.

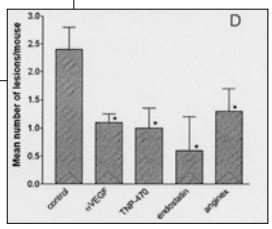
	Day 1	Day 3	Day 5
No. of mice	10	10	8
No. of removed transplants	12	18	13
Presence of endometriotic glands (%)	4/12 (33)	4/18 (22)	8/13 (61)
Proliferative activity			
Ki-67 (%) (median)			
Glandular cells	0	9.68	22.68[a]
Stromal cells	0.47	0.23	0.21
VEGF H-score (mean ± SD)			
Glandular cells	9.50 ± 3.00	6.7 ± 2.63	8.57 ± 1.51
Stromal cells	2.87 ± 2.59	4.00 ± 2.28	7.60 ± 1.71[b]



Nisolle et al Fertil Steril 2000

Transplantation of proliferative endometrium in nude mice and antiangiogenesis

Angiostatic agents
Anti-hVEGF
TNP- 470
Endostatin
Anginex



Nap et al JCEM 2004

Transplantation of proliferative endometrium in nude mice and antiangiogenesis

	vWF-stained vessels	αSMA-stained vessels	vWF-αSMA-stained vessels
Control	13.5 (1–52)	8 (1–29)	4 (0–30)
Anti-hVEGF	8.5 (1–18)[a]	4 (1–17)	1 (0–8)[a]
Endostatin	5 (3–8)[a]	5 (2–8)	0 (0)[a]
Anginex	5 (3–10)[a]	5.5 (3–9)	0 (0–9)[a]

Values are medians (range).
[a] $P < 0.05$ compared to control.

Significant decrease in microvessel density in mice treated with angiostatic agents

Nap et al JCEM 2004

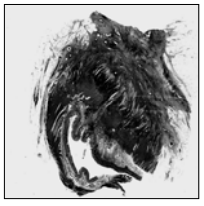
Transplantation of proliferative endometrium in nude mice and antiangiogenesis

Conclusion

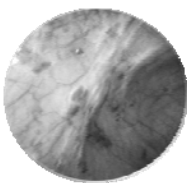
Inhibitors of angiogenesis interfere with the maitenance and growth of endometriosis by inhibiting angiogenesis
Promising therapy?

Nap et al JCEM 2004

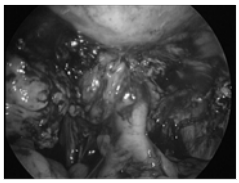
Vascularisation in endometriosis



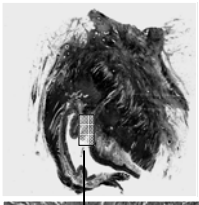
Is DIE vascularisation similar to that observed in peritoneal black lesion?

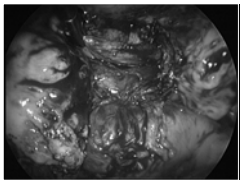


Vascularisation in endometriosis

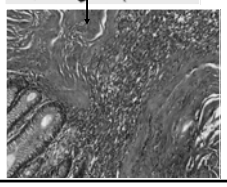


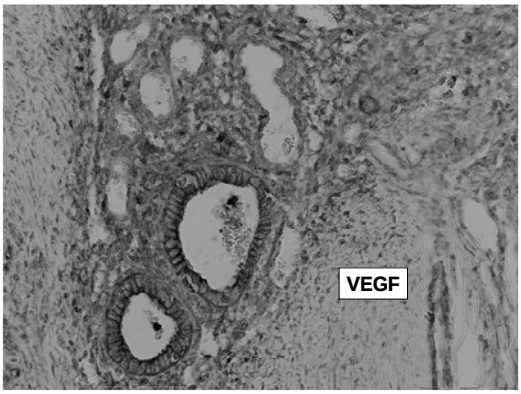
DIE

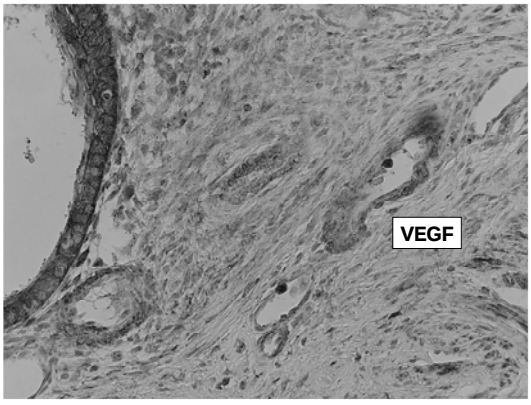


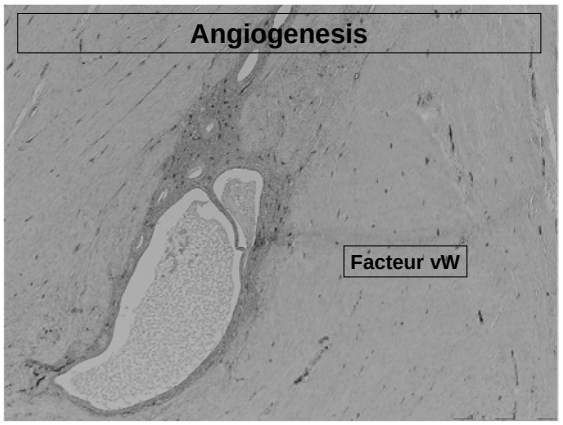


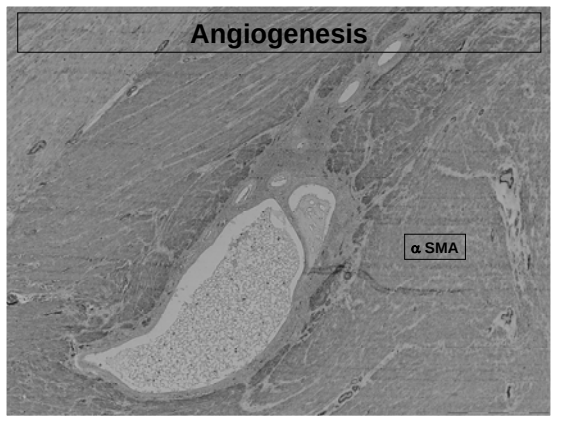
Bowel wall





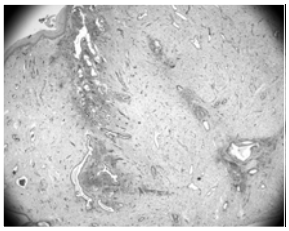






Computerized Image Analysis :

Silvia BLACCHER



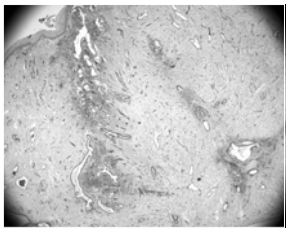
IHC Slide

Binaire Filter

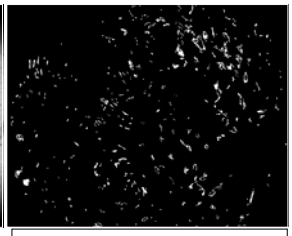
Glandular density

Total glandular surface = 2.06mm²

Glandular density (Glandular surface by tissue surface unit) =0.051



IHC Slide

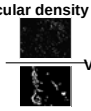


Binaire Filter

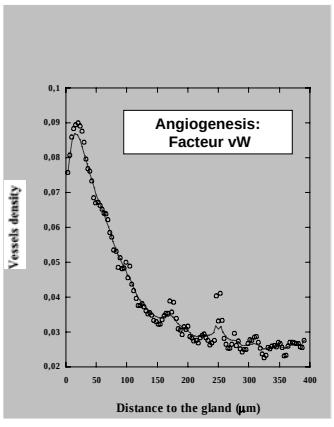
Vascular density

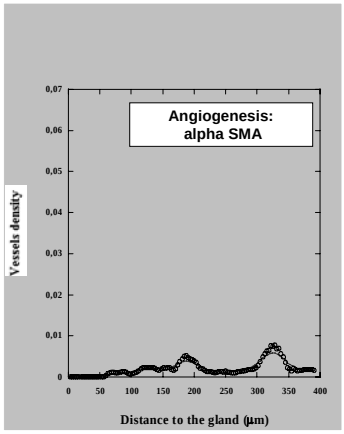
Total Vascular Surface = 1.05mm²

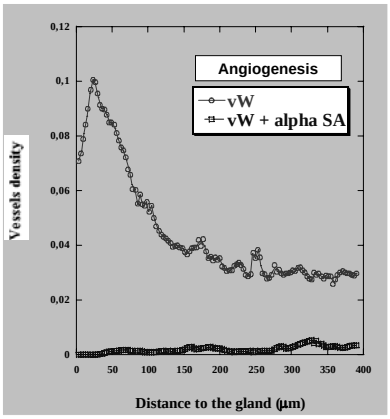
Vascular density (Vascular surface by tissue surface unit) =0.025



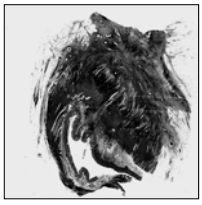
Vascular surface/ Glandular surface=0.51



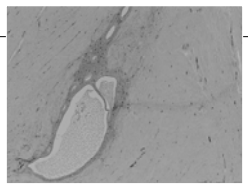




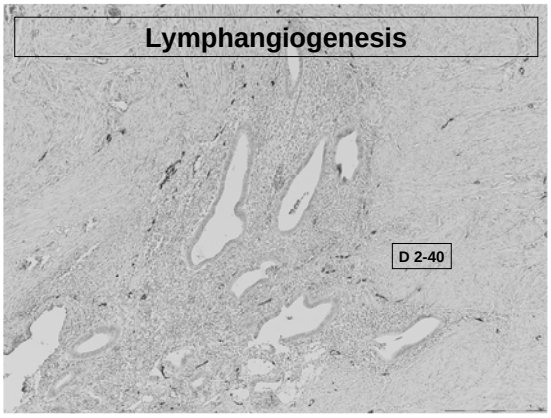
Vascularisation in endometriosis

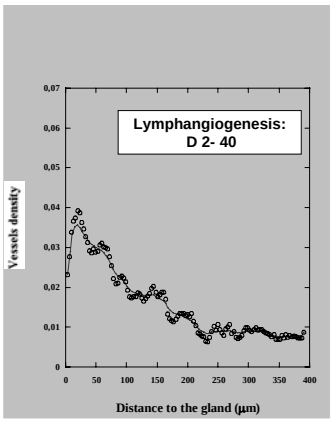


Angiogenesis is observed in DIE
Role in growth?
Role in infiltration?

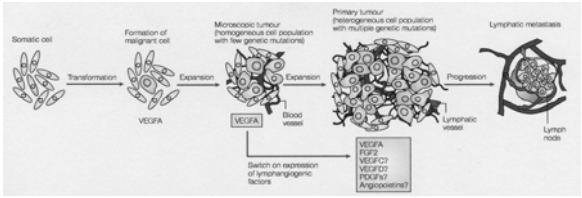


Lymphangiogenesis





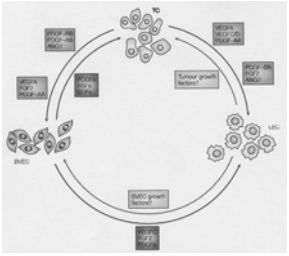
Lymphangiogenesis in malignant tumours



Early stages of malignancy: production of VEGFA
Tumour progression: production of lymphangiogenic factors

Cao Y;Nature reviews 2005

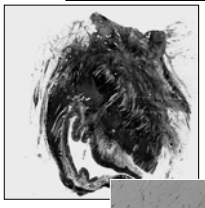
Lymphangiogenesis in malignant tumours



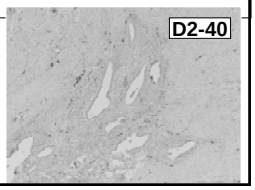
Crosstalk between
Tumour cells
Blood vessel endothelial cells
Lymphatic endothelial cells

LECs might produce growth factors that stimulate the growth of TC and BVECs

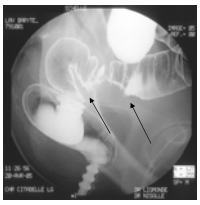
Vascularisation and lymphangiogenesis in endometriosis



Angiogenesis and lymphangiogenesis are observed in DIE
Role in growth?
Role in infiltration?



As in invasive tumours, the growth of DIE could be directly linked to the angio and lymphangiogenetic potential as well as to an extensive fibrotic process that surrounds these nodules



Staff Clinique:
Pr Jean-Michel Foidart, Pr. Michelle Nisolle ,Dr Nervo,
Pr Jean-Pierre Schaaps, Dr Sophie Perrier, Géraldine
Brichant, Bénédicte Balteau, Barbara Deneumostier

Laboratoire-développement des tumeurs:
Dr Agnès Noël, Patricia Gavitelli, Stéphanie Ravet,

Analyse d'Images: Silvia Blacher

Université de Liège
Département de Gynécologie Obstétrique (Prof JM Foidart)

Control of Deep Placentation

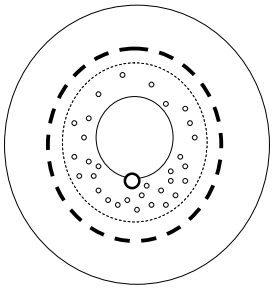
Robert Pijnenborg

K.U.Leuven, Department Woman and Child

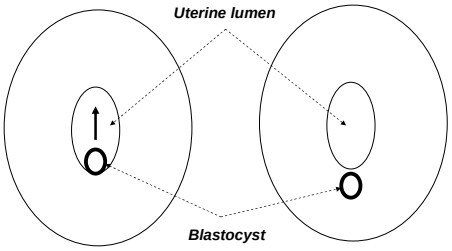
Adenomyosis Symposium, 2007

Control of deep placentation

1. Implantation
2. Decidualization of the endometrium
3. Uterine NK cells
4. The inner myometrium



1. Implantation



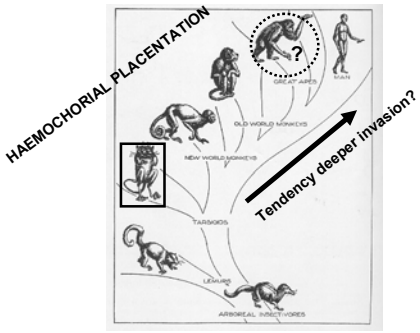
Rhesus monkey:
Superficial implantation

Human:
Interstitial implantation

~ spontaneous decidualization?

1. Implantation

Primate evolution



2. Decidualization of the endometrium

DECIDUA: > *Lat. Decidere = to cast off*

transformed endometrium,
cast off at parturition

Properties

- Endometrial stroma: swelling of fibroblasts
  changes in extracellular matrix
  protein secretion: prolactin
  IGF-BP
  TGF-β
- Spiral arteries: decidual swelling of smooth muscle
  disorganization of muscle wall

2. Decidualization of the endometrium

Possible functions of the decidua

- Glycogen accumulation for fetal (?) or placental (?) nutrition
- Endocrine function: prolactin production
- Protection against trophoblast invasion

Based upon rodent experiments:

Transplantation of trophoblast
into different organs
(including an 'unprepared' uterus)
leads to tissue destruction

(*Kirby & Cowell, 1968*)

2. Decidualization of the endometrium

Possible functions of the decidua

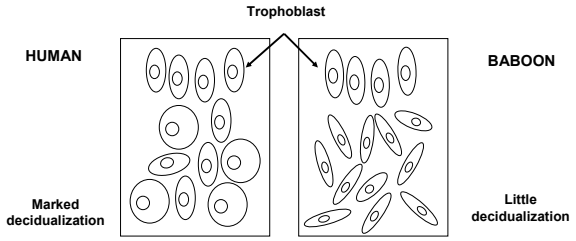
- ❑ Glycogen accumulation for fetal (?) or placental (?) nutrition
- ❑ Endocrine function: prolactin production
- ❑ Protection against trophoblast invasion

Based upon rodent experiments:

Trophoblast outgrowth in normal pregnancy allowed by programmed decidual cell death

(*Billington*, *1971*)

2. Decidualization of the endometrium



- Haig (1993): decidualization protects against invasion
- Ramsey (1976): decidualization promotes invasion

No programmed decidual necrosis/apoptosis during pregnancy !

2. Decidualization of the endometrium

- ❑ Invasion restricting properties of decidua
  - TGF-β secretion (but… also produced by trophoblast!)
  - TIMP secretion to block matrix-degrading MMP action (but… also produced by trophoblast!)
  - IGF-BPI release: thought to block trophoblastic IGF-II autostimulated invasion
- ❑ Invasion promoting properties of decidua
  - Matrix changes: downregulation of cross-linking collagen VI (*Aplin JD et al, 1988*)
  - Activin secretion: stimulates MMP secretion by invasive trophoblast (*Jones RL et al, 2006*)
  - Fas ligand expression restricts numbers of Fas-carrying leukocytes (*Qui Q et al, 2005*)

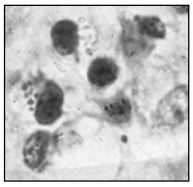
3. Uterine NK cells

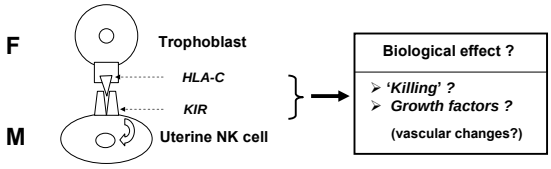
Table 7.1. *Leucocytes in uterine mucosa*

	Non-pregnant endometrium		Early decidua	
	Proliferative	Secretory	Basalis (trophoblast+)	Parietalis (trophoblast−)
Granulocytes				
Neutrophils	−	−/+	−/+	−
Eosinophils	−	−	−	−
Basophils	−	−	−	−
Lymphocytes				
B cells	−(+)	−(+)	−(+)	−(+)
T cells	+	+	+	+
NK cells (LGL)	+	+++	+++++ ⟺	+++
Macrophages	+	+	+++	+

Loke YW & King A (1995)

3. Uterine NK cells





3. Uterine NK cells

Possible functions of uterine NK cells

- **Induction of early (decidual) changes of spiral arteries**

  Absence of uNK cells in immunodeficient TGε26 mice is associated with maintenance of vascular smooth muscle (*Greenwood et al, 2000*)

- **Production of angiogenic factors**

  Human uNK cells contain the angiogenic factors VEGF-C and angiopoietin (*Li XF et al, 2001*)

4. The inner myometrium

DECIDUA

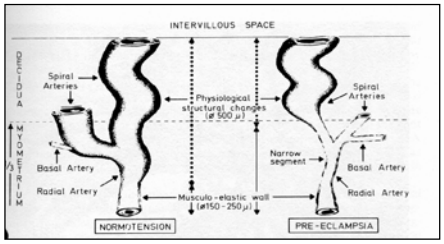
Decidua promotes invasion

INNER MYOMETRIUM

Has the inner myometrium in the human acquired "decidual properties" ?

- Extracellular matrix changes ?
- Factors stimulating MMP release by trophoblast ?
- Altered leukocytic environment?
  - no uterine NK cells !
  - B- and T- cells !
  - other inflammatory cells ?

4. The inner myometrium

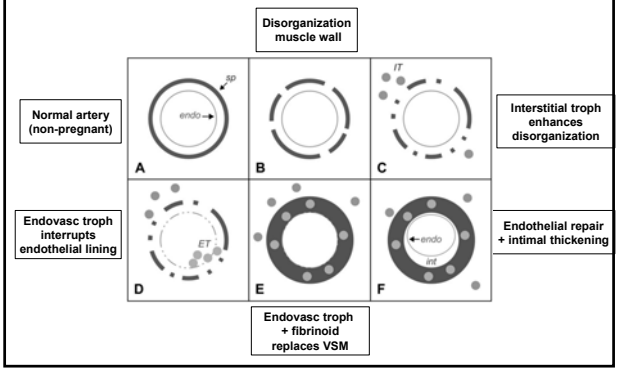


Pre-eclampsia

Physiological changes of pre-eclamptic spiral arteries restricted to the decidua
(*Brosens I et al, 1972*)

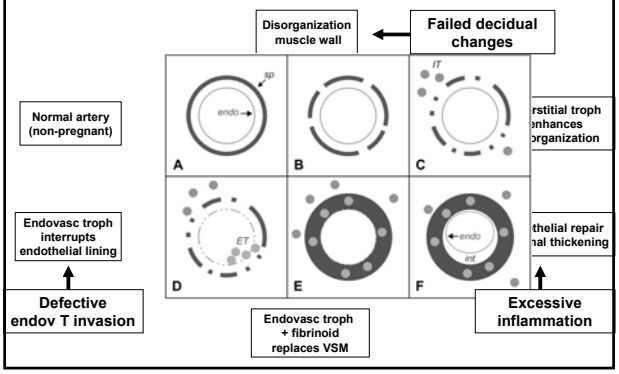
4. The inner myometrium

Multiple steps in vascular remodelling of spiral arteries



4. The inner myometrium

Possible causes of defective vascular remodelling



4. The inner myometrium

The inner myometrium presents a different cellular environment compared to the decidua

- Absence of typical 'swollen' decidual cells
- Absence of uterine NK cells
- Presence of different leukocytic cell populations ? (B-cells? T-cells?)

Trophoblast invasion and inflammation
Trophoblast destroyed by infiltrating maternal leukocytes or macrophages?

Pre-eclampsia as a hyperinflammatory condition ?
(Redman *et al* 1999)

Control of deep placentation

CONCLUSIONS

1. Deep placentation involves different levels of invasion control in successive uterine tissue layers.
2. A possible controlling function (inhibitory or stimulatory) by the decidua is controversial, but in the human there is increasing evidence for a promotory role of decidua.
3. Uterine NK cells interact with invasive trophoblast, probably resulting in growth factor release by uNK cells.
4. The different cellular environment of the myometrium may imply different controlling mechanisms for trophoblast invasion in this uterine compartment.

Embryo-maternal signalling: possible impacts of adenomyosis

A. Herrler

Department of Anatomy and Reproductive Biology

RWTH Aachen

Germany

The embryo maternal signalling is critical for the establishment of an ongoing pregnancy. Several events may negatively influence this embryo maternal dialogue. First of all it has to be distinguished between disturbance of the embryonic and the maternal signalling. Both of them may influence in following the other part of the dialogue and hereby additionally the messages from this side. To develop therapeutical solutions the original key effect has to be spotted.
Embryonic signalling can be negatively influenced initially by an interference during the process of fertilization. This will result in an embryo with reduced viability and hereby reduced signalling activity. Furthermore, delayed fertilization as well as retarded embryonic development would result in a diverse opening of the implantation window in correlation to embryonic development, meaning an embryonic signalling out of time.
Maternal signalling depends on a physiological internal regulation process, resulting in a correctly timed implantation window including a receptive endometrium. To what extent nutritional support is critical during the first 7 days is not finally resolved.
Relating this knowledge to the influence of adenomyosis on embryo –maternal signalling several aspects may be discussed. What about embryonic signalling? Adenomyosis is suspected to influence uterine motility. The fine tuning of uterine motility and in correlation to this the motility of the oviduct as well as the oviductal-uterine-junction is critical for sperm and embryo movements. Disturbed transport of the spermatozoa may result in a disturbed fertilization, leading to an embryo of low vitality and signalling activity. A disturbed embryo movement would result in an embryonic signalling out of place. Furthermore, uterine hypermotility caused by adenomyosis may interfere with embryonic aposition which is prerequsite for implantation. Although adenomyosis often is limited to a circumscribed area maternal signalling may be disturbed in certain sequences influencing the specific micro environment. Adenomyosis has been described to be correlated to a significant change in the arrangement of the immune cells. As immune cells are a main source of maternal signals several cytocines have to be discussed in this context. Furthermore, induction of immune tolerance is a major event in the establishment of early pregnancy.
In a limited experiment adenomyosis did not influence the establishment of pregnancies induced by the transfer of sibling donor embryos. Up to now it has not been solved whether adenomyosis is a major cause for infertility or if infertility is only linked to adenomyosis acausal.

Adenomyosis and ART outcome

Prof. Antonio Pellicer
Instituto Valenciano de Infertilidad (IVI)
University of Valencia
www.ivi.es; apellicer@ivi.es

Adenomyosis & Infertility

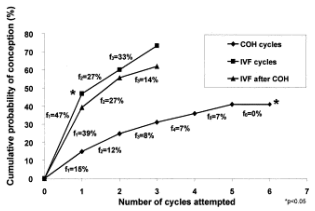
- Present in 1% of female patients (Deviegler et al, 2003)
- Present in aged (40-50ths) parous women (Bird et al, 1972). Age for childbearing delayed
- Strong association between adenomyosis and longlife infertility in the baboon (Barrier et al, 2005)
- Association between pelvic endometriosis and adenomyosis 54% (de Souza et al, 1995) to 79-90% (Kuntz et al, 2005)
- Increased preterm labor (Juang et al, 2006)

ART & Endometriosis

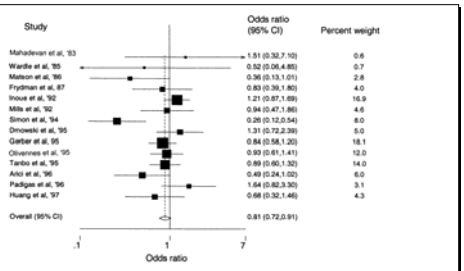
- When to offer IVF?
- Does it affect IVF outcome?
- Is medical therapy preIVF useful?
- Should ICSI always be used?
- Do endometriomas affect IVF?
- Does IVF affect endometriomas?
- If surgery is needed, which technique?

Endometriosis - IVF
When to offer IVF?

Cumulative fecundity rate in IVF
Dmowski et al. **Fertil Steril 2002; 78: 750**



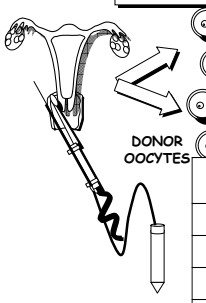
ART & Endometriosis



Endometriosis vs tubal OR 0.56 (CI 0.44-0.7)
Severe vs mild OR 0.60 (CI 0.42-0.87)

Barnhart et al, Fertil Steril 2002

ART & Endometriosis



HEALTHY RECIPIENT

RECIPIENT WITH SEVERE ENDOMETRIOSIS

Variable	Healthy	Endometriosis
Cycles	33	25
Embryos	4,1	4
Implantation (%)	16	14,8
Pregnancy (%)	45,5	40
Miscarriage (%)	16	20
Live birth (%)	27,2	28

Diaz et al.
Fertil Steril 2000; 74:31-4

Adenomyosis & oocyte donation

- Ovarian endometriosis associated in 27.5%
- Uterine fibromas associated in 32.5%
- Diagnosis of adenomiosis by TVU:

  - Hypoechogenic and heterogeneous areas
  - Elliptic intramyometrial lakes>4 mm (specificity 94%)

Adenomyosis & oocyte donation

	ADENOMYOSIS	LOW RESPONDER	P value
Patients (cycles)	30 (53)	54(68)	
Age	36.9±5.8	37.0 ±0.5	NS
Yrs infertility	4.8 ±0.6	3.8 ±1.0	NS
Embryos replaced	3.1 ±1.2	3.6 ±0.8	NS
Implantation (%)	28/158(17.7)	59/246(24.0)	NS
Clinical pregn. (%)	18/53(33.9)	30/68(44.1)	NS
Miscarriage (%)	6/53(11.3)	7/68(10.3)	NS
Term pregn. (%)	12/53(22.6)	23/68(33.8)	NS

Camargo et al, ESHRE 2000

Adenomyosis & oocyte donation

SIBLING OOCYTES

	ADENOMYOSIS	CONTROL	P value
Patients (cycles)	40(60)	60(60)	
Age	38.7±6.8	37.9 ±5.9	NS
Yrs infertility	2.8 ±2.1	2.7 ±1.6	NS
Embryos replaced	2.7 ±1.5	2.7 ±1.6	NS
Implantation (%)	27/160(16.9)	40/161(24.8)	NS
Clinical pregn. (%)	18/60(30.0)	23/60(38.3)	NS
Miscarriage (%)	3/60(5.0)	5/60(8.3)	NS
Term pregn. (%)	15/60(25.0)	18/60(30.0)	NS

Camargo et al, ASRM 2001

Adenomyosis & oocyte donation

- **Retrospective study, January 1st, 2003 to December 31st, 2006.**
- **Our aim was to compare the outcome of oocyte donation (OD) in ultrasound diagnosed adenomyosis and poor responders.**
- **Transvaginal-ultrasound criteria of adenomyosis**.

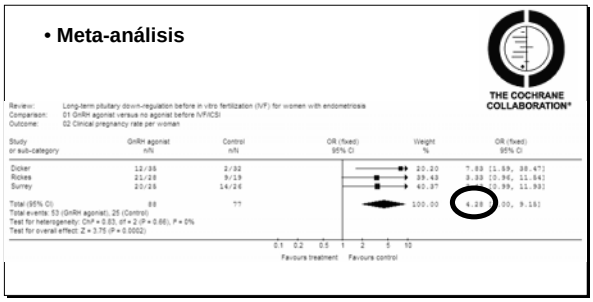
Adenomyosis & oocyte donation

	ADENOMYOSIS	LOW RESPONDER	P value
Cycles	49	660	
Age	40.7±4.8	37.6 ±3.5	<0.05
Yrs infertility	4.8 ±0.6	3.8 ±1.0	NS
Embryos replaced	1.7 ±0.1	1.3 ±0.1	NS
Implantation rate	42.5	37.6	NS
Clinical pregn. rate	64.1	59.3	NS
Miscarriage rate	12.0	27.0	NS

Vergara et al, 2007 (In preparation)

Endometriosis - IVF
Is medical therapy preIVF useful?

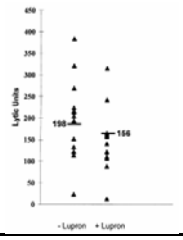
- **Meta-análisis**



Sallam, García-Velasco et al. Cochrane Database 2006

Endometriosis - IVF

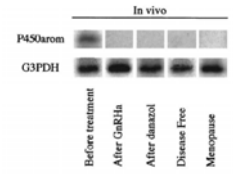
- GnRHa reduces NK cell activity in vitro



Wong et al. Am J Obstet Gynecol 2004

Endometriosis - IVF

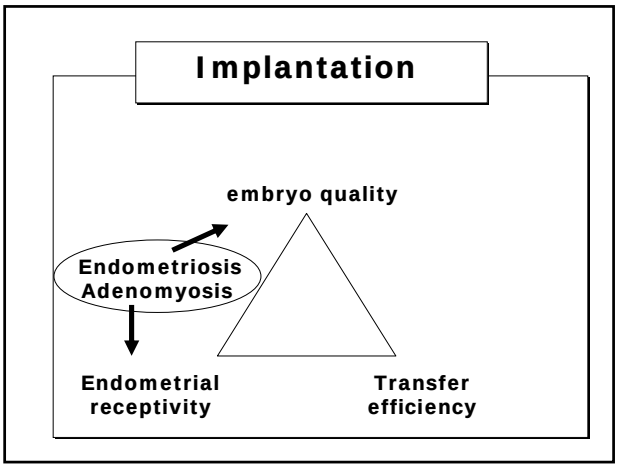
- GnRHa normalizes aromatase p450

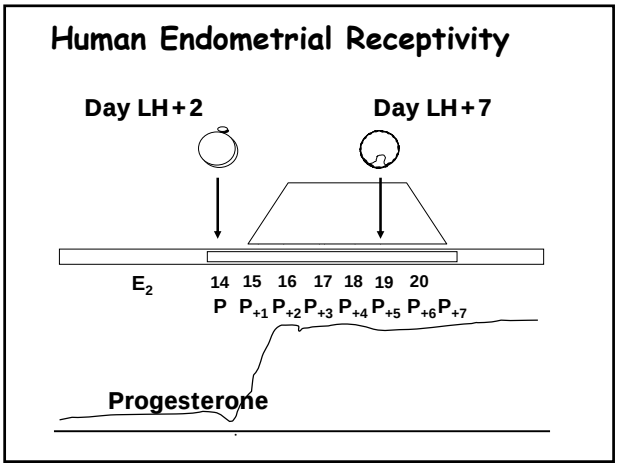


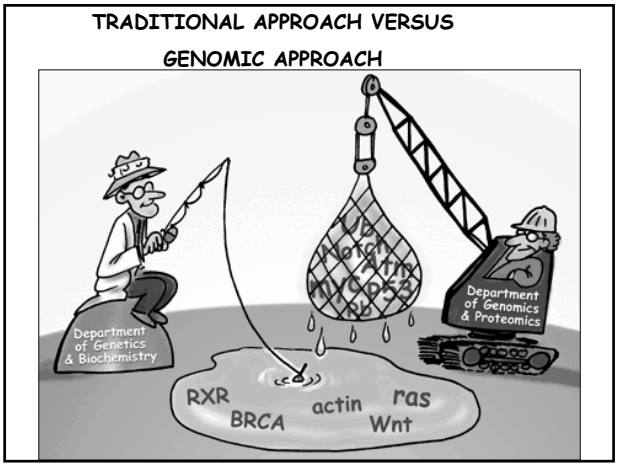
Kitawaki et al. Fertil Steril 2003

Adenomyosis & Infertility

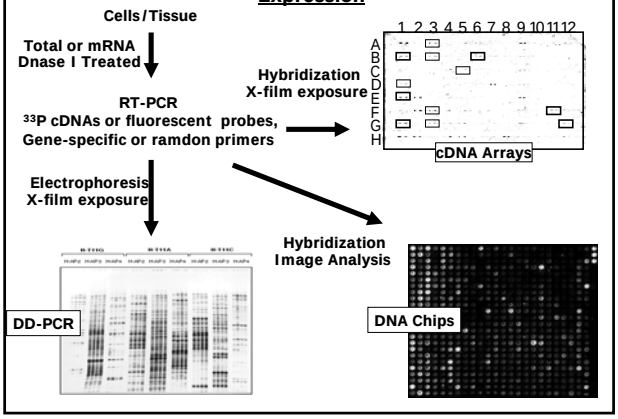
- Uterine hypermotility: alteration of sperm transport (Kissler et al, 2006)
- Altered oxydative stress (Ota et al, 1998, 2000, 2001; Kamada et al, 2000)
- Increased microvessel density (Schindl et al, 2001)
- Altered gene pattern expression (Hever et al, 2006)


Implantation
embryo quality
Endometriosis
Adenomyosis
Endometrial
receptivity
Transfer
efficiency


Human Endometrial Receptivity
Day LH+2
Day LH+7
E2
14 15 16 17 18 19 20
P P+1 P+2 P+3 P+4 P+5 P+6 P+7
Progesterone


TRADITIONAL APPROACH VERSUS
GENOMIC APPROACH
Department of Genetics & Biochemistry
Department of Genomics & Proteomics
RXR
BRCA
actin
ras
Wnt

Analysis of Genome-wide Gene Expression



Gene expression patterns of adenomyosis

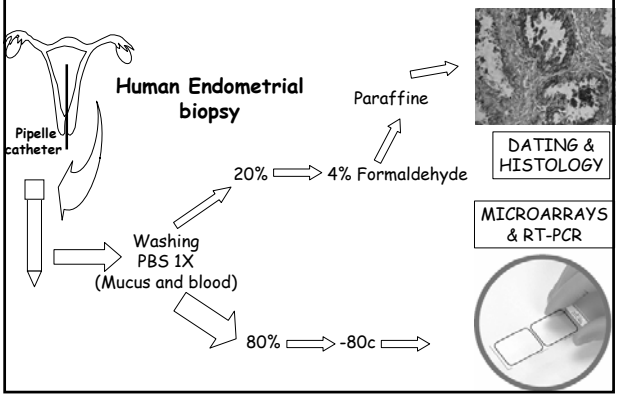
- ☑ **Comparison of gene expression profile of normal endometrium and myometrium; FIBROIDS and ADENOMYOSIS**
- ☑ **Affimetrix U133 Plus 2.0 platform**
- ☑ **2073 genes altered between adenomyosis and normal endometrium and myometrium**
- ☑ **9 functional networks highly expressed in adenomyois (the top ones related to cancer and cell death)**
- ☑ **471 genes differentially expressed between adenomyosis and uterine fibroids**

Hever et al, Mol Hum Reprod 2006; 12: 737-48

EXPERIMENTAL DESIGN

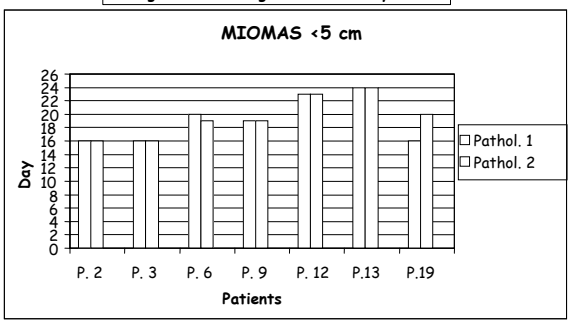
Caucasian Fertile women with normal cycles **No myomas** 18-35 years BMI:19-25 kg/m2	Caucasian **Myomas <5cm** 18-35 years BMI:19-25 kg/m2	Caucasian **Myomas >5cm** 18-35 years BMI:19-25 kg/m2	Caucasian **Myomectomized** 18-35 years BMI:19-25 kg/m2
Natural cycle LH+7 **CONTROLS**	Natural cycle LH+7 **Myomas <5**	Natural cycle LH+7 **Myomas >5**	Natural cycle LH+7 **Myomectomized**
			
n=8	**n=7**	**n=8**	**n=2**

ENDOMETRIAL BIOPSY PROCESSING



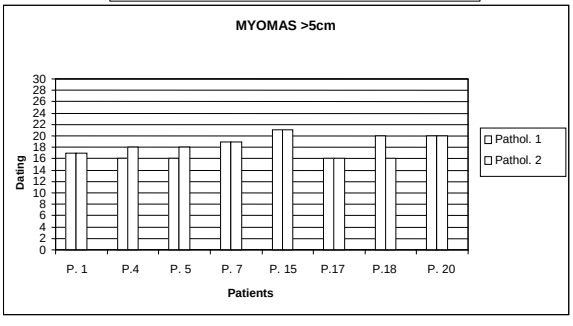
ENDOMETRIAL DATING BY NOYES CRITERIA

Dating mean Pathologist 1: 20.07 days NS
Dating mean Pathologist 2: 19.64 days NS



ENDOMETRIAL DATING BY NOYES CRITERIA

Dating mean Pathologist 1: 18.62 days p<0.01
Dating mean Pathologist 2: 18.62 days p<0.01



ENDOMETRIAL DATING BY NOYES CRITERIA (2 pathologists)

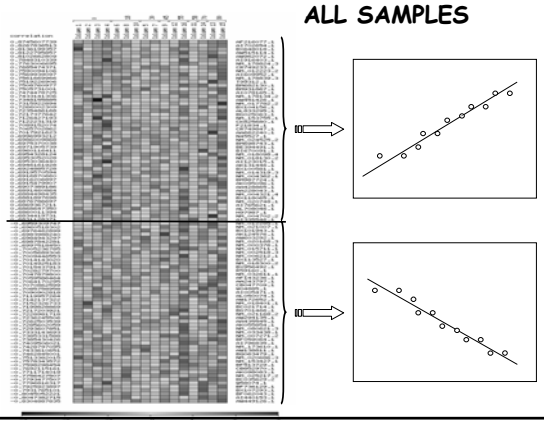
Natural cycle LH+7 **CONTROLS**	Dating mean= 19.54 days	NS
Natural cycle LH+7 **Myomas <5**	Dating mean= 19.85 days	NS
Natural cycle LH+7 **Myomas >5**	Dating mean= 18.62 days	p<0.01

MICROARRAY DATA

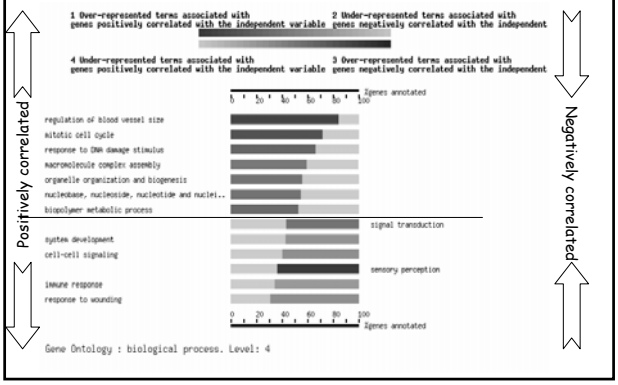
TOTAL ANALYZED
CodeLink Whole Genome Bioarray
(>55,000 gene targets)

- CONTROLS n=8
- MYOMAS <5 cm n=6
- MYOMAS >5 cm n=6
- MYOMECTIZED n=1

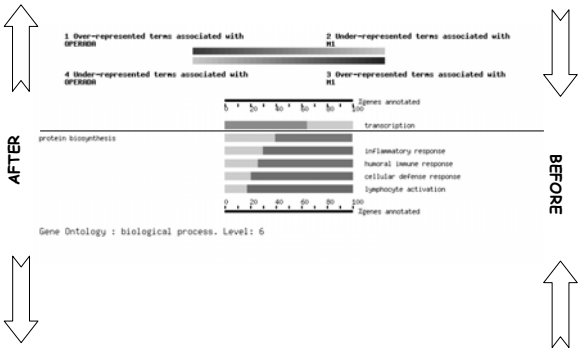
MICROARRAY DATA: CORRELATION ALL SAMPLES



MICROARRAY DATA: GENE ONTOLOGY ALL SAMPLES

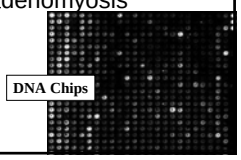


MICROARRAY DATA: GENE ONTOLOGY BEFORE AND AFTER MYOMECTOMY

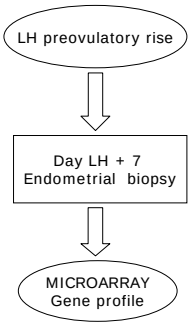


Adenomyosis and Implantation

- Gene Profile during Implantation Window in Adenomyosis
- Observational study
  - Infertile patients
  - Regular menstrual cycles
  - Transvaginal diagnosis of adenomyosis confirmed by MRI.



Adenomyosis and Implantation



Conclusions

- ✓ **Adenomyosis is strongly associated with endometriosis and uterine fibromas, thus being frequently diagnosed in infertile patients**
- ✓ **Whether adenomyosis, per se, causes infertility is not known**
- ✓ **Alterations in the gene expression pattern of the endometrium of women with adenomyosis have been described**
- ✓ **How these alterations affect the window of implantation is not known.**
- ✓ **In the presence of uterine fibromas >5 cm, the gen expression pattern of the endometrium is altered in natural cycles**
- ✓ **Employing the oocyte donation model adenomyosis does not affect endometrial receptivity**

AKNOWLEDGEMENTS

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Carlos Simón

Adenomyosis:
Link with Endometriosis

G. Kunz

Dept Obstet. Gynecol., St.-Johannes-Hospital
Dortmund
Germany

Leuven, 19.04.2007

Adenomyosis: Link with Endometriosis

- Views of Endometriosis
- The Concept of the Archimetra as the Organ of Human Reproduction
- Endometriosis and Adenomyosis – Discover things in common
- Adenomyosis and Infertility
- Conclusions

The team

G. Kunz*, M. Noe*, M. Herbertz*, G. Leyendecker
*(*former) Dept of Obstet. & Gynecol., Darmstadt*

D. Beil, P. Huppert
Dept of Radiology I, Darmstadt

G. Mall
Dept of Pathology, Darmstadt

J. Becker, C. Noe*
Dept of Pharmaceutical Chemistry, Vienna

The Pleiomorphism of Endometriosis

- Mild and moderate endometriosis found during a fertility work-up in sterile patients
- Severe endometriosis with ovarian endometriomas
- Recto-vaginal endometriosis
- Severe juvenile dysmenorrhea with adenomyosis with and without pelvic endometriosis
- Perforating adenomyosis with subsequent diffuse endometriosis

- Endometriosis in fertile women (Moen and Muus, Hum. Reprod. 1991)

Endometriosis - theories and current views

- Coelomic metaplasia (Meyer, 1919)
- Transtubal shedding of normal endometrial cells (functionalis) by retrograde menstruation (Sampson, 1927)
- Endometriosis: an immunological disease (so frequently?)

- Three entities (Nisolle & Donnez, 1998)
- *- ovarian endometriomata - metaplasia*
- *- pelvic endometriosis - retrograde menstruation*
- *- recto-vaginal endometriosis - Müllerian remnants*

- Two entities (Brosens & Brosens, 2000)
- *- superficial endometriosis - retrograde menstruation*
- *- infiltrative endometriosis - BE/JZ disease (Adenomyosis)*

Endometriosis – Adenomyosis: views of our study group

Endometriosis and adenomyosis
constitute a (single) entity with extreme variable phenotypes.

Endometriosis and Adenomyosis are diseases of the Archimetra.

They result from iatrogenic or auto-traumatization
of the archimetra with dislocation of basal endometrium.

What is the Archimetra?

The archimetra is the innermost part of the uterus

Structure

Function

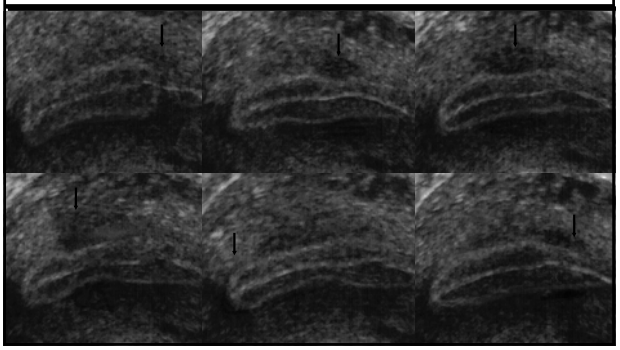
Comparative Morphology

Embryology

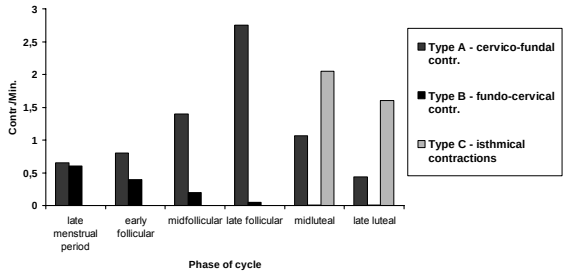
The muscular layers of the human uterus

- **Stratum subvasculare:** predominantly circular arrangement of muscular fibres
- **Stratum vasculare:** Irregular mesh of short muscular bundles
- **Stratum supravasculare:** predominantly longitudinal arrangements of muscular fibers

Video sonography of uterine peristalsis



Uterine peristalsis during the menstrual cycle

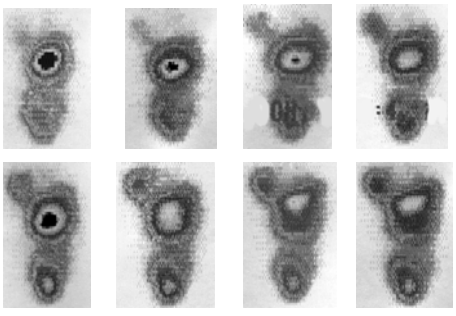


Functions of the peristaltic activity of the stratum subvasculare (Archimyometrium) during the early process of reproduction

- Directed rapid and sustained sperm transport
- High fundal “ipsilateral” implantation of the embryo
- Retrograde menstruation

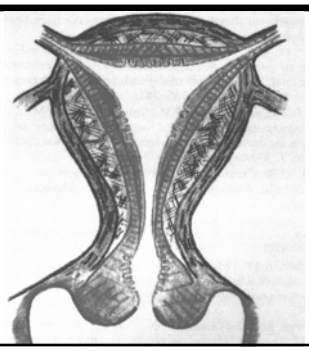
- Kunz et al., 1996, 1998, 2006, 2007

Directed sperm transport - HSSG



Morphological basis of uterine peristalsis and directed sperm transport

The Archimetra and Neometra



Archimetra
(paramesonephric origin)
epithelial endometrium
stromal endometrium
archimyometrium

Neometra
(non-Müllerian origin)
Stratum vasculare
Stratum supravasculare

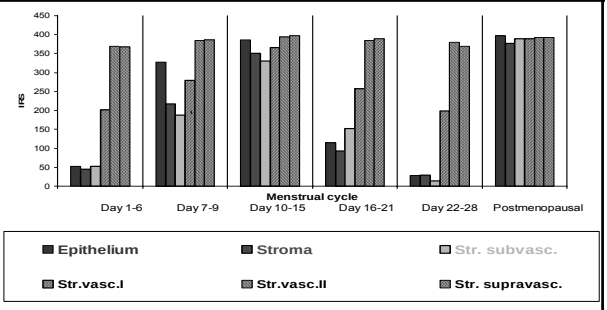
from Noe et al., 1999

Comparative morphology (phylogeny) of uterine/oviductal muscular layers and the ontogeny of the human uterus

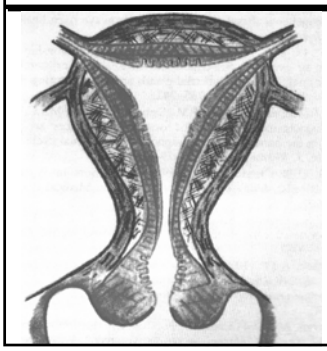
Birds:	Str. subv.	-----	------
Monotr.:	Str. subv.	-----	------
Marsup.:	Str. subv.	-----	Str. suprav.
Rodents:	Str. subv.	-----	Str. suprav.
Human:	Str. subv.	Str. vasc.	Str. suprav.

- 8th week: fusion of paramesonephric ducts
- Midtrimester: circular arrangement of mesenchymal cells
- Midtrimester: primordial uterus with archimyometrium
- Last trimester or after birth: formation of str. supravasulare and vasculare

Immunohistochemistry of oestrogen receptors – the archimetra as an uterine organ of menstrual cyclicity



The Archimetra and Neometra



Archimetra
(paramesonephric origin)
epithelial endometrium
stromal endometrium
archimyometrium

Neometra
(non-Müllerian origin)
Stratum vasculare
Stratum supravasculare

from Noe et al., 1999

Functions of the Architmetra
as controlled by the ovary

- **Preparation of the site of implantation (endometrial proliferation and differentiation)**
- **Uterine peristalsis (directed sperm transport; high fundal implantation; retrograde menstruation)**
- **Inflammatory defence (macrophages; MUC-1; influx of natural killer cells)**

Endometriosis is primarily a disease of the uterus

- **Alterations of the eutopic endometrium**

- **Uterine hyper- and dysperistalsis with impeded sperm transport**

- **Archimetrial infiltrations into the neometra (adenomyosis and its early manifestations)**

The eutopic endometrium in endometriosis I

- **Signs of increased inflammatory defence:**
- **Increased expression of MCP1**
- **Increased attraction of macrophages**
- **Heat shock proteins**
- **Interleukin-6**
- **Complement C3**

- **Abnormal endometrial proliferation**
- **Increased secretion of 125 CA of cells in vitro**
- **Increased concentration of CA 125 in menstrual blood**

The eutopic endometrium in endometriosis II

Increased concentration of E2 in menstrual blood
(Takahashi et al., 1989)

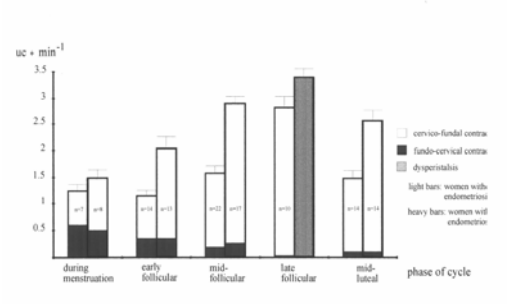
Production of estrogen in the eutopic endometrium
in women with endometriosis and adenomyosis
(Yamamoto et al., 1993)

Pathologic expression of P450 aromatase
(Noble et al., 1996/1997; Kitawaki et al., 1997,2006; Zeitoune and Bulun, 1999)

Endometriosis is primarily a disease of the uterus – results of own studies

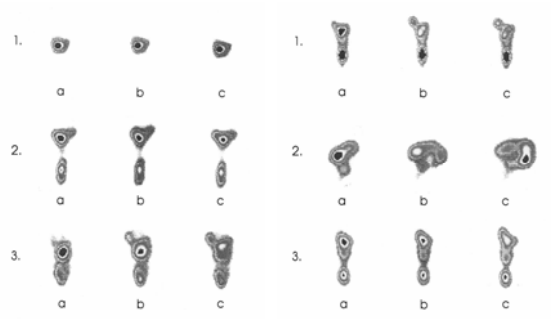
- **Alterations of the eutopic endometrium in women**
- **Uterine hyper- and dysperistalsis with impeded sperm transport**
- **Archimetrial infiltrations into the neometra (adenomyosis and its early manifestations)**

Uterine Peristalsis in Endometriosis

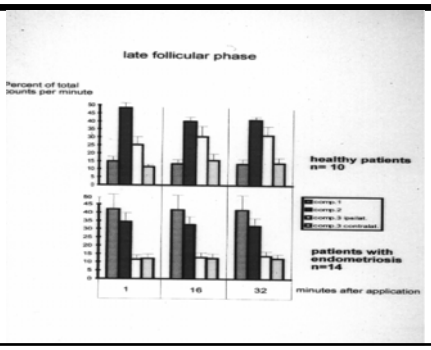


Uterine sperm transport

Healthy **Endometriosis**



Endometriosis: break down of directed sperm transport



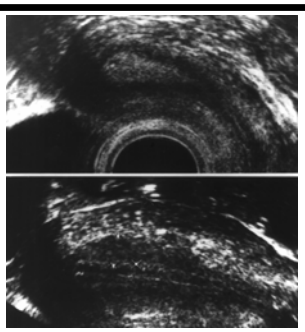
Endometriosis is primarily a disease of the uterus

- Alterations of the eutopic endometrium in women

- Uterine hyper- and dysperistalsis with impeded sperm transport

- Archimetrial infiltrations into the neometra (adenomyosis and its early manifestations)

Archimetrial infiltration of the neometra

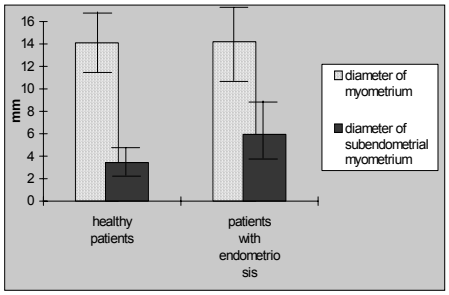


Endovaginal sonography (EVS)

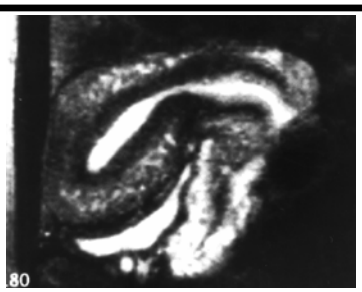
Healthy normal "halo"

Endometriosis expanded "halo"

Archimetrial expansion in endometriosis (EVS)



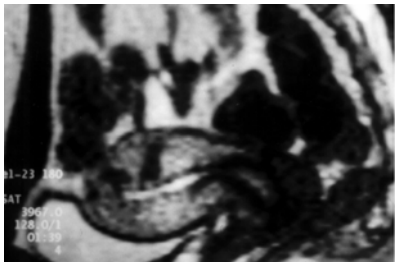
MRI in endometriosis



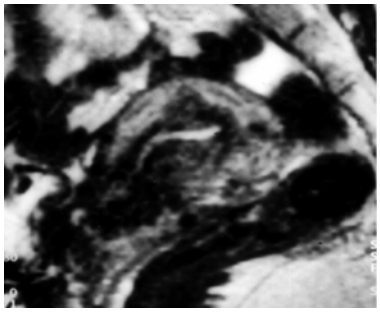
32 years
healthy with
proven fertility

normal
“junctional zone”

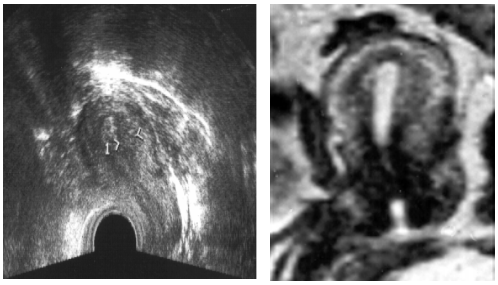
MRI: adenomyosis in moderate endometriosis



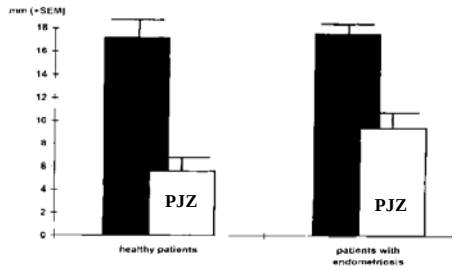
MRI: adenomyosis in recto-vaginal endometriosis



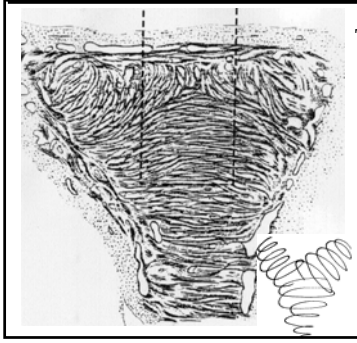
EVS and MRI of the Uterus of a Patient with moderate Endometriosis



MRI: diameter of "posterior junctional zone (PJZ)" in endometriosis



Mechanism of disease



The fundo-cornual raphe of the archimyometrium

modified from Werth and Grusdew, 1898

Aetiology of adenomyosis

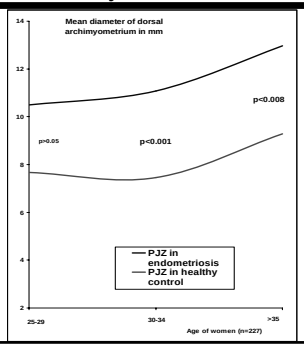
Prevalence of adenomyosis: 69% (Bird et al., 1972), predominantly invasion into the dorsal myometrium

Aetiology not spectacular but rather related to the process of reproduction

Trauma by pregnancy and delivery (Ferenczy, 1998)
Trauma by endometrial ablation (Yue, 1995; McLucas, 1994)

Trauma by chronic peristalsis and hyperperistalsis

Adenomyosis and endometriosis



Obtained from MRI, Kunz et al., in preparation

Adenomyosis versus endometriosis

Adenomyosis

endometrial epithelium

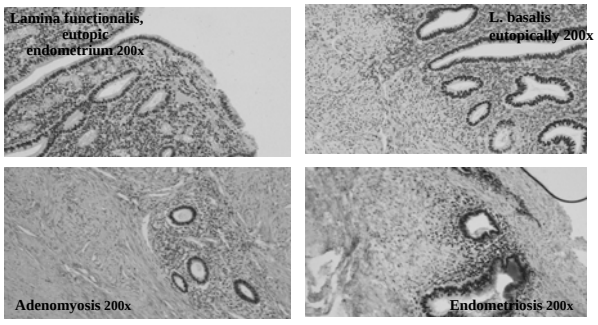
endometrial stroma

Endometriosis

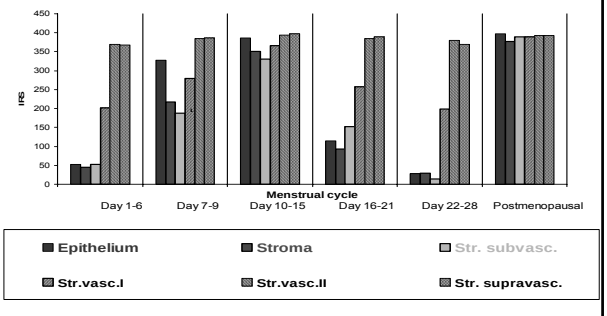
endometrial epithelium

endometrial stroma

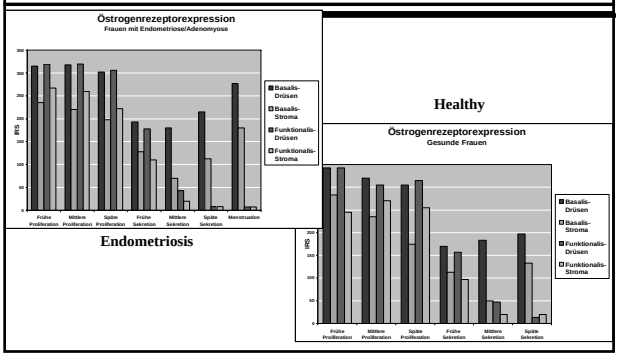
Endometrium can be found eutopically as well as ectopically in endometriosis and adenomyosis



Immunohistochemistry of oestrogen receptors



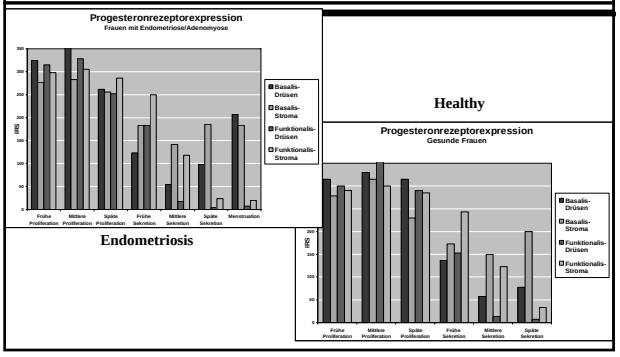
Estrogen receptor expresson in the eutopic endometrium of healthy and endometriotic women from early menstrual phase to proliferative and to secretory to menstrual phases



Endometriosis

Healthy

Progesterone receptor expresson in the eutopic endometrium of healthy and endometriotic women from early menstrual phase to proliferative and to secretory to menstrual phases



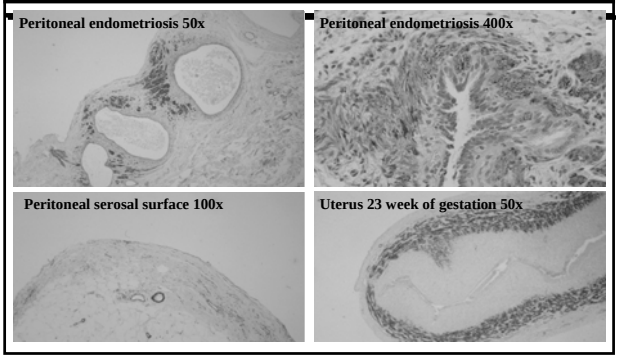
Endometriosis

Healthy

Adenomyosis versus Endometriosis

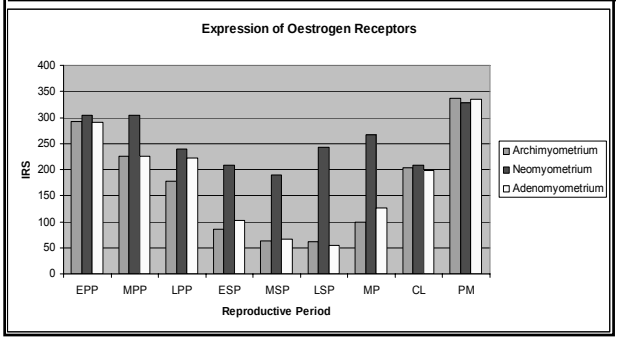
Adenomyosis	**Endometriosis**
endometrial epithelium	**endometrial epithelium**
endometrial stroma	**endometrial stroma**
muscular tissue	**?**

Peristromal smooth musculature (Actin staining)

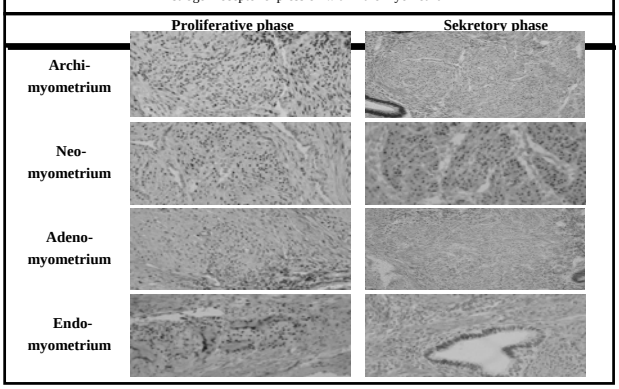


Adenomyometrium is of Archimetrial Origin

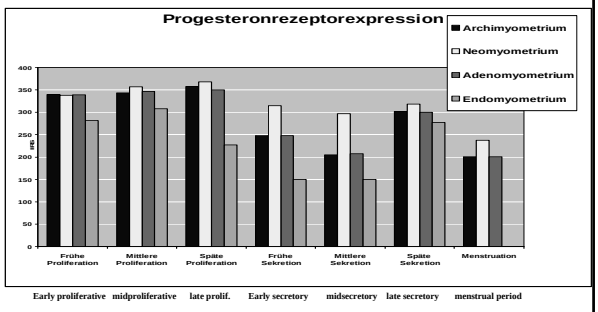
Result of (stemcell-like) endometrial-myometrial "oszillation" as observed in the eutopic endometrial-myometrial junction?



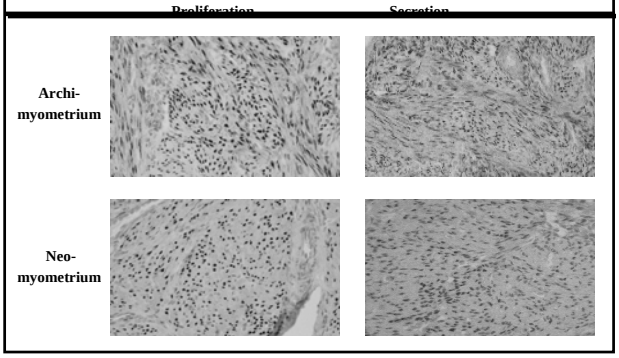
Estrogen receptor expression within the myometrium



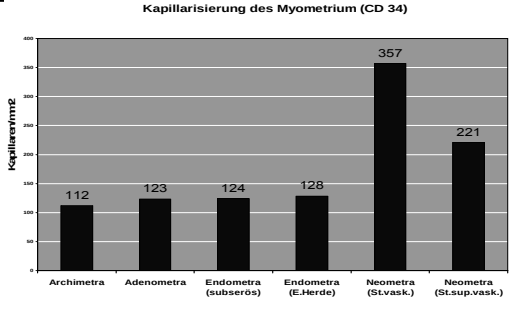
Progesterone receptor expression of the peristromal smooth musculature of endometriotic and adenomyotic foci as compared to the archimetral and neometral myometrium



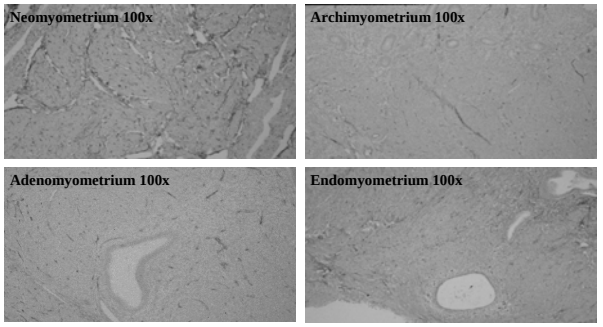
Progesterone receptor expression in the myometrium



Capillarisation of the peristromal smooth musculature in endometriotic (Endometra) and adenomyotic (Adenometra) foci as compared to the archimyometrium (Archimetra) and neomyometrium (Neometra) (unpublished)



Capillarisation of the peristromal smooth musculature in endometriotic and adenomyotic foci and in the archimyometrium and neomyometrium (unpublished)



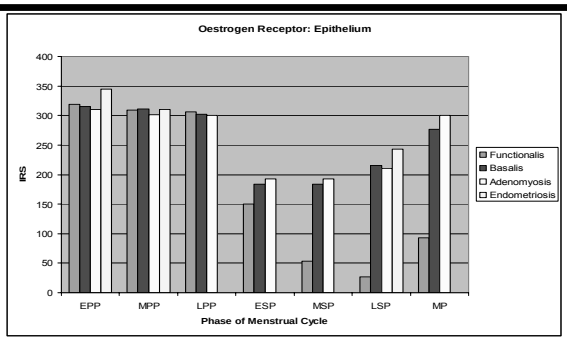
Adenomyosis versus Endometriosis

Adenomyosis	Endometriosis
endometrial epithelilium	endometrial epithelilium
endometrial stroma	endometrial stroma
muscular tissue	**muscular tissue**

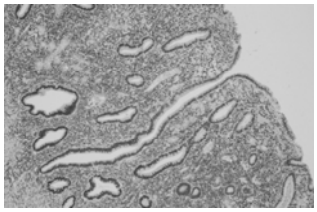
The muscular tissue is of paramesonephric origin

Source of adenomyosis: lamina basalis
Source of endometriosis: lamina functionalis ?

Ectopic Endometrium and the Lamina Basalis

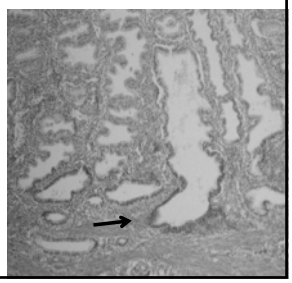


Oestrogen receptor expression in proliferative and late secretory endometrium (100x)

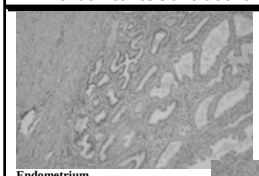


proliferative

late secretory

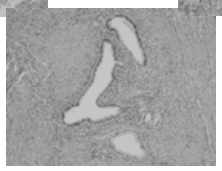


Oestrogen receptor expression in endometrium, endometriosis and adenomyosis during the late secretory phase



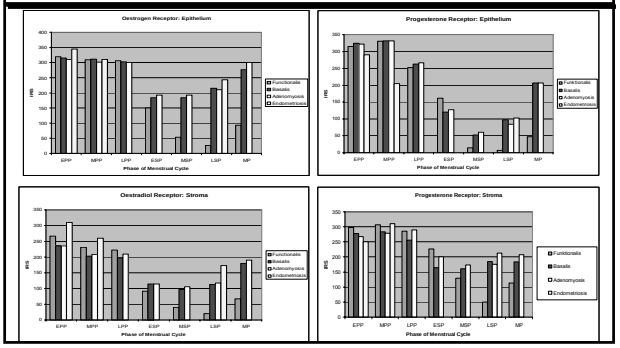
Endometrium

Adenomyosis

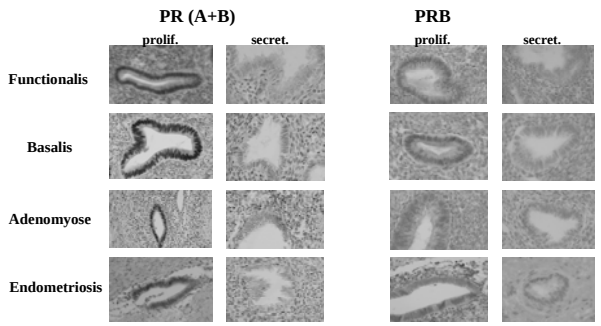


Endometriosis

Ectopic endometrium: lamina functionalis vs lamina basalis



Expression of Progesterone Receptor (PR A+B) and of Progesterone Receptor isoform B (PRB)



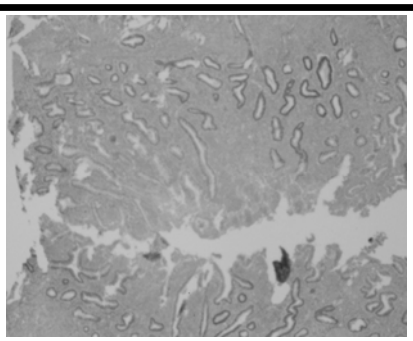
Adenomyosis versus endometriosis

Adenomyosis	Endometriosis
endometrial epithelilium	endometrial epithelilium
endometrial stroma	endometrial stroma
muscular tissue	**muscular tissue**

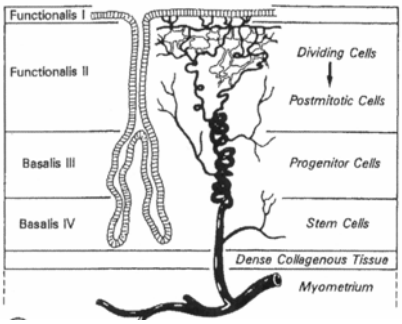
The muscular tissue is of paramesonephric origin

Source of adenomyosis: lamina basalis
Source of endometriosis: lamina functionalis !

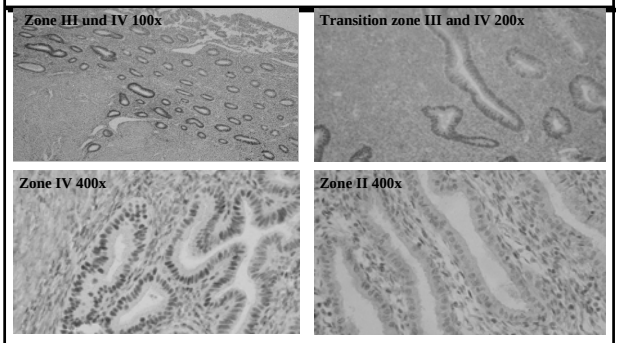
Oestrogen receptor expression during menstruation



Zonal Structure of the Rhesus Monkey Endometrium

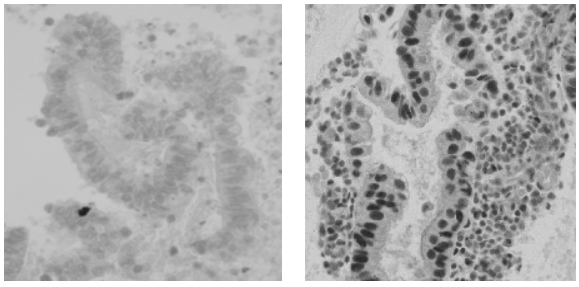


Estrogen receptor expression during menstruation

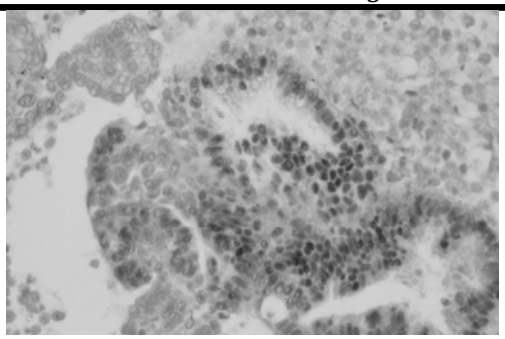


Estrogen receptor expression in shedded endometrial fragments obtained during menstruation

NO endometriosis 400x **WITH endometriosis 400x**



Oestrogen receptor expression in menstrual endometrial fragments



Oestrogen receptor expression in menstrual endometrial fragments

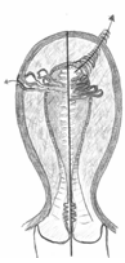
Samples of menstrual blood obtained from 2. and 3. day of cycle (morning samples)

Healthy women: **1/15 (7%)**

Women with endometriois: **9/14 (64%)**

The Uterus in the Pathophysiology of Endometriosis

free of disease	Endometriosis/Adenomyosis
Normoperistalsis directed sperm transport minimal endometriosis of the fertile woman	chronic hyperperistalsis detachment and seeding of basal endometrium microtraumata infiltrative expansion of the archimetra (adenomyosis) dysperistalsis impeded sperm transport



Pathogenesis of Endometriosis/Adenomyosis

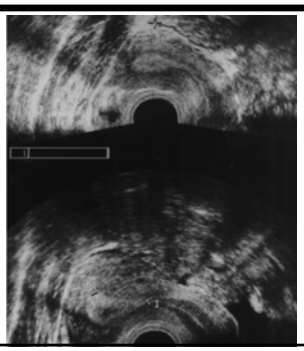
Auto-traumatization and iatrogenic traumatization of the archimetra

Dislocation of basal epithelial endometrium and stroma

Paramesonephric stem cells with reactivation of an embryonal genetic program

Formation of a truncated ectopic archimetra

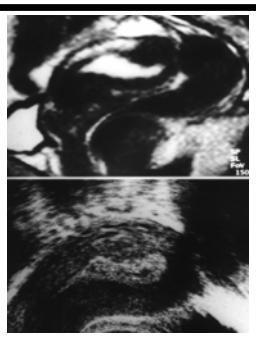
Sonographic exclusion of endometriosis



30 years
intact archimetrial halo
no endometriosis

30 years
destructed archimetrial halo
dysmenorrhea
endometriosis grade I

Adenomyosis without endometriosis



Primary dysmenorrhea

Adenomyosis

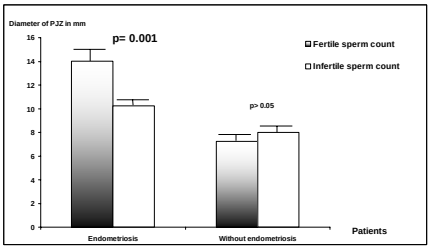
No endometriosis

30 years., primary infertility

Adenomyosis, endometriosis and infertility

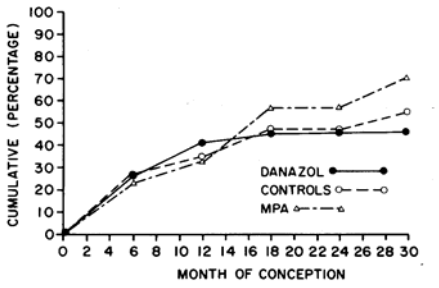
Adenomyosis
Sperm count
Oocyte quality
Link with endometriosis

Adenomyosis, endometriosis and infertility

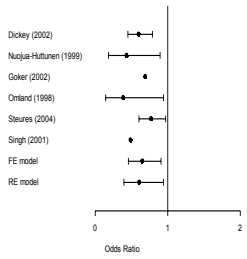


Kunz et al., 2005, Hum.Reprod.

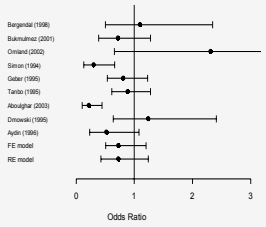
Hormonal treatment of mild endometriosis versus controls - cumulative pregnancy rates



Adenomyosis, endometriosis and infertility



The meta-analysis about the PR of infertile women treated by hormonal stimulation and intrauterine insemination revealed a significantly lower PR of women with endometriosis as compared to the control.



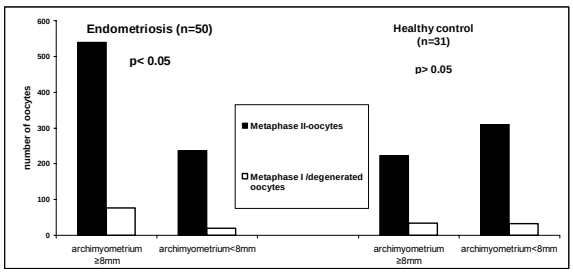
The depiction of the Odds ratios together with the FE and RE models of the PR as related to the number of embryo transfer cycles demonstrates no statistical difference. Women with endometriosis have the same chance to conceive following IVF as the control.

Kunz et al., 2007, submitted

Adenomyosis, endometriosis and infertility

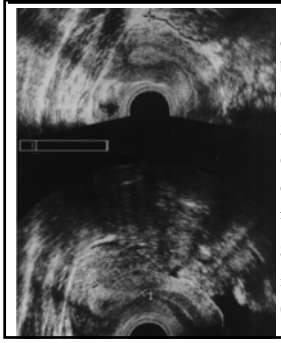
- Results of pregnancy rates in donation programs.
- References reviewed.
- Women with endometriosis, even those with grade III or IV disease, did not experience a reduced pregnancy rate if the oocytes were donated from healthy women without endometriosis as shown in *all* studies (Kunz et al., submitted RBMonline).
- On the other hand Pellicer et al. and Shulman et al. (1994, 1999) demonstrated that oocytes donated by women with endometriosis to women with an ovarian insufficiency resulted in a significantly reduced pregnancy rate as compared to donators without endometriosis.

Adenomyosis, endometriosis and infertility



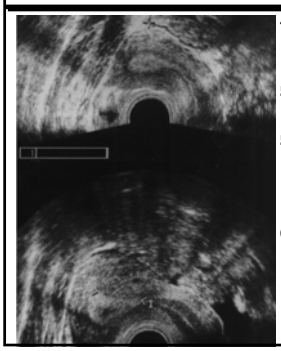
Kunz et al., 2007, submitted

Conclusions I



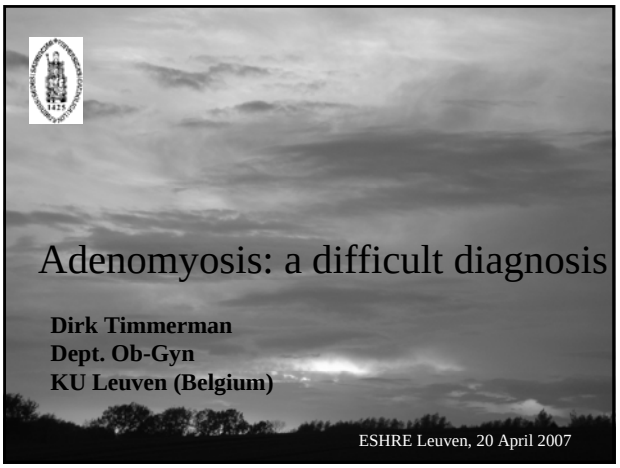
1. Adenomyosis and Endometriosis constitute a pathogenetic entity and are both derived from the basal endometrium ("stem cells").
2. At the ectopic site the displaced tissue may differentiate into all three archimetrial components (glands, stroma, muscular cells); formation of an "ectopic archimetra".
3. The development of the disease is most probably related to the normal process of reproduction (trauma; normo-, hyperperistalsis).

Conclusions II



4. In women with endometriosis and adenomyosis the receptivity of the eutopic endometrium to embryo implantation appears normal.
5. Adenomyosis in endometriosis might impair the mechanism of directed sperm transport.
5. Adenomyosis in endometriosis might compromise the intrafollicular development of oocytes and thus represents a causal factor of subfertility.
6. The infertility in women with endometriosis (and adenomyosis) is best treated by hormonal stimulation and IVF (or donation), not by insemination.

- Thank you for your attention!



Adenomyosis uteri

- Common gynaecologic disorder
- Heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia

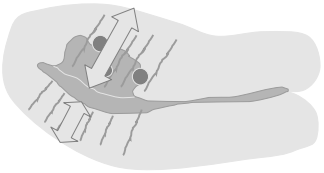
Adenomyosis: presenting symptoms

- Diffusely enlarged uterus with
  - menorrhagia (40-50%)
  - dysmenorrhoea (10-30%)
  - metrorrhagia (10-12%)
  - dyspareunia (typically 1 wk prior menstruation)
  - dyschezia (typically 1 wk prior menstruation)

Adenomyosis: epidemiology

- About 1% of female patients
- 5 - 70% of hysterectomy specimens (Azziz 1989)
- 31% if 3 sections; 61% if 6 sections (Bird 1972)
- More often in multiparous women
- Fourth – fifth decade of life

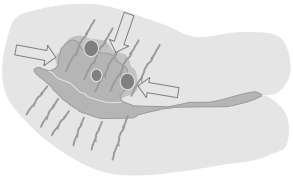
Adenomyosis: morphology



- Asymmetrical uterine enlargement

(or globular appearing uterus)

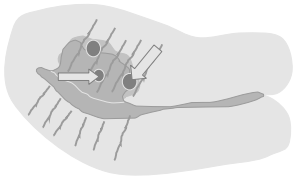
Adenomyosis



- Asymmetrical uterine enlargement
- Ill defined hyperechoic & hypoechoic areas

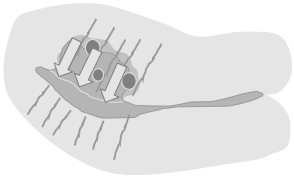
(heterogeneous myometrial echotexture)

Adenomyosis



- Asymmetrical uterine enlargement
- Ill defined hyperechoic & hypoechoic areas
- Small anechoic cysts

Adenomyosis



- Asymmetrical uterine enlargement
- Ill defined hyperechoic & hypoechoic areas
- Small anechoic cysts
- Indistinct endometrial-myometrial border

Adenomyosis: US

Author	Year	Prevalence	Sensitivity	Specificity

Adenomyosis: MRI

- Excellent soft tissue differentiation
- Less operator dependent
- Low intensity area on T2 weighted images
- Focal widening of junctional zone

- High cost
- Limited availability
- 2nd stage test; TVS for initial evaluation

Adenomyosis: TVS vs MRI

Sensitivity Specificity

Adenomyosis: other diagnostic modalities

- X-ray Hysterosalpingography: multiple small (1-4 mm) spicules with saccular endings (‘lollipop-like) extending from endometrium into the myometrium.

→Low sensitivity and specificity.

Adenomyosis: other diagnostic modalities

- Percutaneous or laparoscopic biopsy
- Wood et al 1993 (Med J Aust)

→Percutaneous biopsy in 10 patients

→Useful and safe procedure

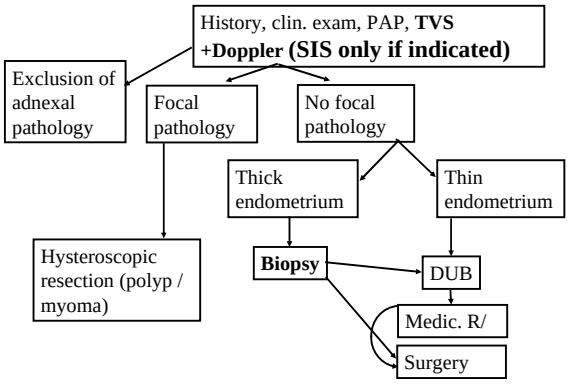
- Brosens et al 1995 (Fertil Steril) (in vitro)

→ High specificity, very low sensitivity

Differential diagnosis

Adenomyosis	Fibroid
■ Elliptical	■ Concentric, round
■ Poorly defined borders	■ Sharply defined
■ Lack of mass effect	■ Mass effect
■ No calcifications	■ Often calcifications
■ Color Doppler	■ Color Doppler

Abnormal bleeding



Conclusions (1)

- Ultrasonography is strongly dependent on operator, equipment, and the patient
- US can not reliably distinguish between different focal endometrial pathologies

Conclusions (colour Doppler)

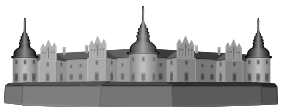
- Morphology of flow can be useful for triage of patients with abnormal bleeding
- In many patients ultrasound with colour Doppler imaging can replace second stage tests (such as SIS and office hysteroscopy)

MRI: Scandinavian experience

Leuven, Belgium

20 April 2007

Viggo Blomlie, MD, PhD,
Stockholm, Sweden



Adenomyosis I

possible assosciation with

- bleeding disorders
- pelvic pain
- infertility
- early pregnancy loss

➢ prognostic and therapeutic implications

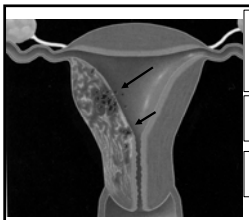
Adenomyosis II

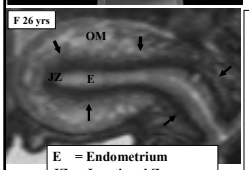
➢ Until recently - diagnosis by surgical exploration/ hysterectomy

➢ Today advancement of non-invasive techniques can allow accurate diagnosis in most instances *.

- TVUS
- MRI

* *Bazot et al. Hum Reprod 2001; 16:2427-2433.*
Dueholm et al. Fertil Steril 2001; 76: 588-594.
Reinhold et al. Radiology 1996; 199:151-158.
Ascher et al. Radiology 1994: 190:803-806.





E = Endometrium
JZ = Junctional Zone
OM = Outer Myometrium

Adenomyosis
- ➢ histological diagnosis
- ➢ endometrial glands and stroma within myometrium
- ➢ hyperplastic smooth muscle cells

➢ Histology: Glandular extension > 2.5 mm below the endometrial - myometrial interface.

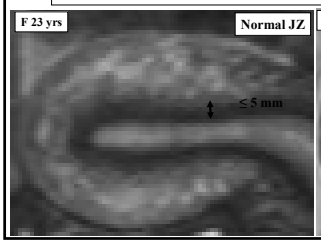
Myometrium – light microscopy
- ➢ 1 zone: myometrium seen as a homogenous structure

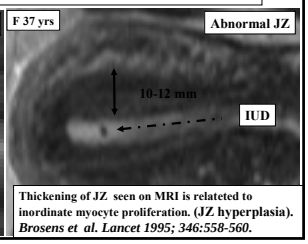
MRI
- ➢ Junctional zone (JZ) described with MRI. *Hricak et al. Am J Roentgenol 1983;141:1119-1128.*
- ➢ Myometrium: 2 zones
  - JZ
  - outer myometrium (OM).

Despite the lack of histological distinction between JZ and OU on light microscopy, these zones are structurally and biologically different.

Junctional zone (JZ) and Adenomyosis

- Normal JZ: ≤ 5 mm
- Adenomyosis: Thickening of JZ.
  JZ ≥ 12 mm highly predictive of histological adenomyosis.
  Reinhold. Radiology 1996; 199:151-158.
- Focal
- Diffuse

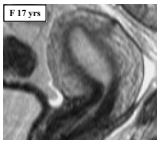




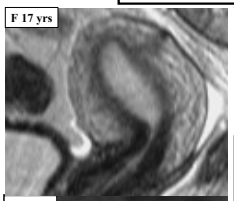
Thickening of JZ seen on MRI is relateted to inordinate myocyte proliferation. (JZ hyperplasia).
Brosens et al. Lancet 1995; 346:558-560.

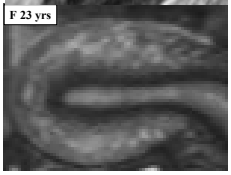
Junctional zone (JZ) and Adenomyosis: Imaging with MRI

- When to scan:
  - not during the menstrual phase (day 1 and day 2 of menstruation).
  - between day 8-16? (max growth of JZ between days 8-16).
- Normal thickness of JZ:
  - ≤ 5mm??
  - related to the time of the menstrual cycle - proliferative phase
    - secretory phase
  - related to age of the premenopausal women?
- Diagnosis of adenomyosis by MRI:
  - to day JZ ≥ 12 mm highly predictive of adenomyosis
    Histology: Glandular extension > 2.5 mm
  - more stringent diagnostic criteria
    - imaging with high field MRI systems (3T)
      → high resolution imaging
      → diffusion imaging
      → mapping of protons and relaxation times
      → MR Spectroscopy (MRS)



Similarities between JZ and endometrium (E)





A1. Ontogeny
- JZ is like endometrium of Müllerian origin.
- OM is of non-müllerian, mesenchymal origin.

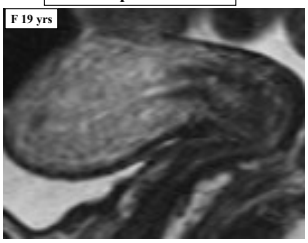
A2. Functional similarities JZ/E
- Cyclic changes of JZ mimic those of endometrium.
  Hormon dependent - ER and PR expression.
  (max growth of JZ between days 8-16).
  Wiczyk et al. Fertil Steril 1988; 49:969-972.

OM does not exhibit cycle-dependent changes in steroid hormone receptor expression.
Noe et al. Human Reprod 1999;14: 190-197)

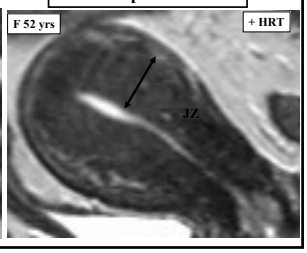
A2. Functional similarities JZ/E

- **Suppression of ovarian activity results in an indistinct *JZ*.**
  (contraceptive pills, gonadotrophin-releasing hormone analogous, postmenopausal women).
- **HRT results in the reappearance of the *JZ*. *McCarthy et al. Radiology 1986; 160:119-123.***

Premenopausal women

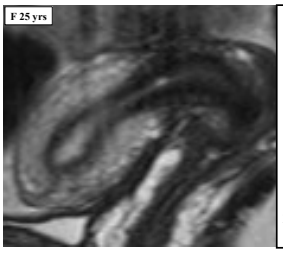


Postmenopausal women



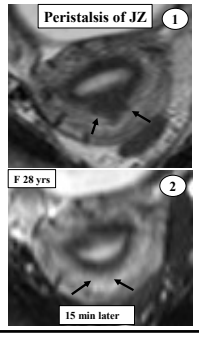
B. Differences between JZ and outer myometrium (OM).

A1. Ontogeny
- **JZ is like endometrium of Müllerian origin.**
- **OM is of non-müllerian, mesenchymal origin.**



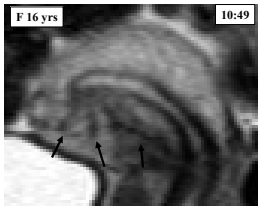
	JZ	OM
1. Myocytes		
a) nuclear area per unit area	3	1
- nucleo-cytoplasmatic ratio	↓	
- smooth muscle density	↑	
b) water content	↓	
c) phosphomonoester - MRS (P-31) (diverse biochemical constitution JZ/OM)		↓
2. Extracellular matrix per unit volume. Different components.	↓ A	B

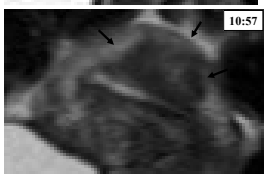
B. Differences between JZ and outer myometrium (OM).



	JZ	OM
3. Muscle fiber arrangement	circular	M/L
4. Peristalsis in non-pregnant uterus[1]	+	
5. Vascular density ↑ immunostaining for the vascular endothelial cell marker CD 31. *Tetlov et al. Ultrasound Obstet Gynecol 1999; 14:188-193*	↑	

[1] *Birnholz. Fertil Steril 1984; 41:157-158. (TAUS)*





Peristalsis of JZ

JZ: Hormone dependent structure that governs uterine peristalsis outside pregnancy

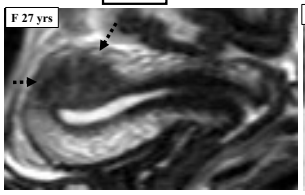
Reproduction
- sperm transport
- implantation of embryo
- development of a functional placenta
- endometrial differentiation

Menstruation (desidualisation)

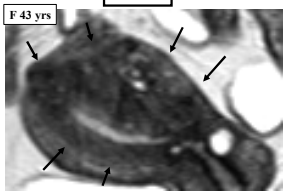
Defects in structure and function of JZ
- infertility - impaired sperm transport
  - implantation failure
- adenomyosis and endometriosis
- bleeding disorders
- pelvic pain

Adenomyosis

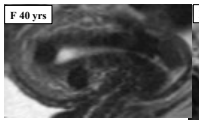
1. Focal

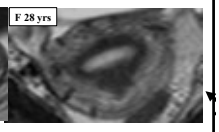


2. Diffus



- DD: Focal thickening
  - uterine peristalsis
  - leiomyoma

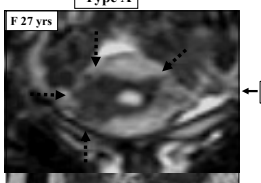


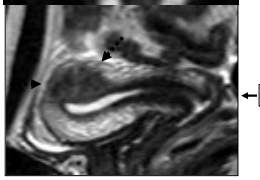


- DD: Diffuse thickening
  - physiological change

Focal Adenomyosis

Type A

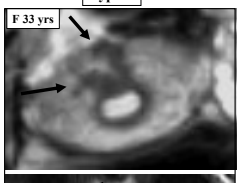


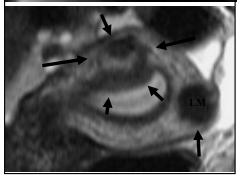


CorT2

Sag T2

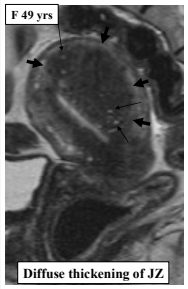
Type B



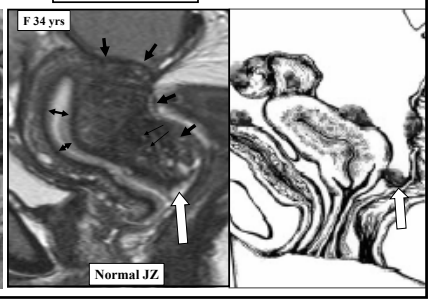


Diffus adenomyosis

Type A (common)

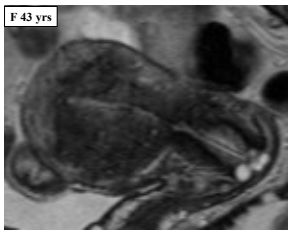


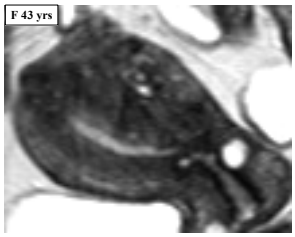
Type B (uncommon)

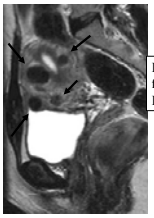


The posterior uterine wall is the area most frequently and severely affected.

[1] Ferenczy. Hum Reprod Update 1998; 4:312-322.
[2] Zaloudek & Norris. In Kurman RJ (ed). Blaustein's pathology of the Female Genital Tract. 3rd edn. New York. Springer Verlag; 1987:374-528.
[3] Bohlman et al. AJR Am J Roentgenol 1987; 148:765-766.
[4] Togashi et al. Radiology 1988; 166:111-114.







MRI and US with Adenomyosis

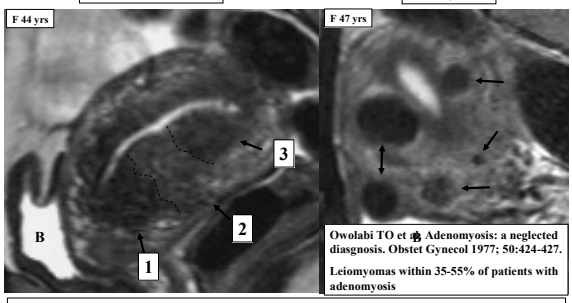
Bazot M et al. Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis:correlation with histopathology. Hum Reprod 2001; 16:2427-2433.

120 patients remmited for hysterectomi were included in a prospective study to compare TAUS, TVUS and MRI.

	TAUS	TVUS	MRI
Sensitivity	32.5 %	76.4 %	77.5 %
Spesificity	65 %	92.8 %	92.5 %
Pos pred val	95 %	73.8%	83.8 %
Neg pred val	97 %	88.8%	89.2 %

Diffuse adenomyosis

Leiomyomas

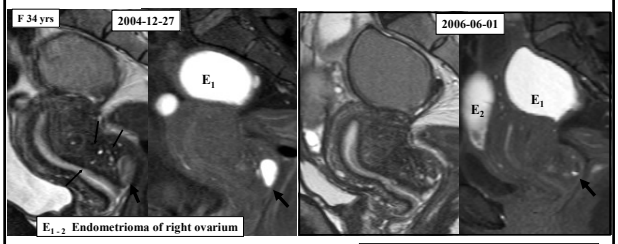


Owolabi TO et al. Adenomyosis: a neglected diasgnosis. Obstet Gynecol 1977; 50:424-427.

Leiomyomas within 35-55% of patients with adenomyosis

Bazot M et al. Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis: correlation with histopathology. Hum Reprod 2001; 16:2427-2433.

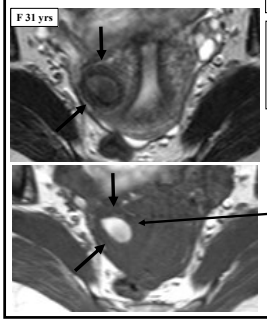
Adenomyosis may coexist with Endometriosis



Kunz et al. Hum Reprod 2005; 20:2309-2316[1].
Leyendecker et al. Ann NY Acad Sci 2004; 1024:338-355.
Kunz et al. Hum Reprod 2000; 15:76-82[1].

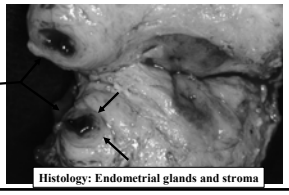
Azziz. Obstet Gynecol 1989; 16:221-235.
Counseller. Am J Obstet Gynecol 1938; 36:877-886

Adenomyotic cyst or endometriosis of the uterus



Pelvic pain. Suspected endometriosis

1. Laparoscopy:	No endometriosis
2. Ultrasound:	Intramural leiomyoma
3. MRI:	Endometrioma-like lesion in the outer myometrium. JZ normal.
4. During surgery:	Leiomyoma within the uterus (palp)

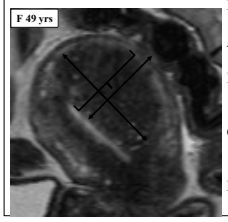


Histology: Endometrial glands and stroma

MRI and Adenomyosis

- Normal thickness of JZ:
  - related to period of menstrual cycle
  - related to age of the premenopausal woman

- Grading system for adenomyosis: Histology & MRI - not to different



MRI

A presence of adenomyosis (JZ ≥ 12 mm)

B depth of penetration (% of myometrial wall)

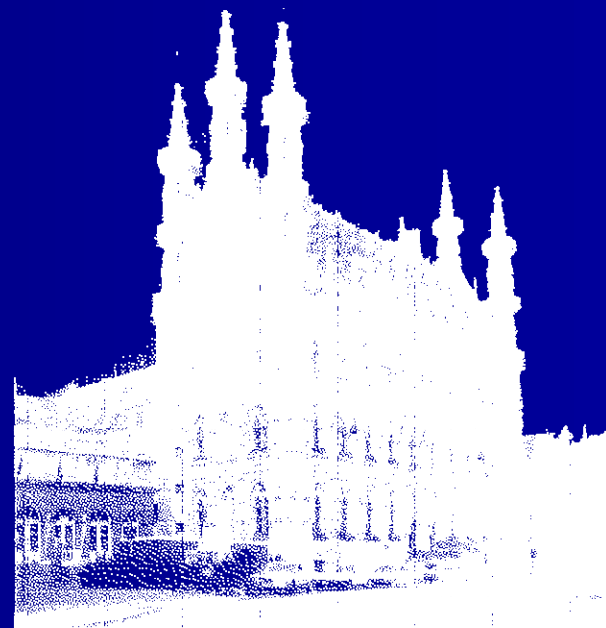
C degree of spread volume or measurement

D configuration of lesion → diffuse
→ focal

Adenomyosis a reproductive disorder
ESHRE Campus workshop
Leuven, Belgium
19 - 20 APRIL 2007

Adenomyosis and diagnostic endoscopy

Rudi Campo, MD
Leuven Institute for Fertility and Embryology
LIFE
Leuven - Belgium



Diagnostic Endoscopy

1. Laparoscopy?
   To invasive
   Limited and not proven diagnostic capacity
2. Transvaginal Laparoscopy ?
   Less invasive but not routinely performed
   Limited and not proven diagnostic capacity
3. Ambulatory Hysteroscopy?

Diagnostic Hysteroscopy

1. Technique and Feasibility of diagnostic Hysteroscopy ?
   Proper scientific evidence
2. Findings ?
   Terminology, Incidence, Significance
3. Case reports on adenomyosis
4. See and threat in ambulatory environment?

AIM of Diagnostic Hysteroscopy

- Visualisation of cervix and uterine cavity
- Simple - Safe - Efficient
- Office or Ambulatory procedure
- Can be repeated easily - screening procedure

Feasibility of Diagnostic Hysteroscopy

Prospective multi-centre randomised clinical trial

GRADE A EVIDENCE

By reducing the diameter of the hysteroscope the effects of patient parity and also surgeon's experience are no longer important !!!

Campo R, Molinas CR et al, Hum Reprod *2005*

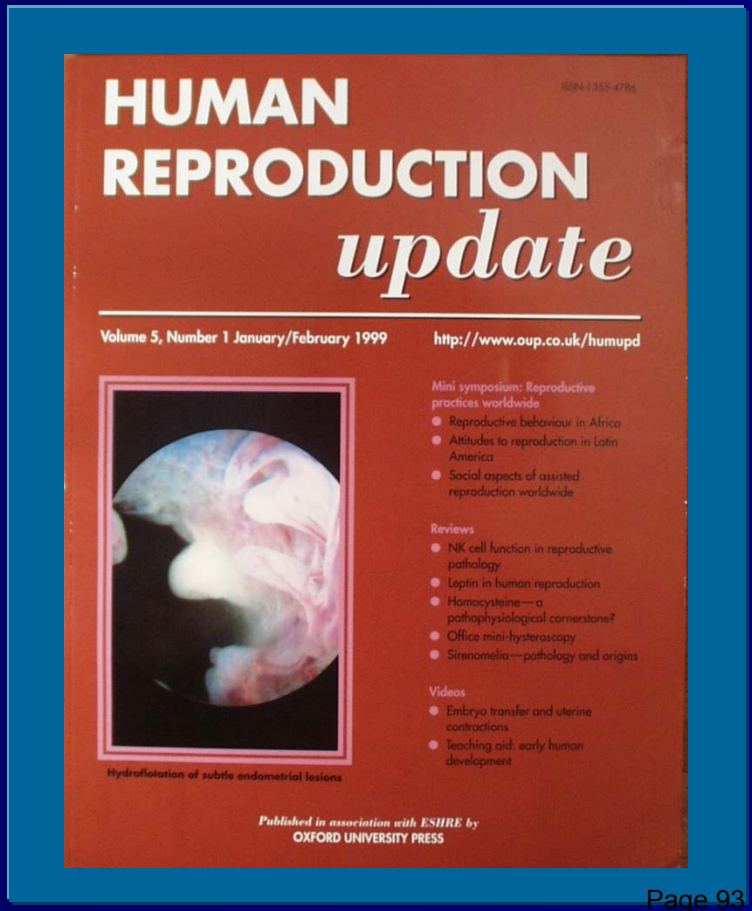
Feasibility of Diagnostic Hysteroscopy

4 important conditions

- Ambulatory or office endoscopic unit
- Watery distension medium
- Small diameter instrumentation with high optical quality
- Atraumatic technique

Office environment

Watery distension medium



Hydro-flotation
subtle lesions !!

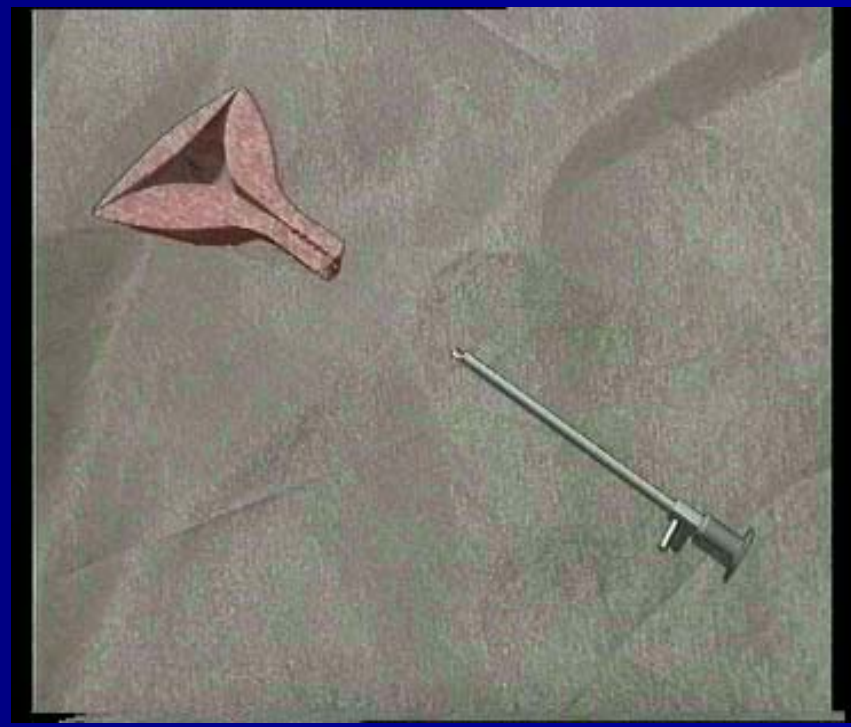
Grade A evidence
Less painful !!

Small Instrument

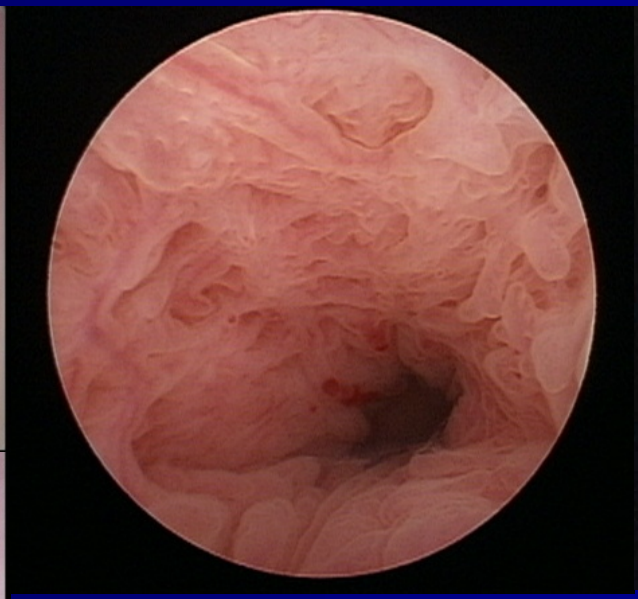
Hysteroscope	diameter	
• 30° rod lens optic:	**2.0 mm**	2.9 mm
• Diagnostic single flow sheath:	**2.8 mm**	3.7 mm
• Operative single flow sheath:	3.6 mm	4,3 mm
• Operative continuous flow sheath :	4,2 mm	5.0 mm

Atraumatic insertion technique

- No speculum
- No tenaculum
- No cervical dilatation
- No anaesthesia, no analgesia
- Atraumatic and sight controled insertion of the hysteroscope.



Atraumatic insertion technique



Atraumatic insertion technique

Feasibility of office hysteroscopy

Campo R, Molinas CR et al, Hum Reprod *2005*

Conventional hysteroscope
vs.
Mini-hysteroscope

Prospective multi-centre randomized clinical trial

Prospective, Multicentre, Randomised Controlled Trial

Campo R, Molinas CR et al, Hum Reprod 2005

To score objectively

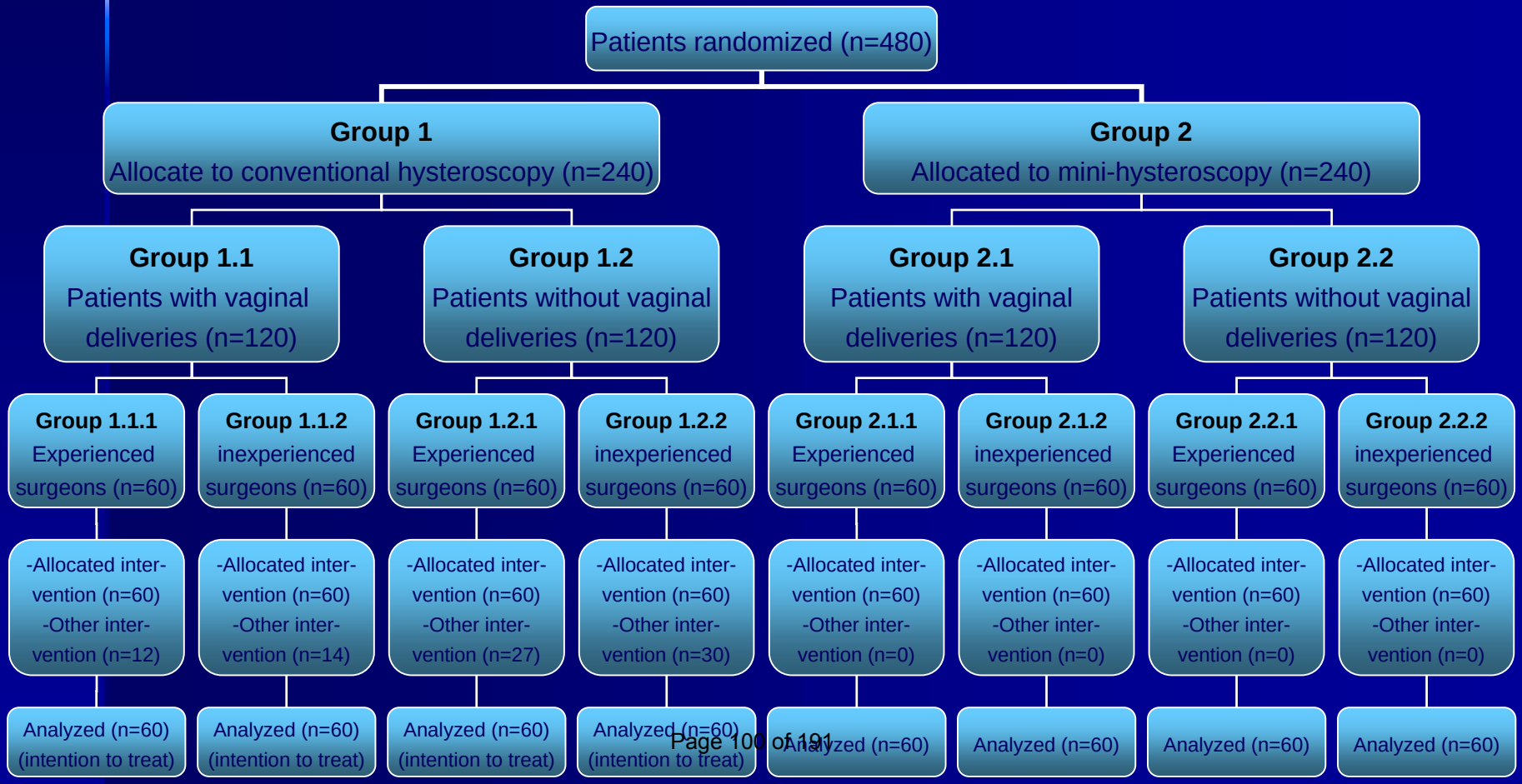
- Pain
- Visualisation quality

Stratified for

- Total instrument diameter
- Vaginal delivery (0 versus >=1)
- Surgeons skills

Trial Profile: RCT

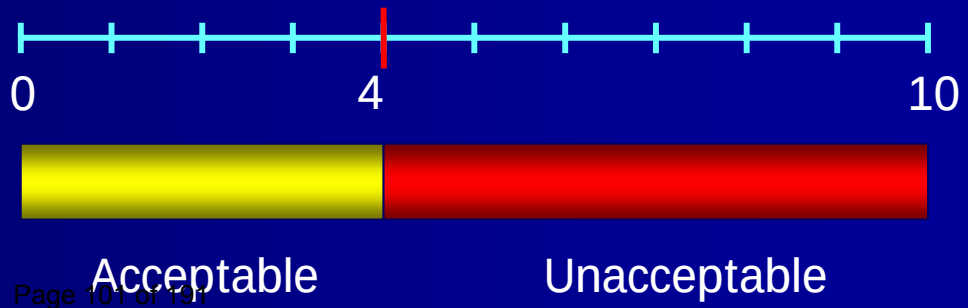
Campo R, Molinas CR et al, Hum Reprod 2005



Pain

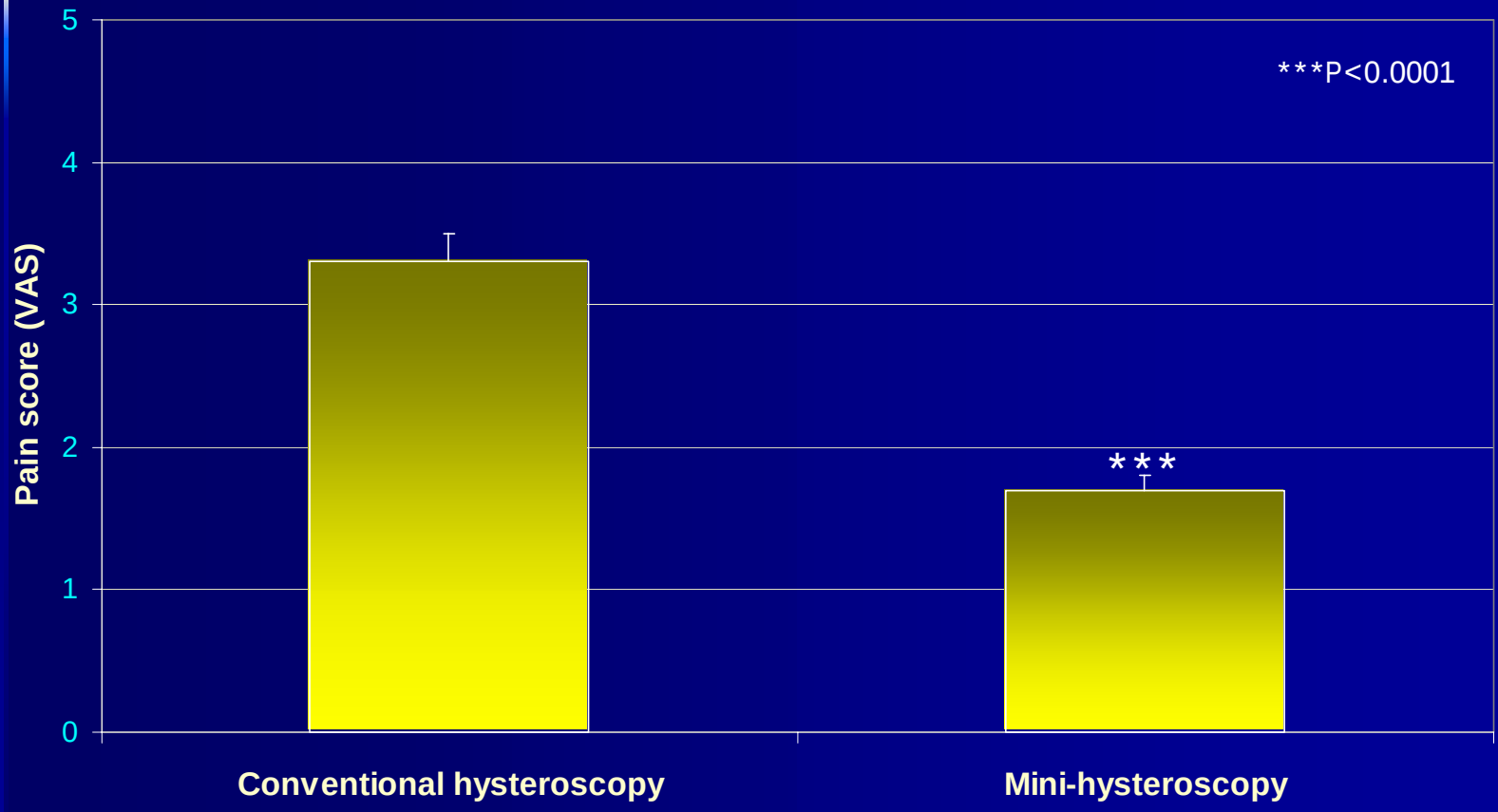
Campo R, Molinas CR et al, Hum Reprod 2005

- By patients
- At the end of the procedure
- Visual Analogue Scale (VAS)



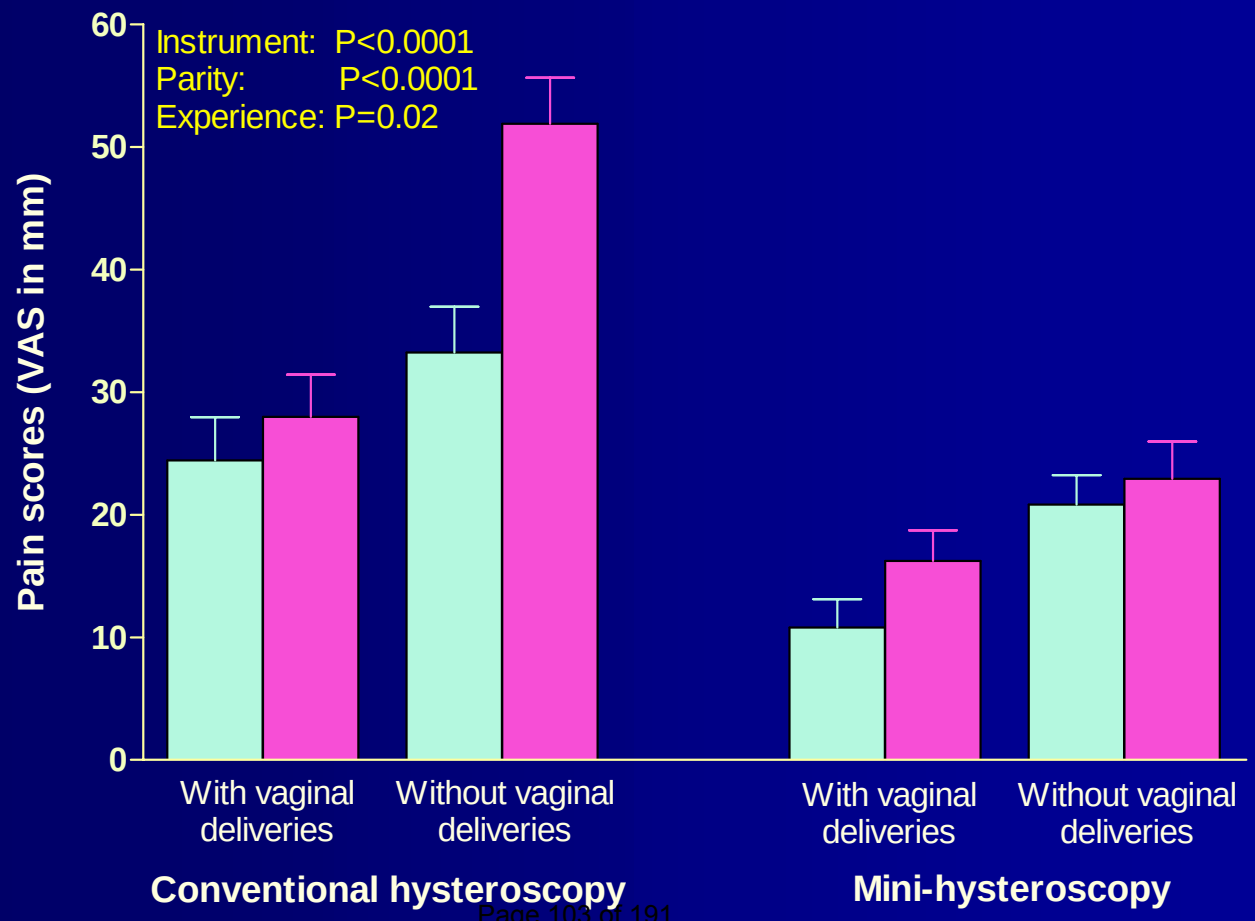
Pain Scores

Campo R, Molinas CR et al, Hum Reprod 2005



Pain Scores

Campo R, Molinas CR et al, Hum Reprod 2005



3-way analyses (proc GLM)

Visualization of uterine cavity

Campo R, Molinas CR et al, Hum Reprod 2005

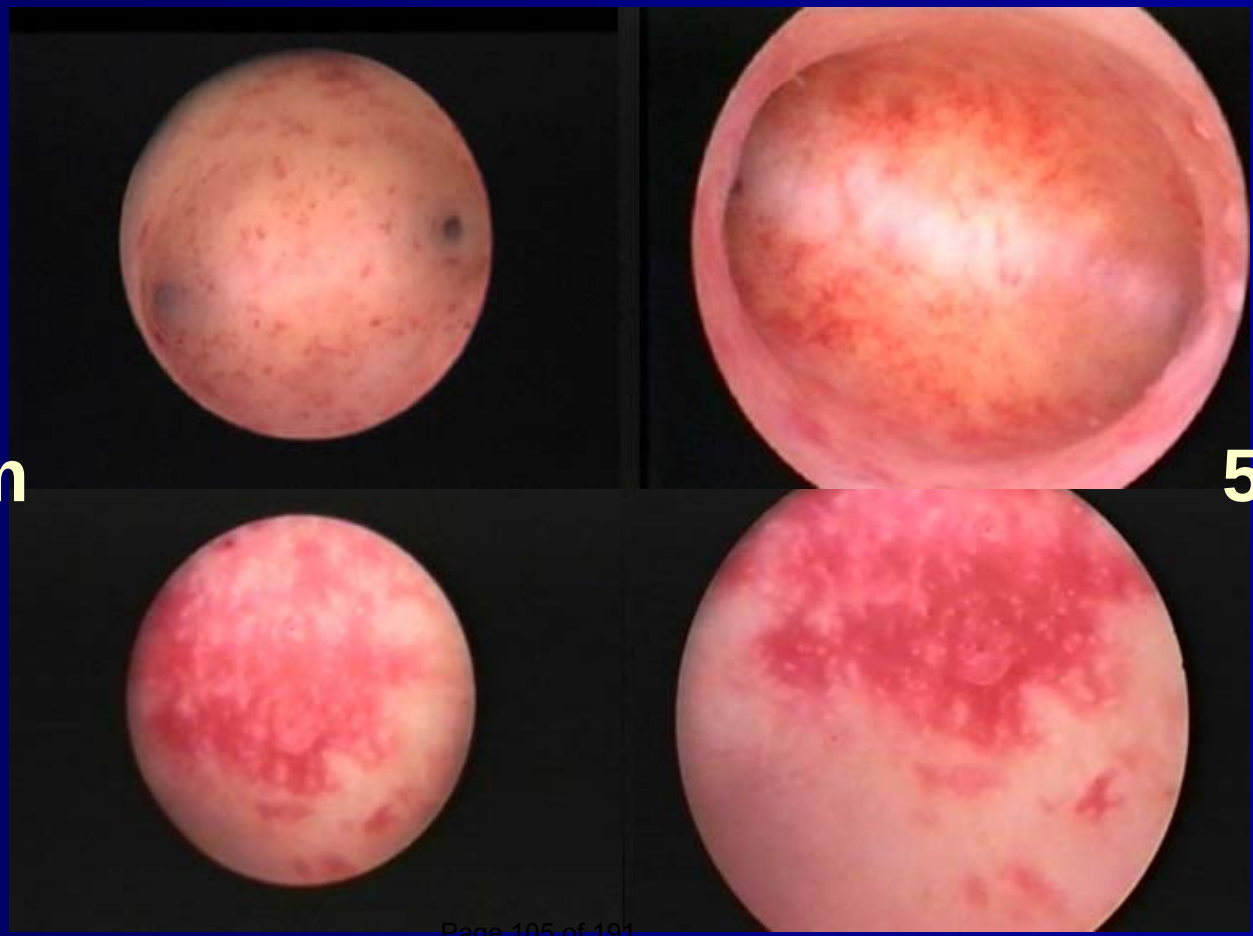
- By surgeons
- During the procedure

Score

- 0: No
- 1: Insufficient
- 2: Sufficient
- 3: Excellent

Instrument diameter and visualisation

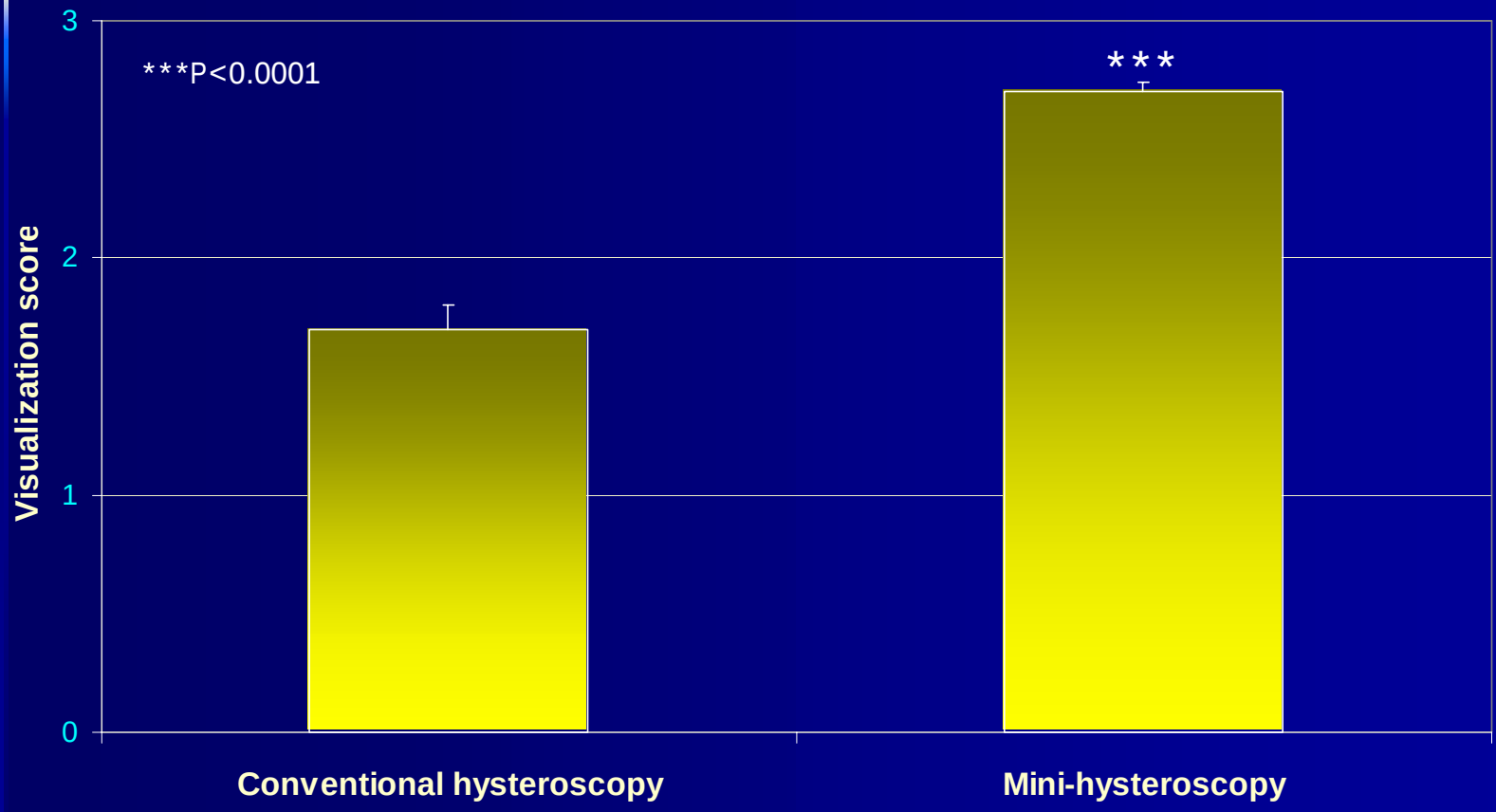
3,5 mm



5,0 mm

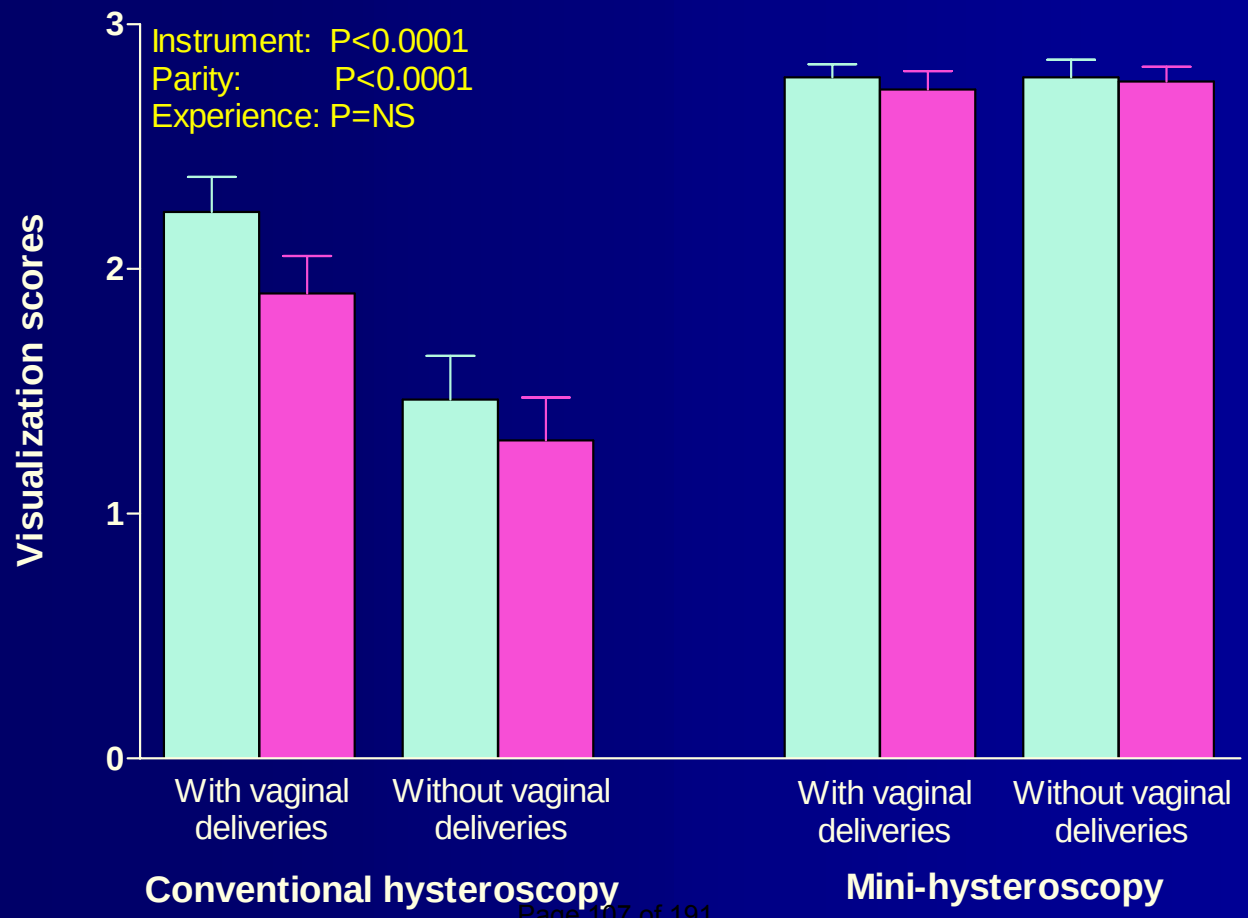
Visualization Scores

Campo R, Molinas CR et al, Hum Reprod 2005



Visualization Scores

Campo R, Molinas CR et al, Hum Reprod 2005



3-way analyses (proc GLM)

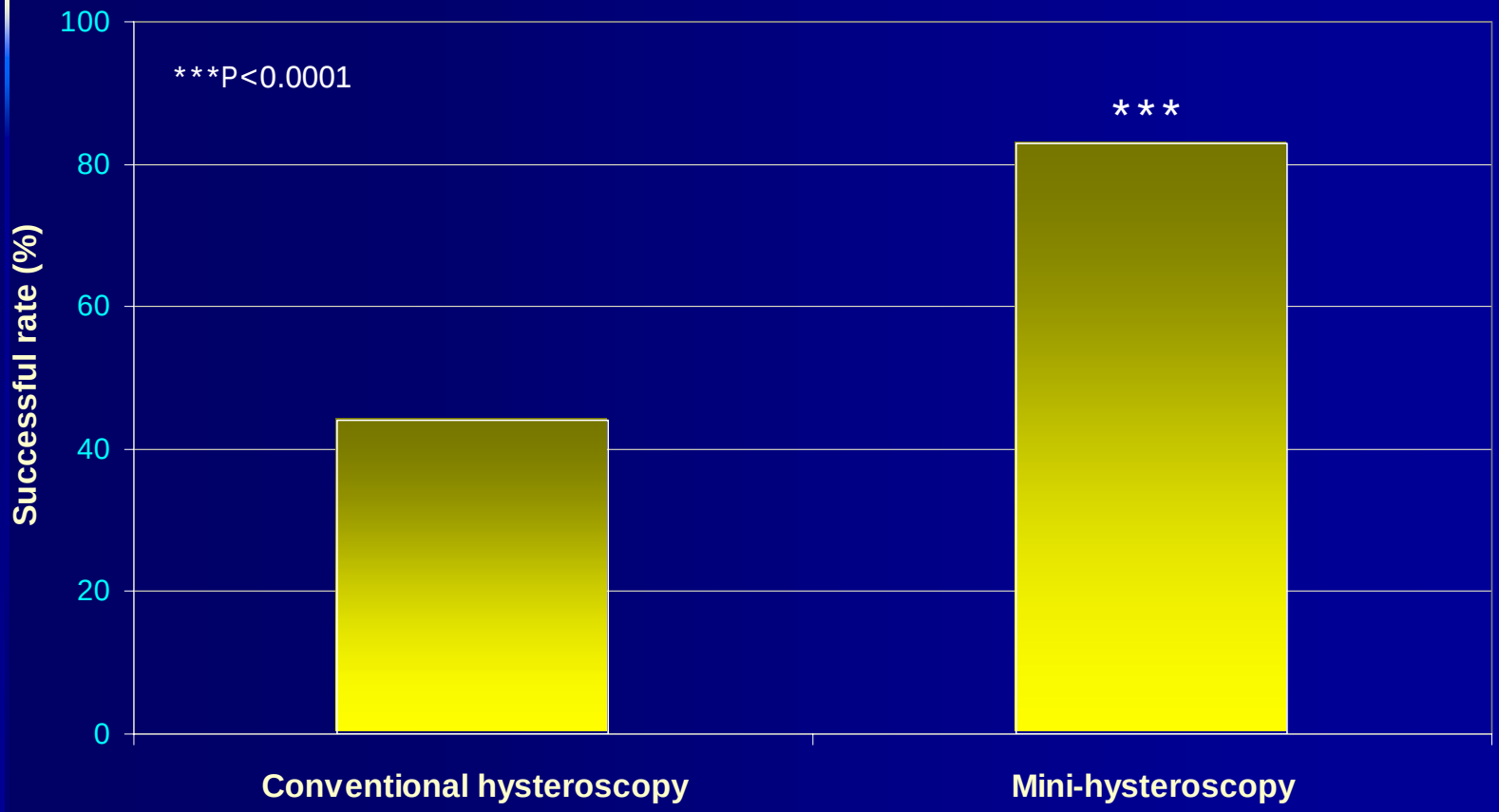
Success rate

Campo R, Molinas CR et al, Hum Reprod 2005

- Calculated:
  - Pain <4
  - Visualization >1
  - No complications

Success rate

Campo R, Molinas CR et al, Hum Reprod 2005



Feasibility of office hysteroscopy

Prospective multi-centre randomised clinical trial

GRADE A EVIDENCE

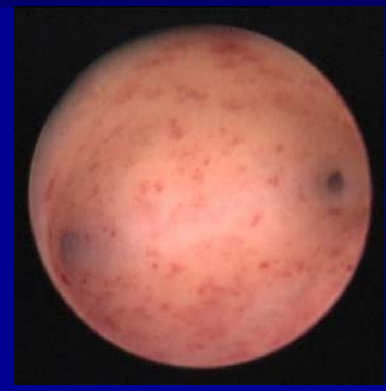
By reducing the diameter of the hysteroscope the effects of patient parity and also surgeon's experience are no longer important !!!

Campo R, Molinas CR et al, Hum Reprod *2005*

Diagnostic Hysteroscopy

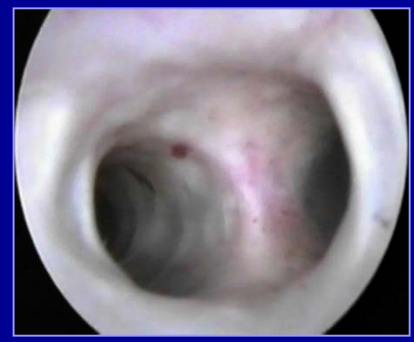
- Technique and Feasibility of diagnostic Hysteroscopy ?
- Findings ?
  Terminology, Incidence, Significance
- Case reports on adenomyosis
- See and threat ?

Findings



Normal

Abnormal



- Congenital malformations
- Polyp – Myoma
- Adhesions

Subtle lesions

- Lesions of unknown pathological significance

Findings

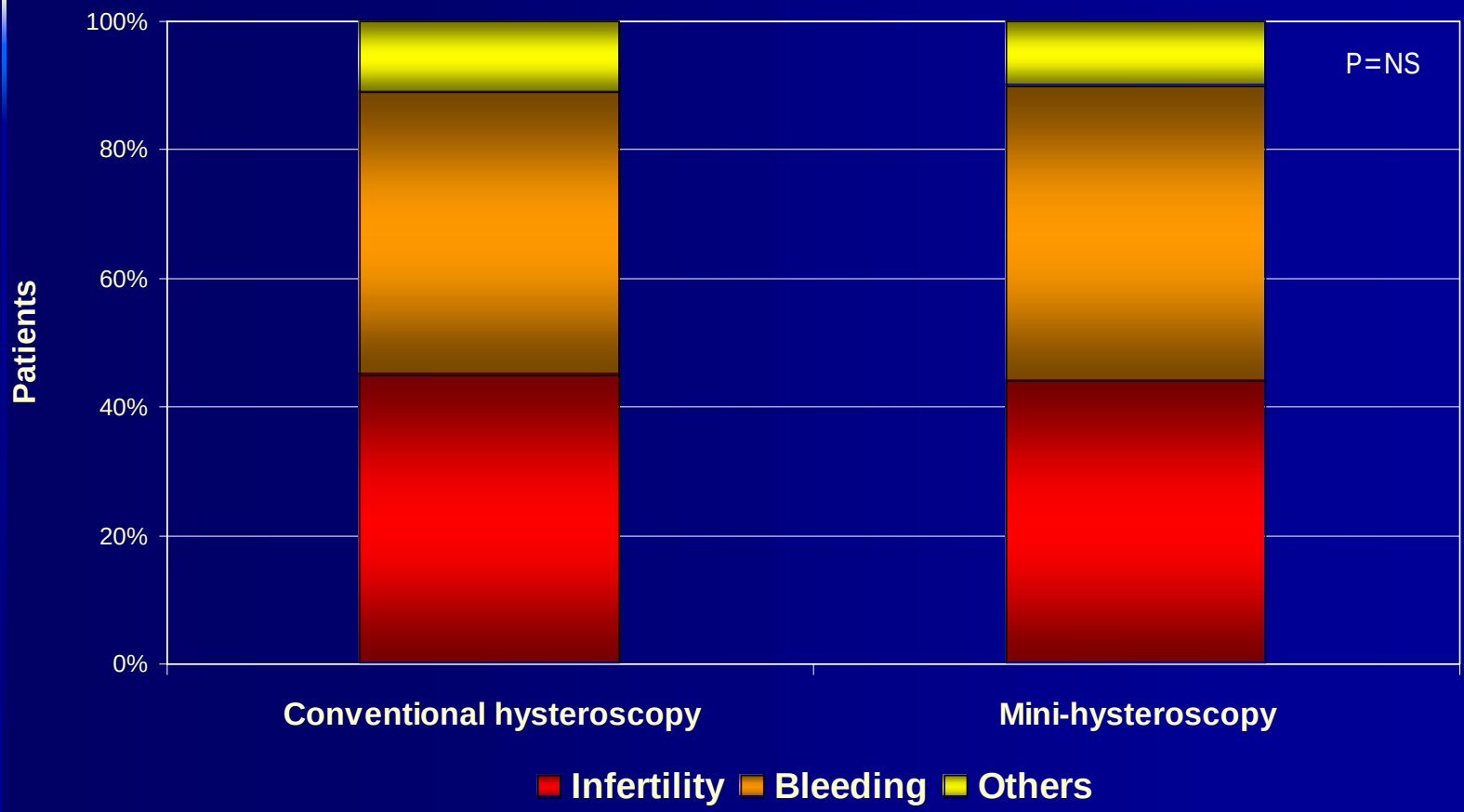
Prospective multi-centre randomized clinical trial

Different pathology in infertile versus AUB patients

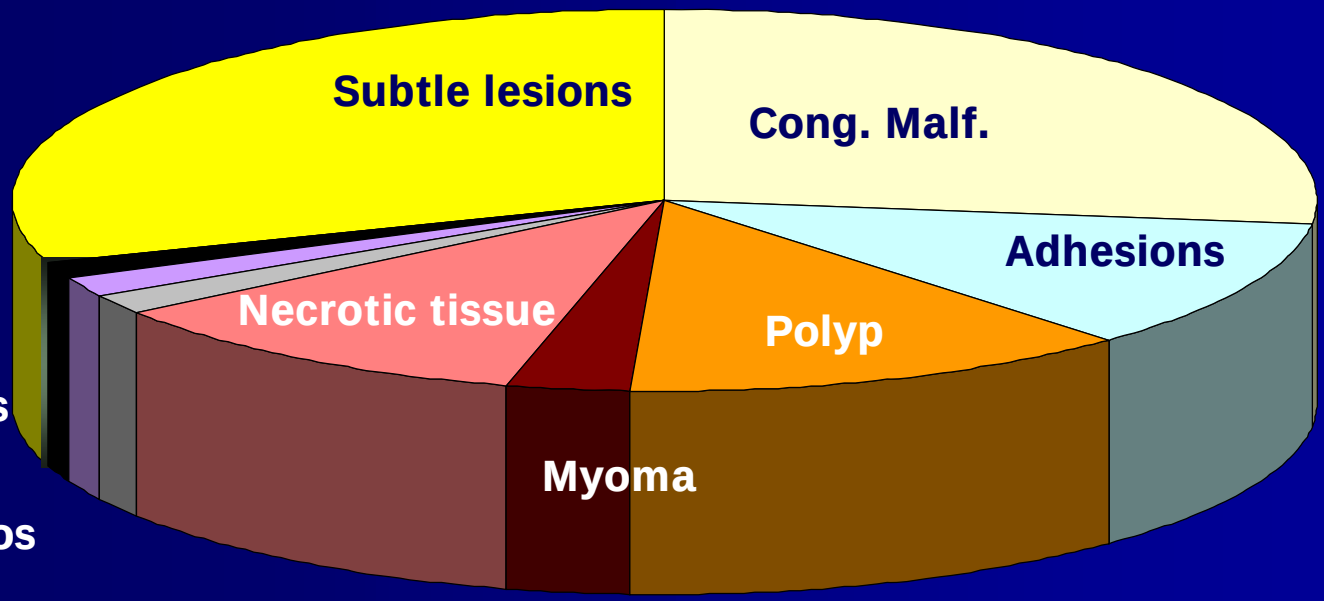
Molinas CR, Campo R et al Best Pract Res Clin Obstet Gynaecol. 2006 Mar 20

Indications

Campo R, Molinas CR et al, Hum Reprod 2005

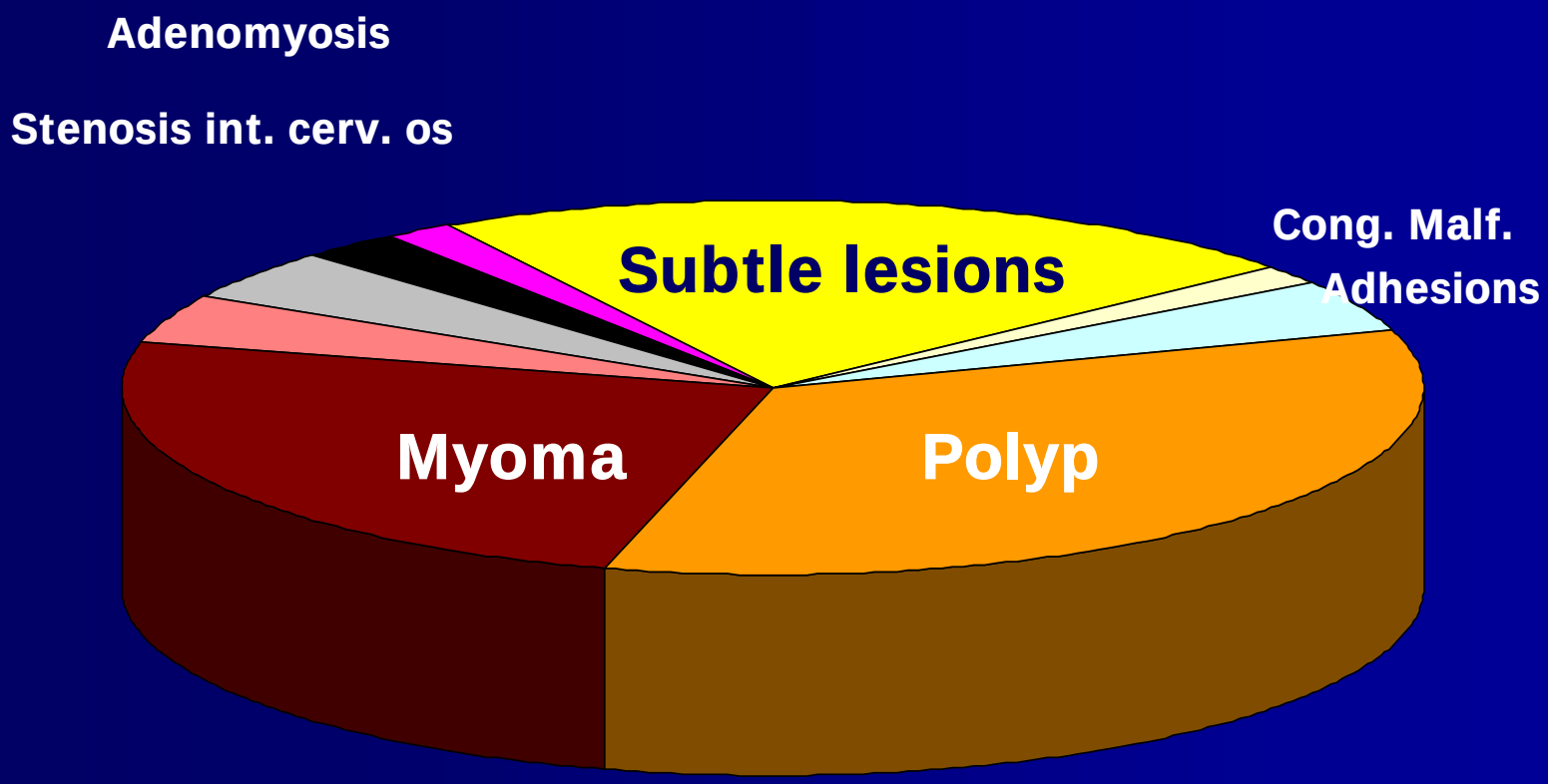


Abnormal findings in patients with infertility



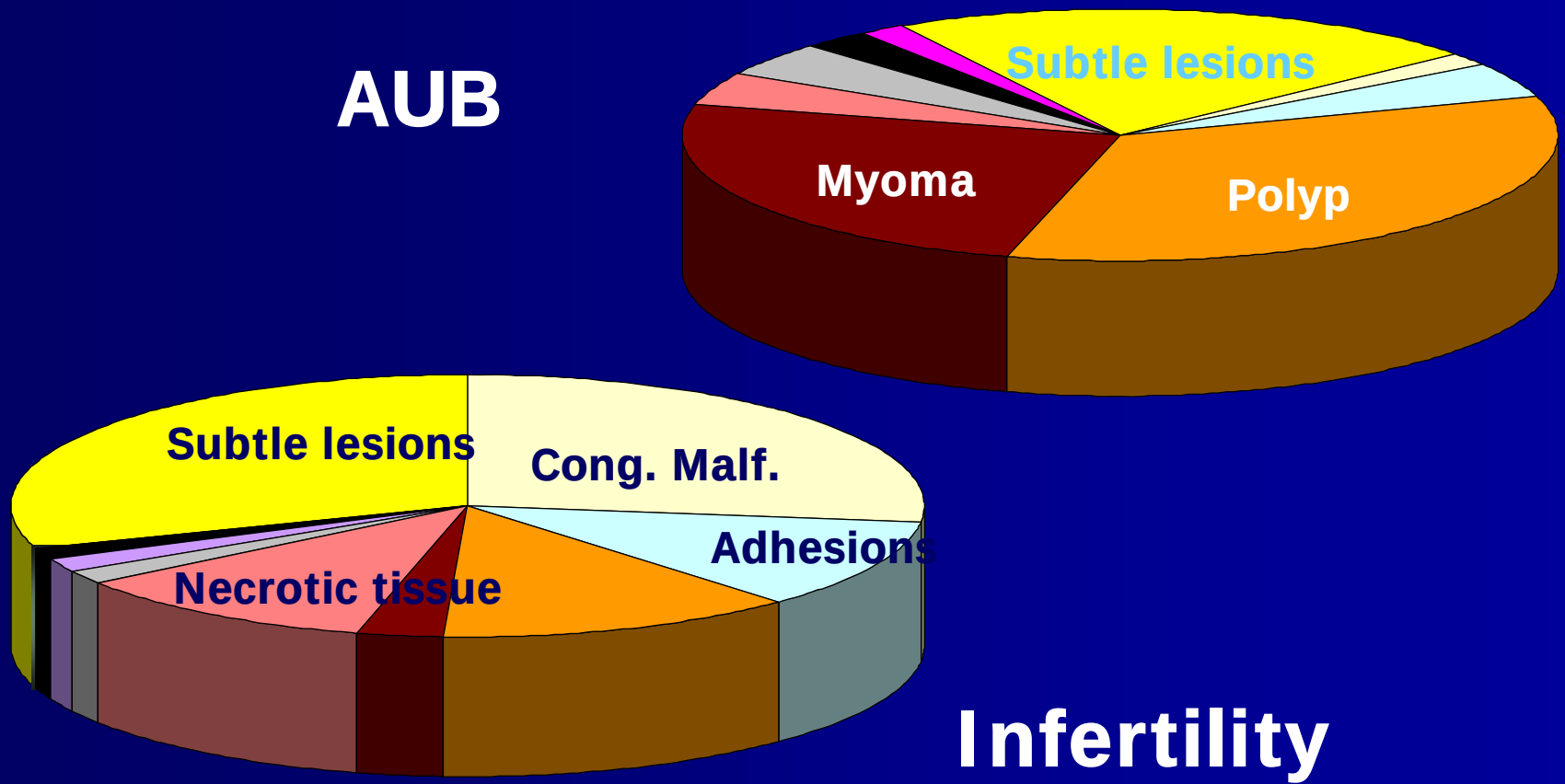
Molinas CR, Campo R et al Best Pract Res Clin Obstet Gynaecol. 2006 Mar 20

Abnormal findings in patients with AUB

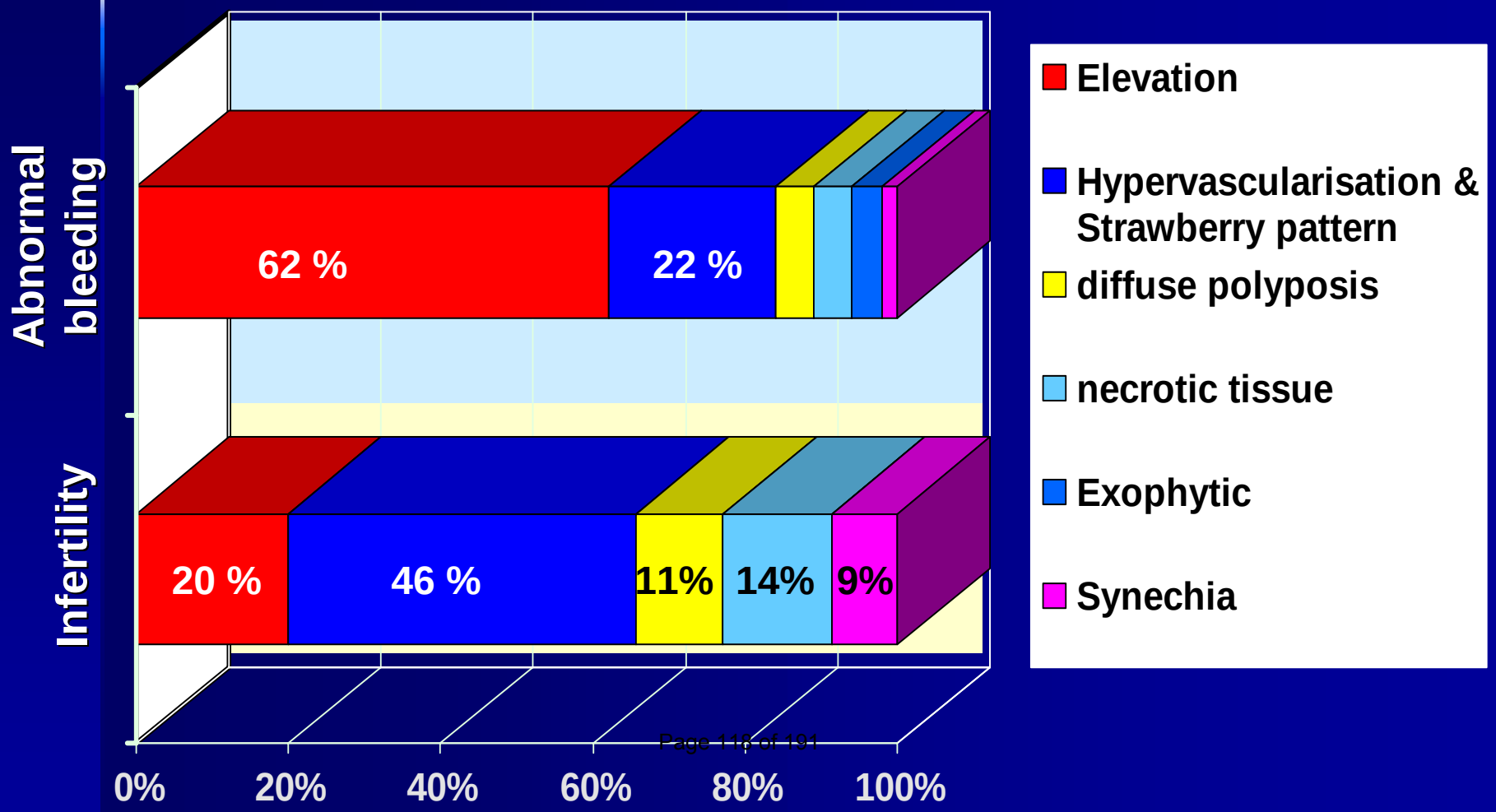


Molinas CR, Campo R et al Best Pract Res Clin Obstet Gynaecol. 2006 Mar 20

Abnormal findings



Subtle lesions



Subtle lesions ??

effect of magnifying and hydroflotation

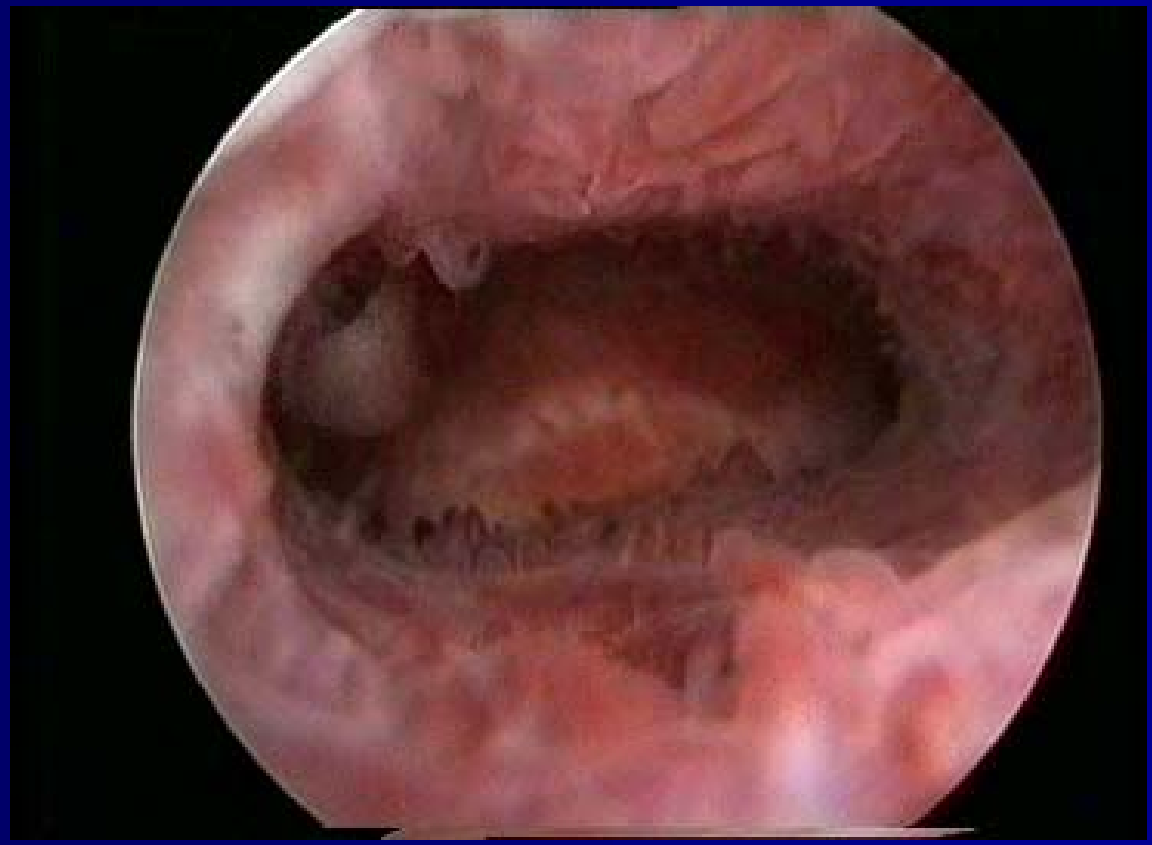
- These subtle or incipient lesions:
  significance unclear but could be associated with infertility.

Subtle lesions

Lesions of unknown pathological significance

- Diffuse polyposis
- Strawberry pattern
- Hypervascularization
- Mucosal elevation
- Endometrial defects
- Others

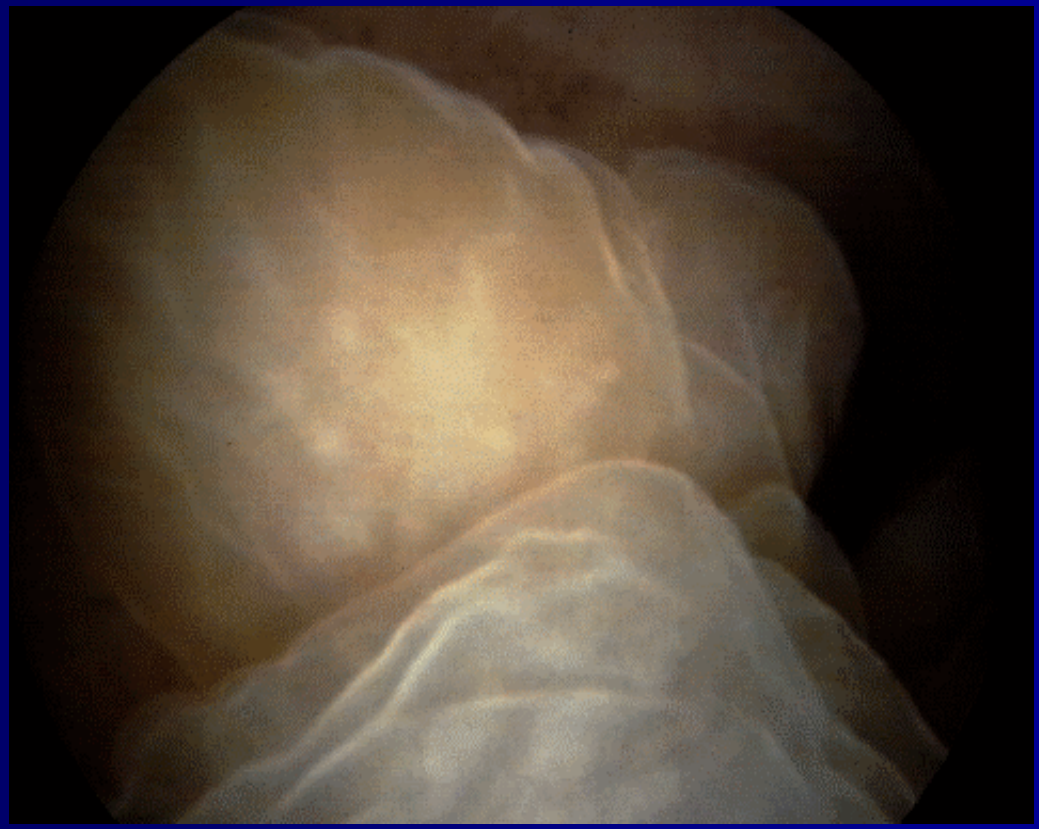
Diffuse polyposis



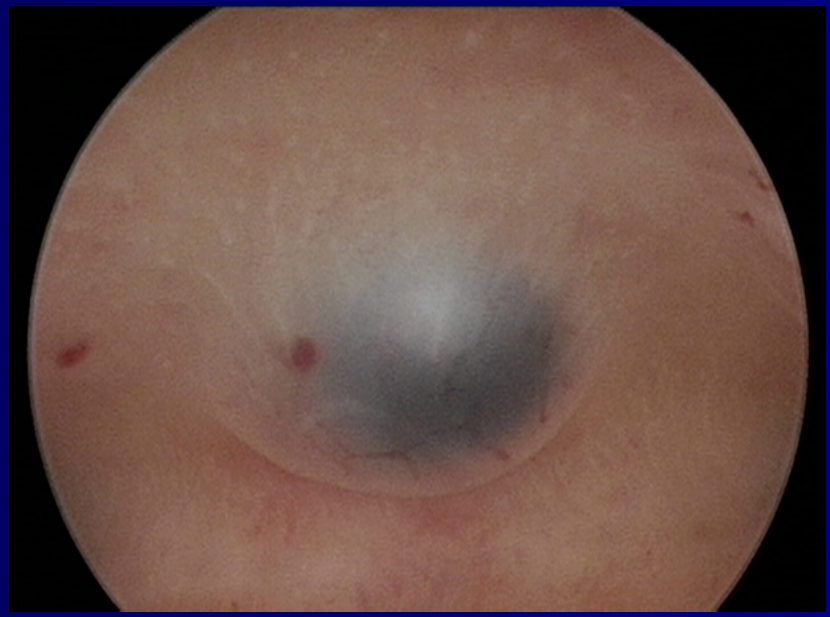
Strawberry pattern

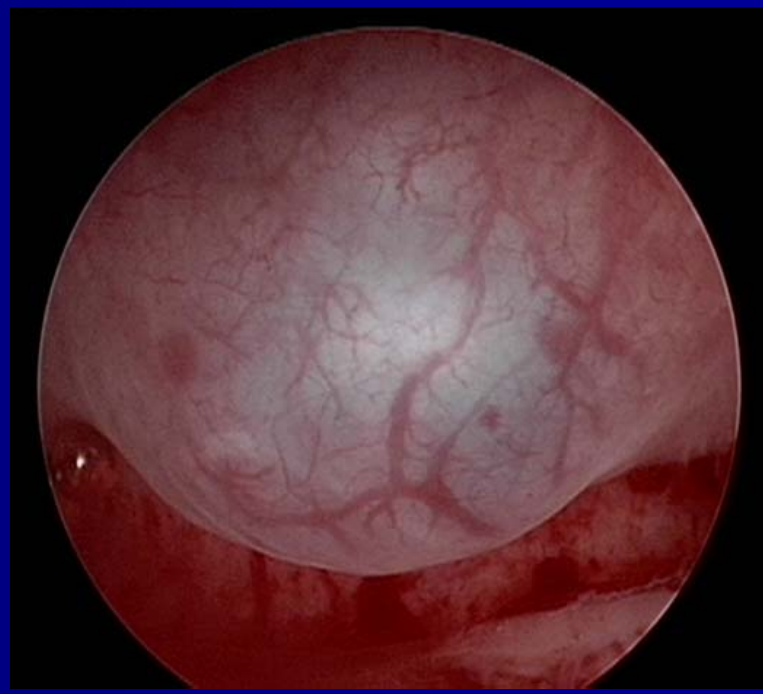
Hypervascularisation

Localised mucosal elevation

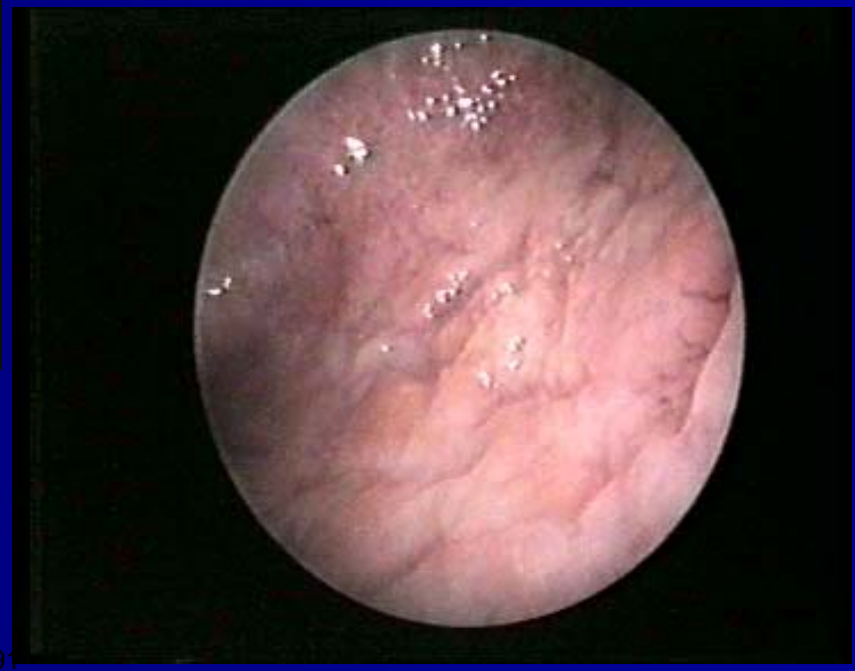


Mucosal elevation



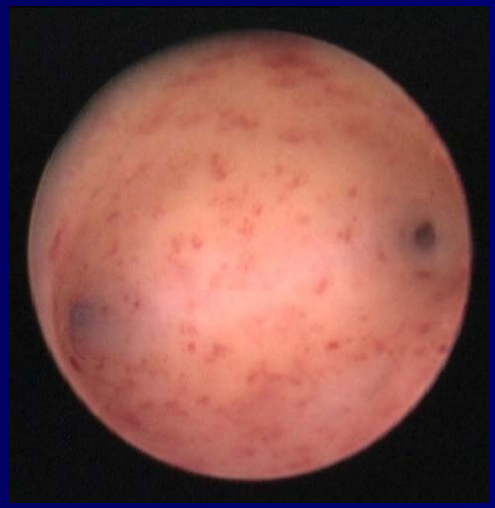


marked localised vascular pattern



Endometrial defects

Subtle laesions and Adenomyosis



Proper Uterine diagnosis ?

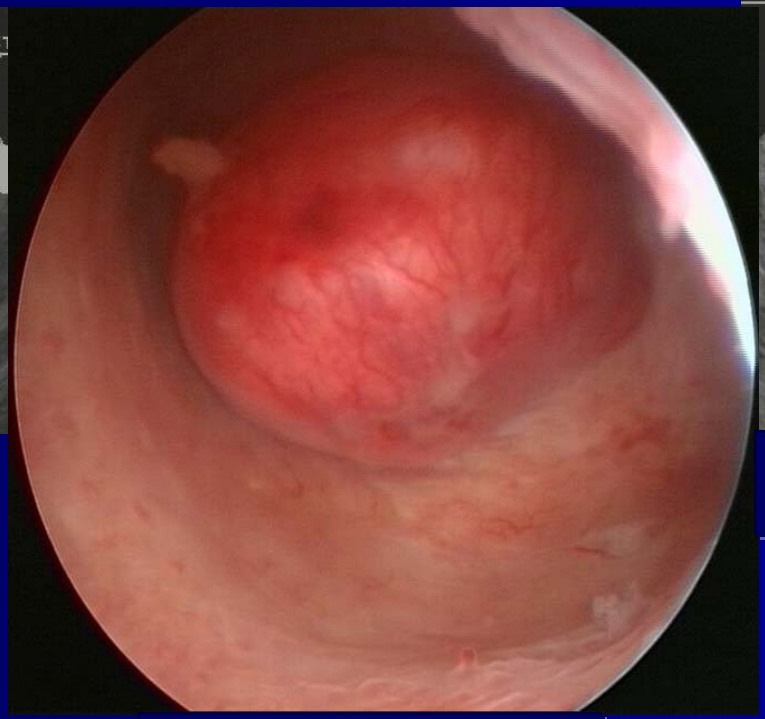
First line - ONE STEP - procedure

- Ultrasound TvS - abdominal
- Fluid Mini - Hysteroscopy
- Kontrast sonography

low risk – low cost – high compliance

Proper uterine diagnosis ?

Ultrasound



Hysteroscopy

Kontrast sonography

Proper Uterine diagnosis ?

When do we have to enlarge the diagnosis

- Ultrasound
  Distortion of homogenous myometrium
  Increased myometrial thickness >15mm
- Hysteroscopy
  Endometrial defect
  Reddisch endometrium of unknown origin
  Subtle cystic lesions
  Localised vascular pattern

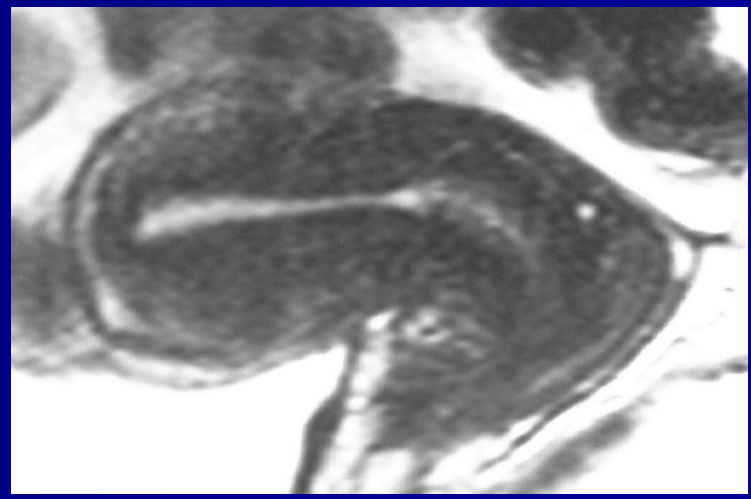
Diagnostic Hysteroscopy

- Technique and Feasibility of diagnostic Hysteroscopy ?
- Findings ?
  Terminology, Incidence, Significance
- Case reports on adenomyosis
- See and threat ?

Case 1

unexplained infertility
- **> 6 years**
- **< 35 years**
- **3 IVF top quality embryo's**
- **PGD normal genetics**

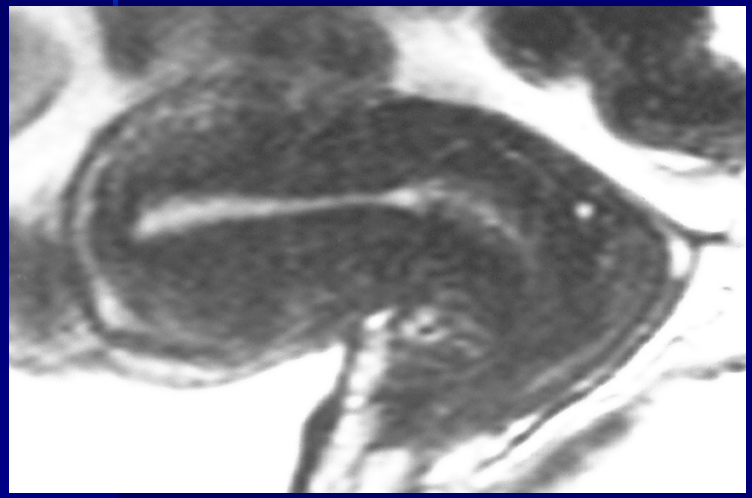
NMR

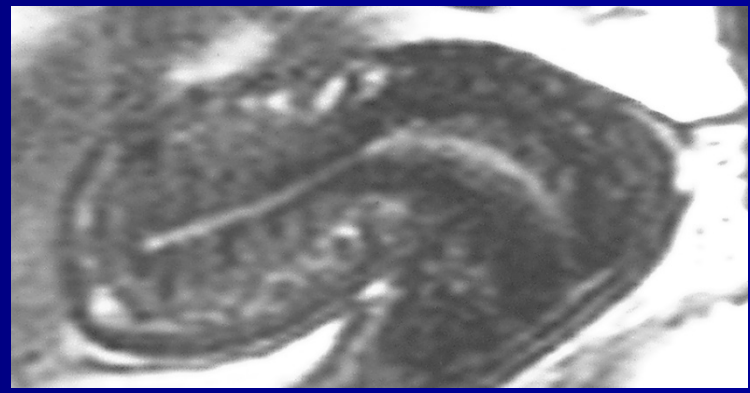


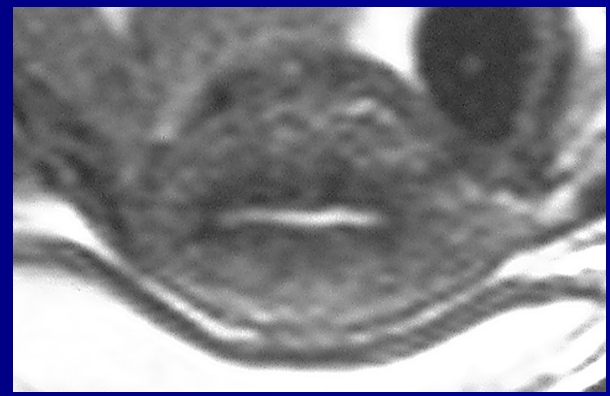
Case 1

unexplained infertility

NMR after 3 months

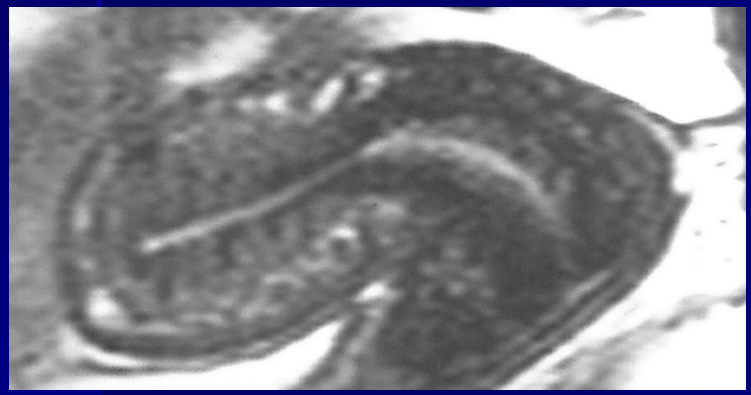






Case 1

unexplained infertility



Viable pregnancy with at term delivery of normal female after first ivf attempt

Case 2

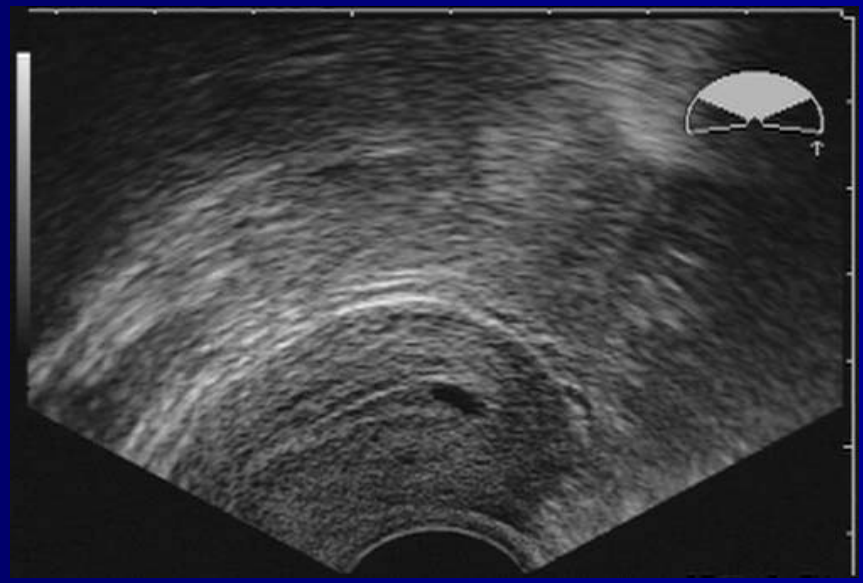
Subtle lesion at exploration

23-year-old patient of Indo-African origin
presented with a primary infertility of 20 months

Case 2

Ultrasound

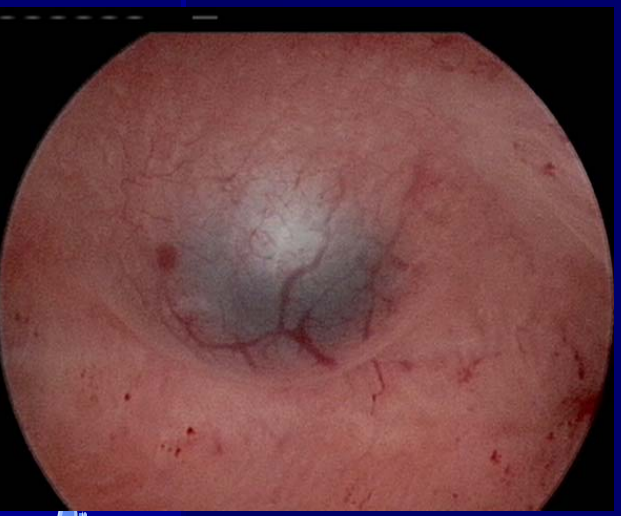
fundus a small oval shaped and translucent area

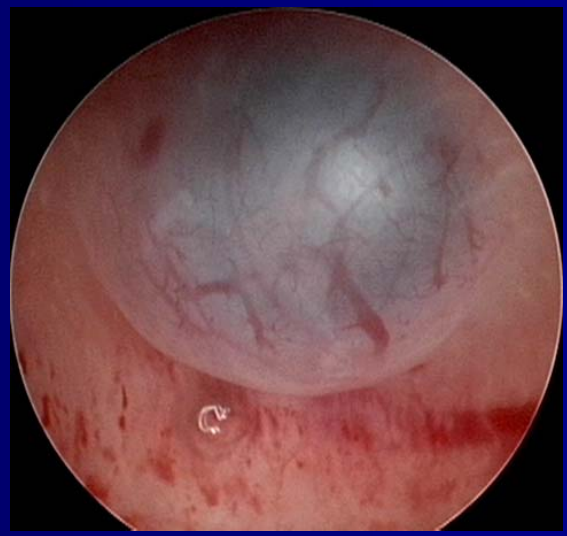


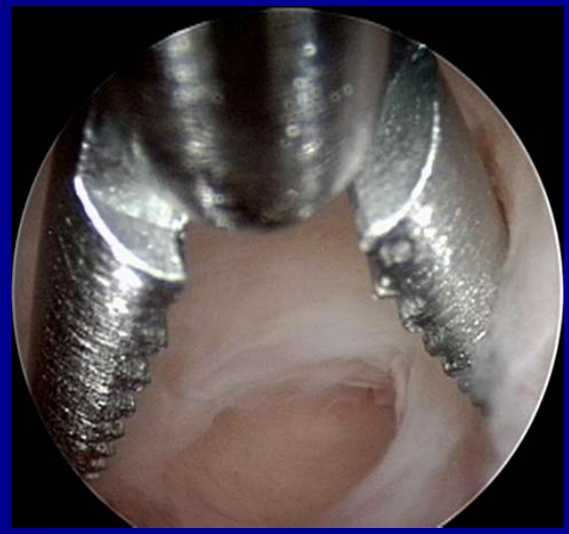
Case 2

Mini Hysteroscopy

dark blue cystic lesion on the anterior wall near the fundus







Case 2

Post operative features

Histology confirms adenomyosis.

NMR post operative shows no further evidence for adenomyotic lesions.

Spontaneous normal ongoing intra-uterine singleton
pregnancy one month after NMR.

Diagnostic Hysteroscopy

- Technique and Feasibility of diagnostic Hysteroscopy ?
- Findings ?
  Terminology, Incidence, Significance
- Case reports on adenomyosis
- See and threat ?

See and threat !
Ambulatory Endoscopic Unit

- No conventional OR
- No general anaesthesia, only sedation

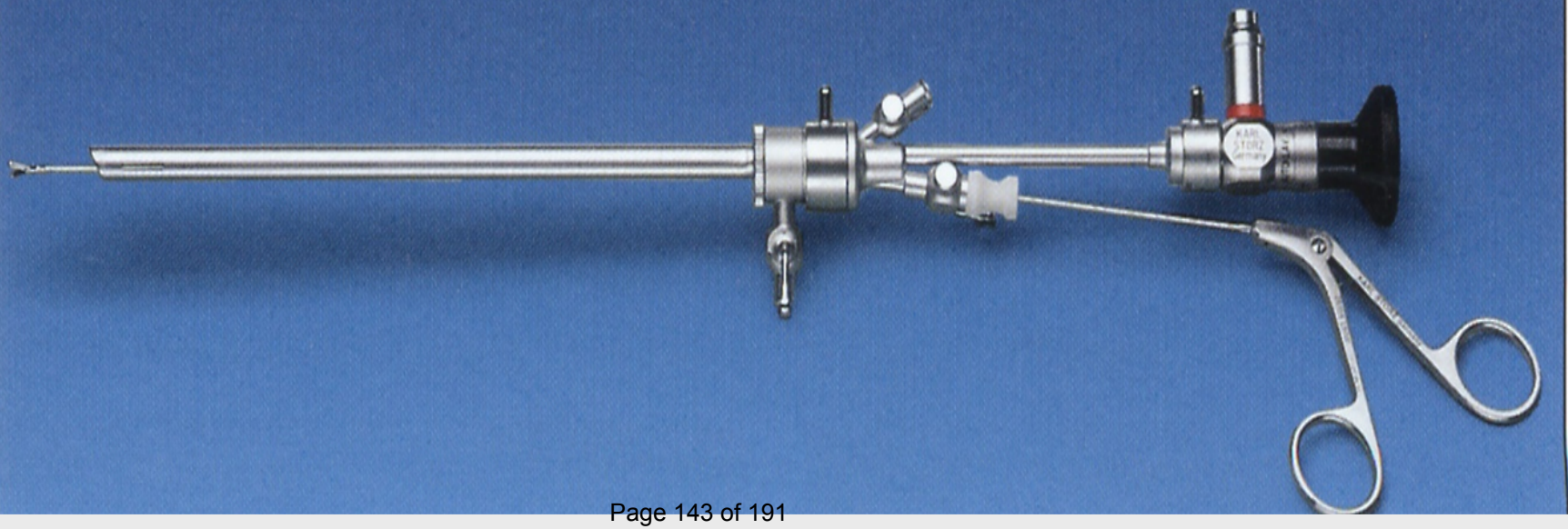
See and threat !
Ambulatory Endoscopic Unit

TELE PACK

comprehensive, multifunctional and compact documentation terminal that can be used as a compact system in the doctor's office

Ambulatory operative Hysteroscope

• 30° rod lens optic:	**2.0 mm**	**2.9 mm**
•Operative single flow sheath:	3.6 mm	4,3 mm
• Operative continuous flow sheath :	4,2 mm	5.0 mm



Ambulatory operative Hysteroscopy

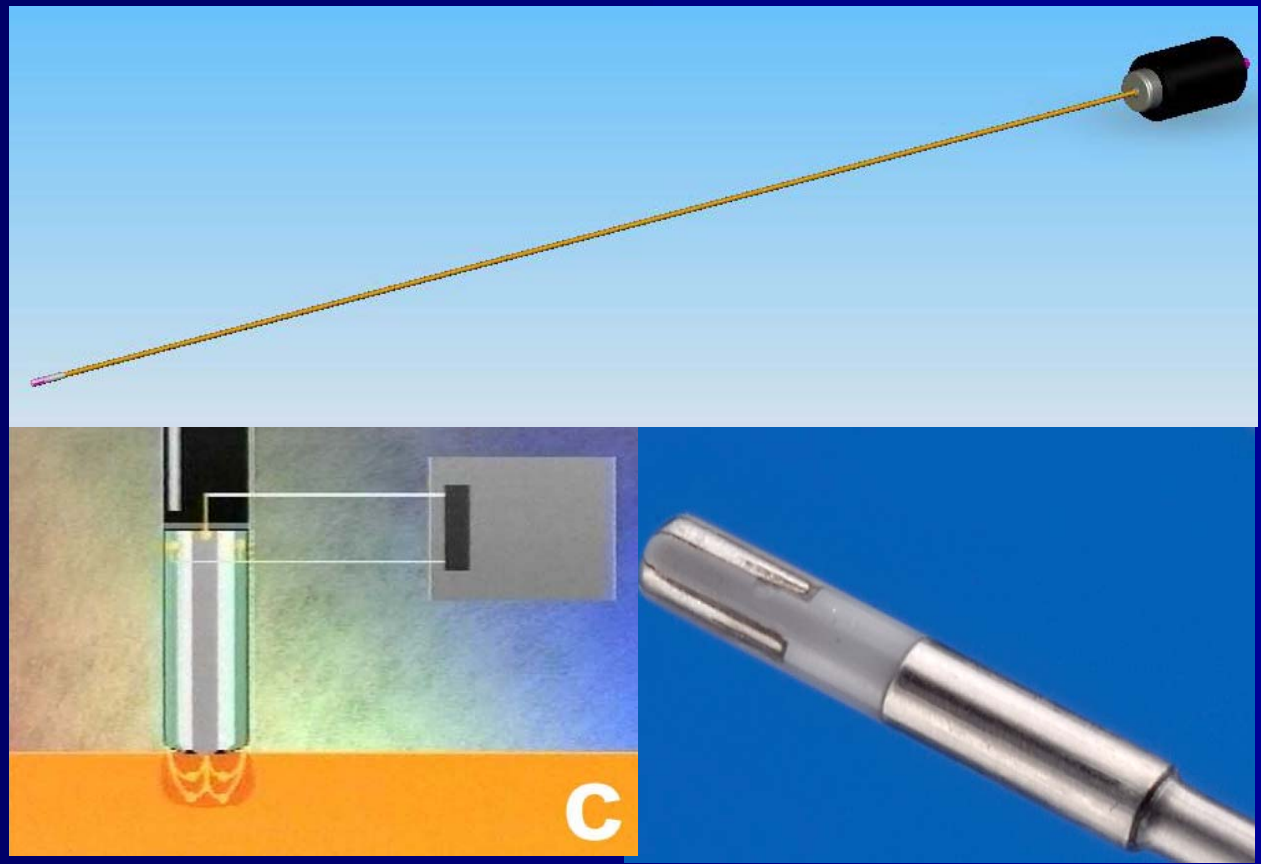
5 French Mechanical probes

Ambulatory operative Hysteroscopy

5 French Bipolar probes

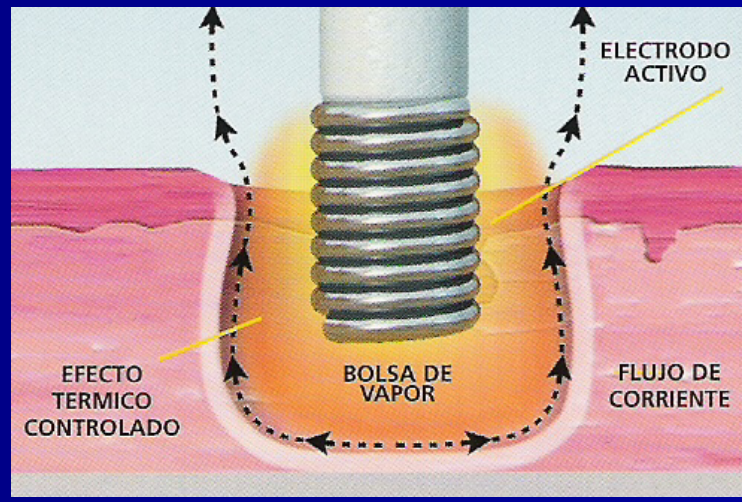
- **Bicag (Storz)**
- **Bipolar needle (STORZ)**
- **Versapoint (GYNECARE)**

Bipolar coagulation probe (Storz)



BIPOLAR NEEDLE (STORZ)

VERSAPOINT (GYNAECARE)



Vaporisation

Ambulatory surgical intervention

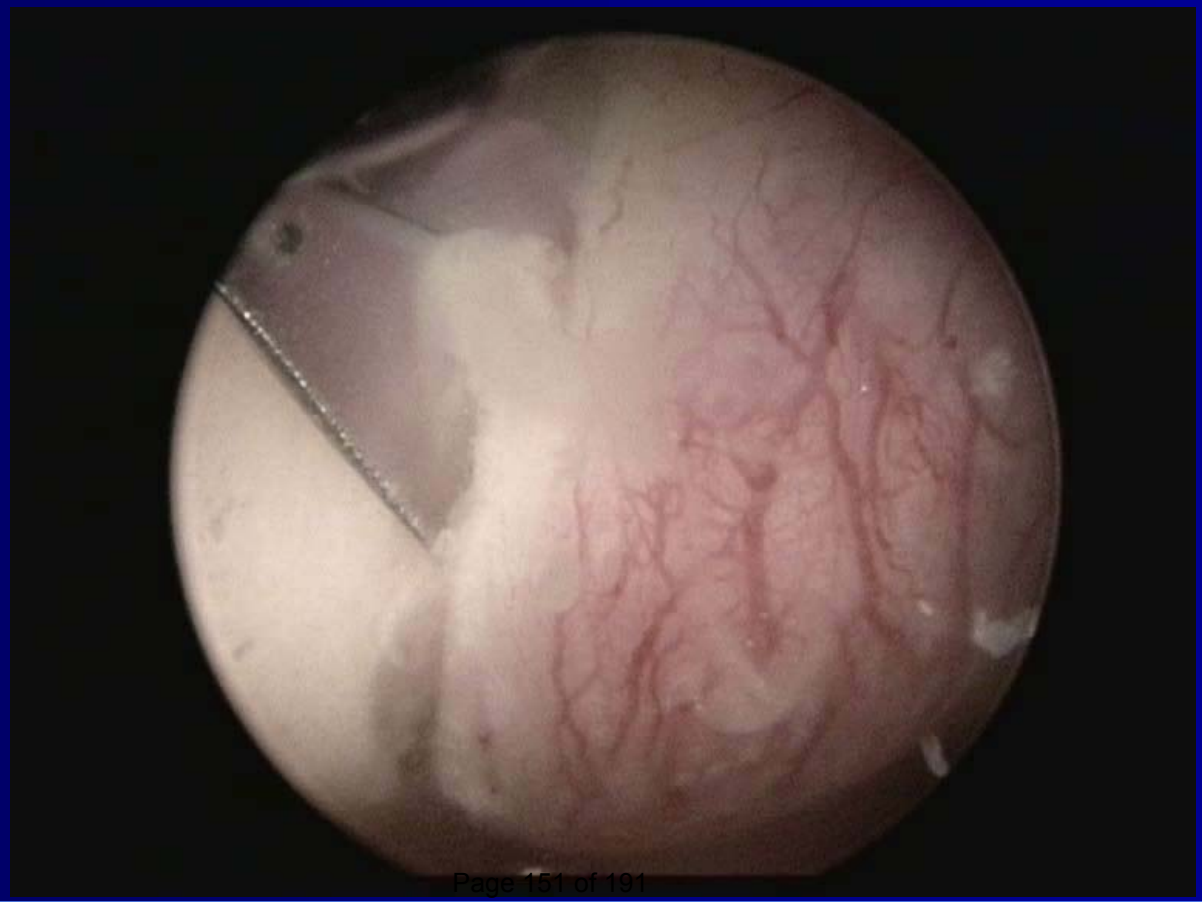
DD Myoma Type 2 – adenomyoma

Ambulatory surgical intervention

Focal hypervascularisation

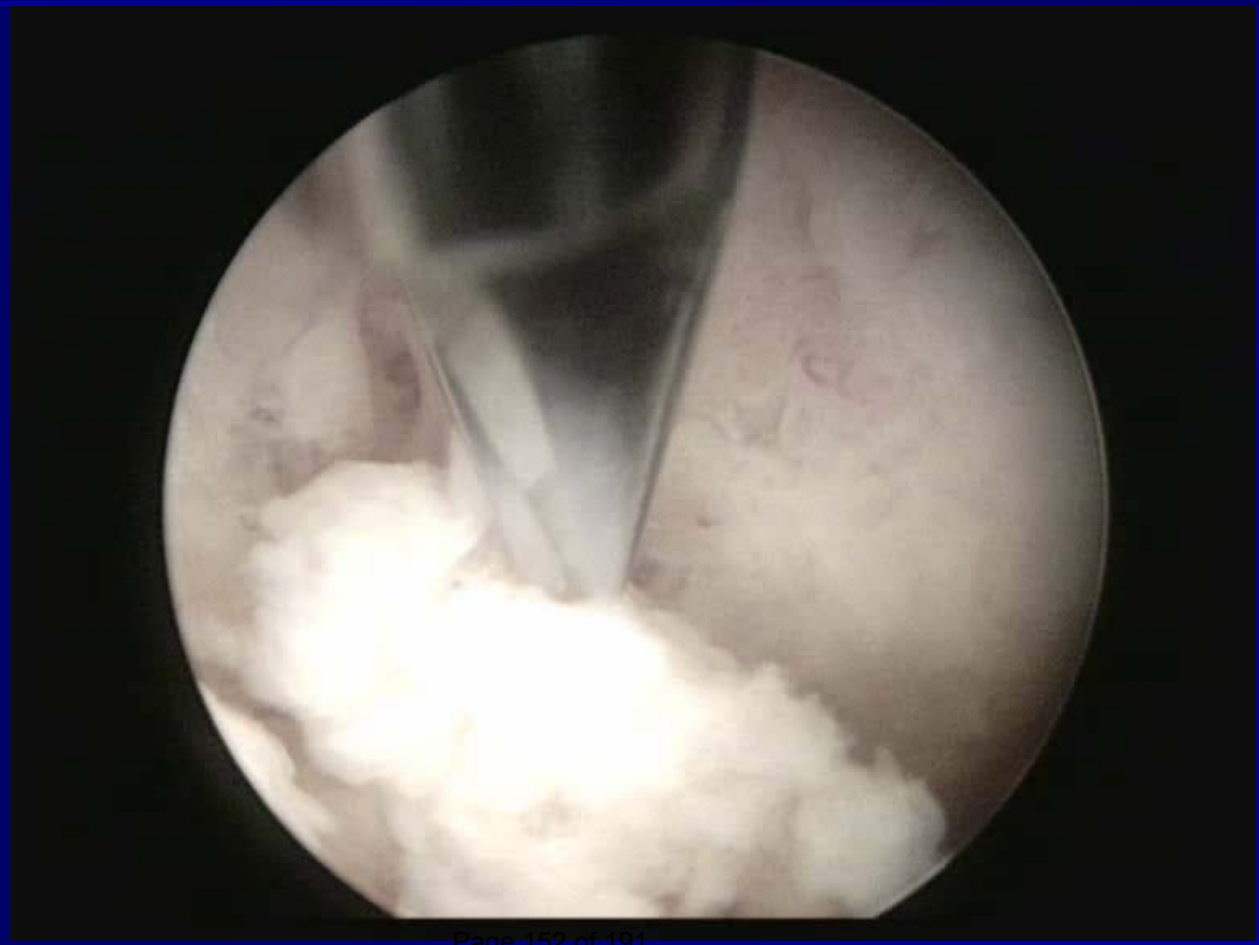
Ambulatory surgical intervention

Resection with scissors



Ambulatory surgical intervention

Resection with scissors



Conclusions 1

New developments have made office hysteroscopy and transvaginal ultrasound the first line procedure in patients with AUB and infertility.

Both can be performed on a routine base by every trained gynaecologist .

Conclusions 2

Diagnostic mini - hysteroscopy is an accurate tool for visualising the uterine cavity with high visualisation capacity for subtle lesions.

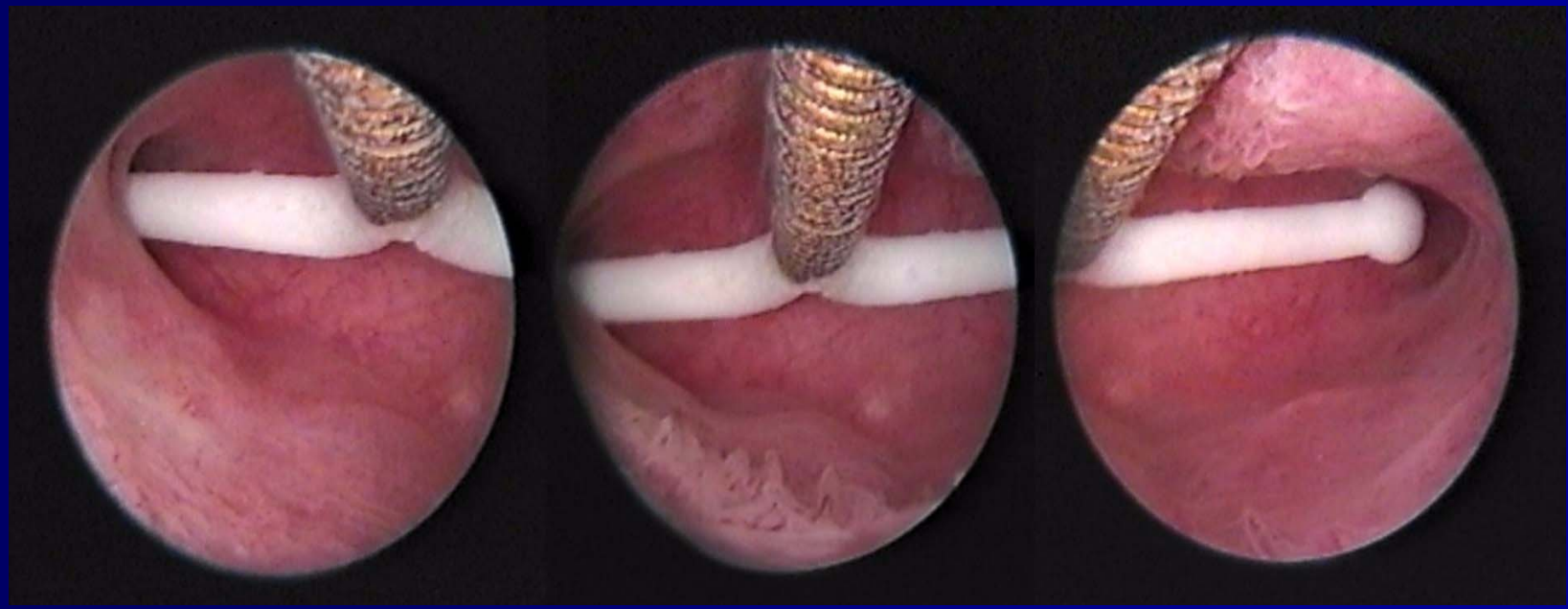
Hysteroscopy is limited to the observation of surface of the endometrium and can neither diagnose nor exclude adenomyosis.

Conclusions 3

The visual inspection of the endometrium in patients with adenomyosis can reveal significant findings .

Mini Hysteroscopy in combination with transabdominal ultrasound provides the possibility to enlarge the diagnostic procedure with a minimal invasive surgical act aiming an endoscopic inspection of the myometrium and resection of suspicious myometrial areas for histological examination.

Ambulatory hysteroscopy a tool for every Gynaecologist .



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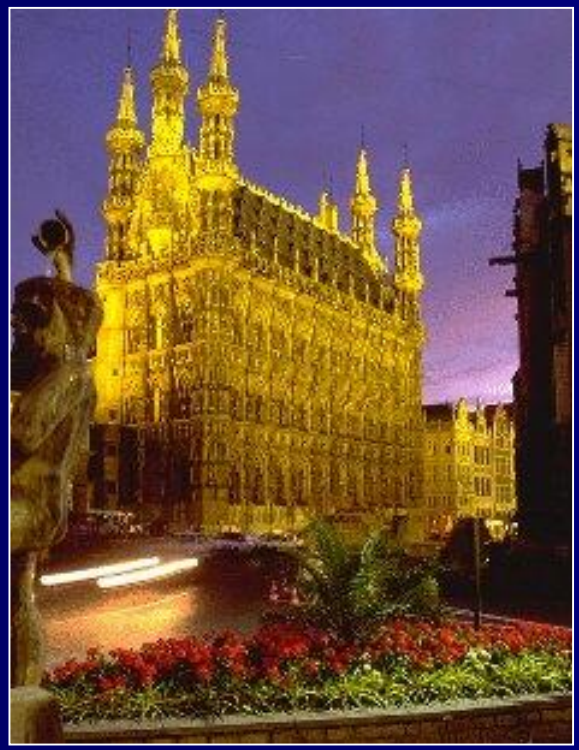

Rudi Campo
Stephan Gordts
Patrick Puttemans
Roger Molinas
Sylvie Gordts
Marion Valkenburg
Ivo Brosens

ADENOMYOSIS AND REPRODUCTION

IS SURGERY OF ANY BENEFIT:

PREVENTION AND TREATMENT ?

S. GORDTS

ESHRE CAMPUS
LEUVEN, 19-20 APRIL 2007

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Adenomyosis - Pathogenesis

Presence of endometrial glands and stroma deep within the myometrium (>2.5 mm frpm EJZ)

It is a myoproliferative disease of the inner myometrium and is further characterized by an altered local paracrine and immune microenvironment

J. Brosens and I. Brosens 1998

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Adenomyosis - Characteristics

Comparable with low grade malignancies:

- potential local invasion
- angiogenesis
- cellular proliferation

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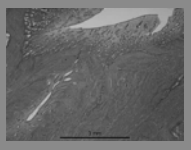
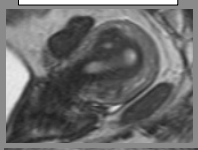
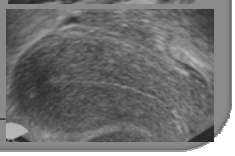
Adenomyosis - Incidence

Rear clinical diagnosis
common histological diagnosis



Clinical entitiy
TVS and MRI





Incidence: 5- 70 %
retrospective studies

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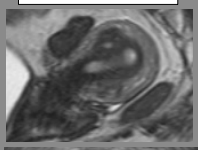
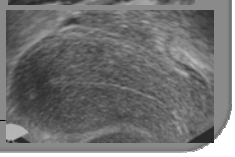
Adenomyosis - Incidence

Clinical entitiy
TVS and MRI

subfertility
dysmenorrhea
menorraghia

Incidence: 28/56 50%





Brosens J et al.1995 Lancet,346

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T2-weighed NMR imaging in adenomyosis

NMR visualises the distortion of the myometrial architecture

Accurate soft tissue contrast

Non invasive

Differentiates focal and diffuse adenomyosis

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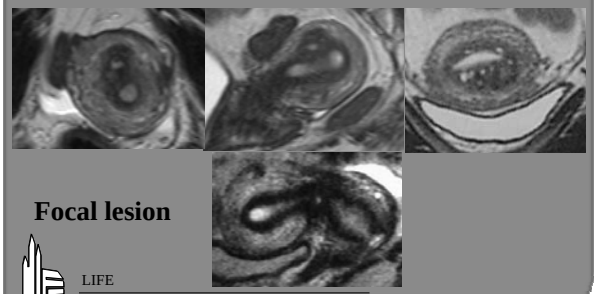
NMR is an accurate technique to detect uterine adenomyosis



Focal lesion

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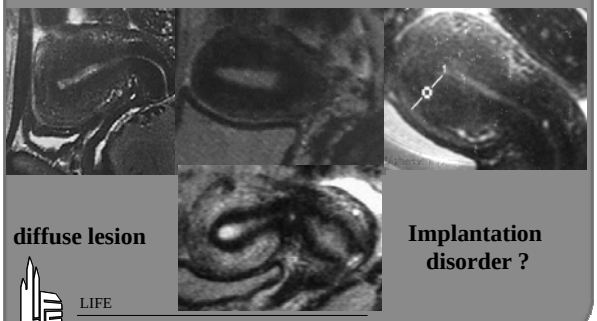
NMR is an accurate technique to detect uterine adenomyosis



diffuse lesion

Implantation disorder ?

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Junctional Zone Myometrium

Functional important entity in reproduction

- **Ontogenetically related to endometrium**
- **Cyclic changes in SSH receptors**
- **Role in gamete transport and implantation**

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Junctional Zone Myometrium Important role in Reproduction

Functional important entity in reproduction

- **Early changes from time of implantation**
- **Decidualisation and trophoblast invasion**
- **Defective transformation of JZ spiral arteries in spectrum of pregnancy complications**

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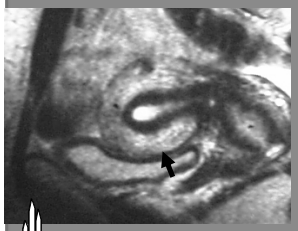
THE OUTER MYOMETRIUM

Less important role in reproduction



Muscle contractions during delivery

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ADENOMYOSIS AND REPRODUCTION

Relation ?

Disturbed JZ activity *(Kunz et al, Brosens J et al)*

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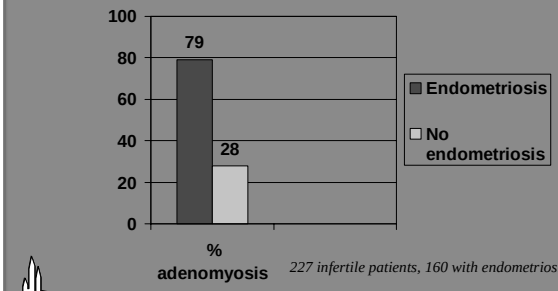
Infertility:Adenomyosis and endometriosis (MRI)



227 infertile patients, 160 with endometriosis

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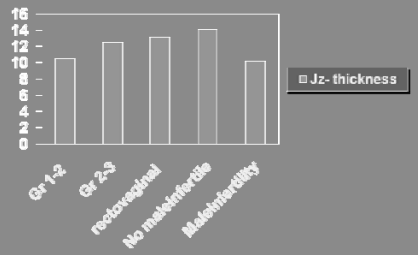
Kunz, Human Reprod 2005

Endometriosis: Jz-zone thickness and degree of endometriosis, infertility



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Kunz, Human Reprod 2005

ADENOMYOSIS AND REPRODUCTION

Relation ?

Disturbed JZ activity *(Kunz et al, Brosens J et al)*

Experimental data baboons:
necropsy *(n=37)* with adenomyosis
all life long infertility
43% also endometriosis
(Barrier Br et al Fertil Steril 2004)

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ADENOMYOSIS AND REPRODUCTION

Relation ?

Adenomyosis negative impact on pregnancy rate after colorectal resection endometriosis.
(Darai et al Fertil Steril 2005)

Occurence of pregnancies after reductive treatment

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NMR JZ thickness predicts IVF failure

Piver P. et al, ESHRE, Berlin 27 – 30 June 2004

Predictive value for implantation failure is 97 %

Odd ratio per patient is 39

Odd ratio per transfer is 39

Conclusion :
NMR should be offered at every patient after 2 ivf failures ?

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Adenomyosis and previous surgery

Simultaneous disruption of endometrium and myometrium:

- Caesarian sectio
- myomectomy
- spontaneous abortion (OR 1.7- 4.35)
- D&C (OR 2.2 – 15.5)
- endometrial ablation

(Parazzini et al,1997; Curtis et al; 2002,Levgur et al, 2000)

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Adenomyosis and previous surgery

Adenomyosis pos	Adenomyosis neg		
		Odds ratio	95% Conf.int
48,8 %	41,0%	1.37	1.05-1.79

Panganamamula Obst.& Gynec.2004, 104

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Adenomyosis and previous surgery

	Odds ratio	95% Conf.int.
Gravidity	1.09	1.01-1.17
Uterine leyomyoma >2cm	0.33	0.25-0.44
Any previous surgery	1.39	1.05 – 1.84

Panganamamula Obst.& Gynec.2004, 104

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ADENOMYOSIS AND TREATMENT

Hormonal: GnRha, anti-oestrogens
Danazol, MPA, LN-IUD
anti-aromatase ?

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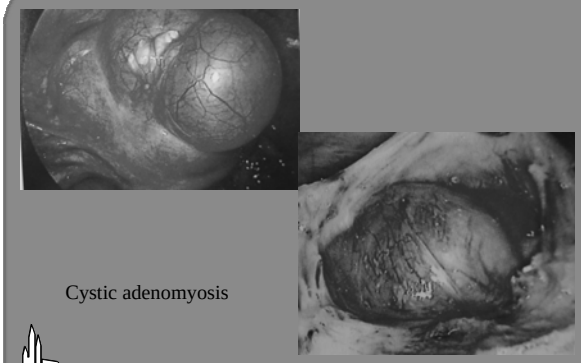
ADENOMYOSIS AND TREATMENT

Surgery: **hysterectomy (subtotal)**
endometrial ablation/resection
excision (laparoscopy/-tomy)
hysteroscopic excision
laparoscopic myometrial coagulation
embolisation; MRI focused US
photodynamic therapy



Cystic adenomyosis

From M Hessling , 2005 Endo-Press,Tuttlingen

ADENOMYOSIS AND TREATMENT

Surgery – *clinical aspects*:

- darker color, less firm consistency
- no well defined cleavage plane
- dichotomous disease
  - -disruption JZ
  - -secund.infiltr. myometrium
- more difficult wound apposition

ADENOMYOSIS AND TREATMENT

Reductive surgery: difference with myomectomy

no obvious plane of cleavage

adenomyosis infiltrates normal myometrium

⇩

excision of diseased area substracts myometrial mass from the total uterine volume

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ADENOMYOSIS AND TREATMENT

Reduction in myometrial capacity:

↑ abortion
premature labour
uterine rupture
incidence C-section

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Fertility and cytoreductive surgery for adenomyosis

Wang C-J et al. (Fertil Steril 2006)	2	>4;9y	Danazol	C-section
Wang P-H et al.(Fertil Steril, 2000)	3	>5y	GnRha	C-section
Kenny PJ et al. (Fertil Steril,2000)	8		GnRha	7 pregn
Ozaki et al (Int J Fert, 1999)	1	>4y	GnRha	C-section
Huang et al (1998)	1	8y	GnRha	C-section
Lin J et al. (Chin Med J, 2000)	1	5y	GnRha	C-section

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Fertility and cytoreductive surgery for adenomyosis

Yap C (Fertil Steril, 1997)	52	23.1%	3 ruptures
Fedele et al. (Hum Reprod ,1993, 8)	18	72,2%	
Nezhat et al. (Obst&gynec, 2001,97)	9	56%	
Liu X et al,(XueBao,1998,20)	26	71%	(focal adeno)
		21,4%	(diffuse adeno)
Wood (Hum Rreprod Upd,1998,4)	16	56%	

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Adenomyosis and concomitant disease

	Endo	Myoma
Fedele et al. Hum Reprod ,1993, 8	21.4%	25.0%
Liu JAAGL, 2004,11	24.6%	
Nezhat Obst Gyn,2001, 97	56%	22%
Takeuchi J Min Inv Gynec. 2006,13	78%	

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ADENOMYOSIS and REPRODUCTION STAGING

"The sine qua non in designing a staging system is a proven progression through subsequent steps of increasing severity that are causally linked with the outcome of interest".
Canis (1995)

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ADENOMYOSIS and REPRODUCTION STAGING

Many unanswered questions:
- is adenomyosis a progressive disease?
- clinical correlation between extent and severity?
- is simple JZ hypertrophy really adenomyosis?
- which is prognostic value of staging system?
- choice of therapy influenced by staging?

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ADENOMYOSIS and REPRODUCTION Proposal STAGING

Stage 0	solitary junctional zone hyperplasia without infiltration myometrium
Stage 1	a: focal thickening of junctional zone < 20 mm
	b: focal thickening of junctional zone >20 mm
Stage 2	a: diffuse adenomyosis with less than 1/3 of myometrium involved
	b: diffuse adenomyosis with more than 1/3 of myometrium involved
Stage 3	uterine adenomyosis and extra-uterine localization (RV, bladder)

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ADENOMYOSIS and REPRODUCTION CONCLUSIONS

Limited number available date

TVS/MRI made from adenomyosis a clinical entity

Decreased fertility through involvement of junctional zone

Cyto reductive treatment results in amelioration of fertility

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ADENOMYOSIS and REPRODUCTION
CONCLUSIONS

Surgery : higher risks for impaired pregnancy outcome

Staging is mandatory to standardize treatment outcome

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Uterine Artery Embolization
and
Adenomyosis

James B. Spies M.D.
Professor of Radiology
Georgetown University School of Medicine
Washington, DC

Overview

- Background
- Classifying patterns of adenomyosis
- Uterine embolization technique
- UAE and adenomyosis
  - Short and mid-term outcomes
- Current recommendations

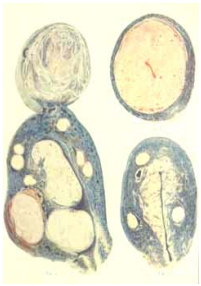
Adenomyosis

- First described in 1860 by Rokitansky
- Defined as heterotopic endometrial tissue within the myometrium.
- Incidence ranges from 5 to 70% of hysterectomy specimens.
- Present in 15% of patients with fibroids.
- Most common in women in their 40's and 50's.

Adenomyosis

Pathologic findings

- Presence of endometrial glands and stroma deep within myometrium
- When diffuse, causes uterine enlargement up to 12 weeks size or larger
- Cystic spaces may develop
- Mass-like adenomyomas may form
- Primarily proliferative pattern histologically



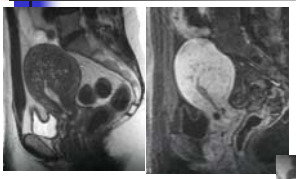
Adenomyosis

MRI Findings

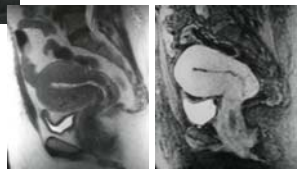
- Diffuse or focal thickening of the junctional zone
  - Greater than 12 mm
- May appear mass-like
- Variable enhancement
- Mild distortion of the endometrial canal
- On T2W images, may have foci of increased signal

Patterns of Disease

Diffuse Adenomyosis



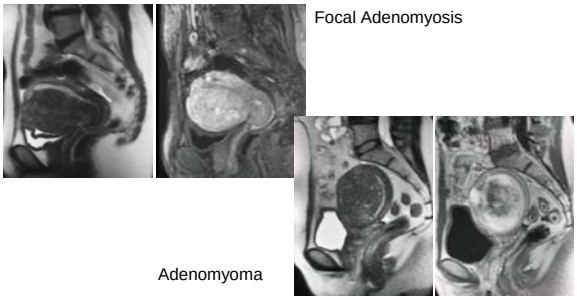
Diffuse Severe



Diffuse Mild

Patterns of Disease

Focal Adenomyosis



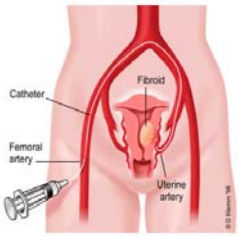
Focal Adenomyosis

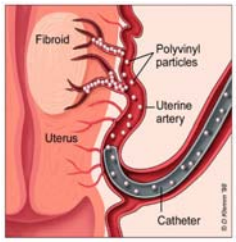
Adenomyoma

Measuring outcome from treatment

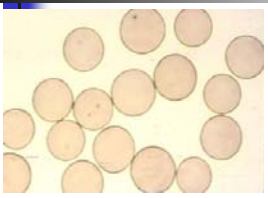
- Limitations
  - What type of disease is included?
    - Diffuse or focal? With or without fibroids?
  - How is the extent of disease defined?
    - Thickness of junctional zone?
    - Average, greatest or least depth?
  - How is imaging outcome measured?
    - Thickness of JZ, perfusion?
  - How is the technique of therapy defined?
    - What is appropriate endpoint of embolization?

UAE Technique

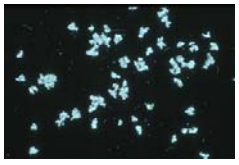




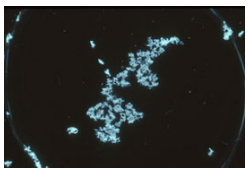
Embospheres® Microspheres



Polyvinyl Alcohol Particles



500-700 micron PVA Dry



Same sample with saline

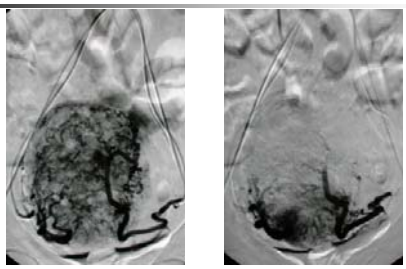
Technique

Digital Roadmapping

Technique

Coaxial micro-catheter

Pre and Post Embolization



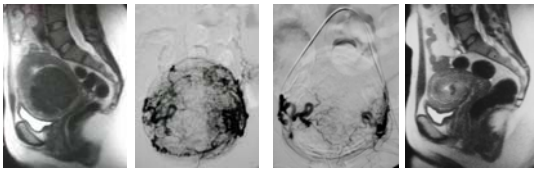
Free-flow Embolization with preservation of uterine artery flow
"5 cardiac beat residual flow"

Adenomyosis and Fibroids

- First application of uterine embolization was is combined disease.
- Most experience to date suggests that when fibroids dominant or co-dominant compared to adenomyosis, results similar to fibroids alone.
- Some cases of failure to improve attributed to adenomyosis

Adenomyosis and Fibroids

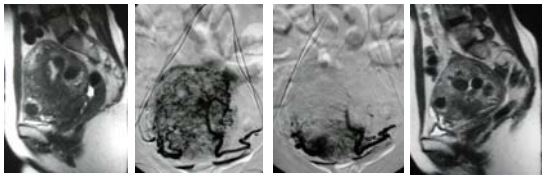
Minor adenomyosis, dominant fibroid



Pre MRI | Pre Angio | Post Angio | 3 mo MRI

Adenomyosis and Fibroids

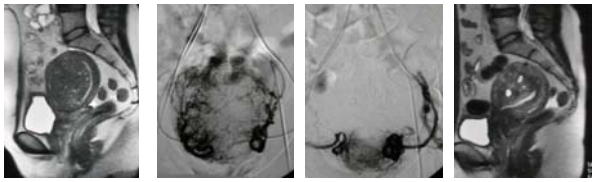
Co-dominant adenomyosis and fibroids



Pre MRI | Pre Angio | Post Angio | 3 mo MRI

Adenomyosis and Fibroids

Adenomyoma



Pre MRI | Pre Angio | Post Angio | 3 mo MRI

Adenomyosis and Fibroids

Outcome from embolization

- Albany Experience*
  - 15 patients:
    - 9 with both fibroids and adenomyosis
    - 5 diffuse adenomyosis
    - 1 focal adenomyosis
  - Regression in uterine volume, focal adenomyoma volume, and thickness of the junctional zone
  - 90% of patients had improvement in menstrual bleeding

*Siskin G et al. Uterine artery embolization for the treatment of adenomyosis: Clinical response and evaluation with MR imaging. AJR 2001;177:297-302.

Adenomyosis and Fibroids

Outcome from embolization

- Georgetown Experience*
  - 30 patients
    - 27 with both fibroids and adenomyosis, 3 pure adenomyosis
  - Imaging at 3 months
    - Junctional zone thinned by mean of 33%
    - Mean uterine volume decreased 40%
    - Junctional zone/myometrial ratio not changed
    - Regions of devascularization in 12
  - Clinical outcome:
    - 25 of 30 (83%) improved at 3 months
    - 20 of 20 (100%) improved at 12 months
    - Hysterectomy in 3 pts by 1 year- failure or recurrence

•Jha R, et al. Adenomyosis: MRI of the uterus treated with uterine artery embolization. AJR 2003;181:851-856.

Uterine Embolization

Pure or dominant adenomyosis

- Mechanism unclear
  - Adenomyosis is an infiltrative process, not a defined separate mass like a fibroid.
    - Angiographic endpoint less clear
    - Temporary occlusion of central uterine vessels, causing ischemia of central myometrium and adenomyosis.
  - Is the goal of embolization infarction of the adenomyosis or merely partial devascularization?

Imaging findings

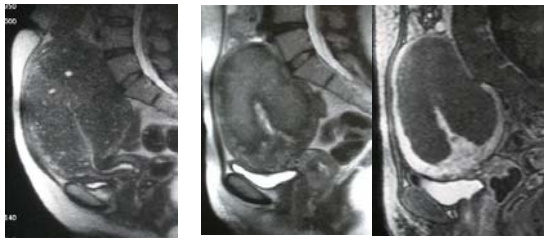
Embolization for pure adenomyosis

- May show partial or complete infarction of adenomyosis
  - Uncertain if infarction required for long-term relief.
  - Symptoms usually improve regardless
- Junctional zone thins, but JZ-myometrial ratio does not change
- Fourteen of 19 (74%) had at least some areas of devascularization.
- Pattern of disease did not change in any patient.

*Kitamura y, et al. MRI of Adenomosis: Changes with uterine artery embolization. AJR 2006;186:855-864.

Uterine embolization

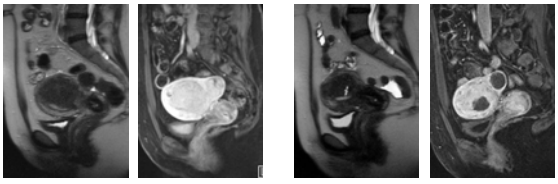
Infarction of adenomyosis



Pre UAE Non-Contrast | 3 mo Non-contrast | 3 mo Contrast

Uterine embolization

Partial infarction of adenomyosis



Without contrast | With contrast | Without contrast | With contrast

Pre-embolization | Post-embolization

UAE for pure Adenomyosis

Clinical Outcome

- Georgetown Experience*
  - 19 patients pure or dominant adenomyosis
  - 18 completed clinical questionnaires at 3 months
    - 16 (88.9%) improved.
  - 11 completed clinical questionnaires at 1 year
    - 10 (91%) with continued improvement.
- No clear relationship between pattern of disease, devascularization and clinical response.

*Kitamura y, et al. MRI of Adenomosis: Changes with uterine artery embolization. AJR 2006;186:855-864.

UAE for pure Adenomyosis

Long-term Clinical Outcome

- Korean Experience*
  - Long-term follow-up (N=66)
    - All with adenomyosis alone, aggressive embolization technique.
  - Of 66, 12 lost to follow-up- analysis of 54 patients
    - Min. follow-up 3 years- mean 4.9 years (range 3.5-5.8).
  - Of 54, 4 immediate failures, 19 relapses
  - 31 (57.4%) had has long-term success.
  - Imaging Outcome
    - 65% complete necrosis in focal adenomyosis
    - 69% partial infarction in diffuse adenomyosis

Kim MD et al. Long-term results of uterine artery embolization for symptomatic adenomyosis. AJR 2007;188:176-181.

UAE for pure Adenomyosis

Clinical Outcome

- Paris Experience*
  - 18 patients pure adenomyosis
    - Used limited embolization technique
  - Short term
    - At 6 months 15 of 16 (94%) improved menorrhagia.
    - 44% of patients required additional treatment during follow-up
      - 5 (28%) underwent hysterectomy

•Pelage JP et al. Mid-term results of uterine artery embolization for symptomatic adenomyomsis: Initial experience.Radiology 2005;234:948-953.

UAE for pure Adenomyosis

Discussion

- Very limited data currently available
- Uncertain if infarction of adenomyosis is key to avoid recurrence.
- Still unclear if pattern of disease predicts success
- Variable rates of recurrence
  - May reflect different embolization techniques
  - May reflect natural variability due to small sample size.

UAE for pure Adenomyosis

Discussion

- Only 2 studies with results beyond 1 year.
  - Long-term data conflicting
  - Recurrence between 44% at 2 years and 43% at 3 years
- Further study clearly needed before broad use.
  - May require multi-center study to accrue sufficient patients.

Current Consensus

- Fibroids and adenomyosis
  - UAE effective particularly if fibroids dominant.
- Adenomyosis withour fibroids
  - Focal adenomyosis/adenomyoma
    - UAE likely effective
  - Diffuse adenomyosis
    - UAE uncertain effectiveness long-term
    - Anticipate recurrence of 40% at 2-3 yrs.

Possibilities of MRI focused ultrasound in the treatment of adenomyosis

J. Rabinovici (IL)

Lecture slide outline and syllabus:

Current treatment options for adenomyosis include:
- Surgery.
- Medical therapy.
- UAE ?

Complications and side-effects of current treatment regimen:
- Surgery.
- Medical therapy.
- UAE.

Biggest problem in adenomyosis treatment: Diagnosis!

There is a need for a non-invasive, diagnosis-based adenomyosis therapy.

MRgFUS for uterine fibroids:
- Principles of MR-guided high focus ultrasound surgery (MRgFUS)
- MRgFUS enables heat ablation of multiple types of tumors/diseases
- To date > 2500 treatments world-wide for uterine fibroids.
- Diagnostic MRI part of preparation for MRgFUS.
- Detection of solitary adenomyosis and concomitant leiomyoma and adenomyosis.

Diagnosis/treatment chart for MRgFUS for uterine fibroids.

Can/should adenomyosis be treated by MRgFUS?
- Focal vs. diffuse adenomyosis.
- Heat ablation destroys normal endometrium.
- Heat therapy has been used for deep adenomyosis.

In some early cases of combined fibroid/adenomyosis MRgFUS was successful.

First pregnancy after MRgFUS was in a patient with focal adenomyosis.

Prospective study to examine the efficacy of MRgFUS in adenomyosis.
- Presentation of the study protocol.
- Presentation of the early clinical results of the study.

ADENOMYOSIS A REPRODUCTIVE DISORDER

ESHRE Campus 2007

Leuven, April 19-20, 2007

ADENOMYOSIS:
THE PLACE OF MEDICAL TREATMENT

P.G. Crosignani (Milano)

MEDICAL TREATMENT OF ADENOMYOSIS

There is no "evidence-based medicine" to guide us in the medical treatment of adenomyosis

(Rabinovici and Stewart, Best Prac.Res., 20, 617-636, 2006)

ADENOMYOSIS: THE CLINICAL CONDITION

- Often asymptomatic
- Prevalence: over 40 years
- Symptoms:
  - dysmenorrhea
  - menorrhagia
- Adenomyosis is frequently associated with:
  - endometriosis
  - uterine leiomyomas

(Novak's Gynecology, Lippincott Williams & Wilkins, 13th edition, Philadelphia, 2002)

TREATMENT OF SYMPTOMATIC ADENOMYOSIS

- Definitive cure: hysterectomy/ovariectomy
- Suppression of symptoms:
  - non-steroidal antiinflammatory drugs
  - OCs
  - progestogen

(Novak's Gynecology, Lippincott Williams & Wilkins, 13th edition, Philadelphia, 2002)

MECHANISM OF DYSMENORRHEA

- Pain arises from the release of prostaglandins

  (Lundström and Gréen, Am. J. Obstet. Gynecol., 130, 640-646, 1978)
- Severity correlates with the extent of disease

  (Kim et al., Clin. Radiol., 59, 520-526, 2004)

MECHANISMS OF HEAVY MENSTRUAL BLEEDING I

- ↑ endometrial surface
- Altered PGE/PGF2α balance
- Hampered myometrial contractility
- ↑ vascularization

(The ESHRE Capri Workshop Group, Endometrial bleeding, HRU, 2007)

MECHANISMS OF HEAVY MENSTRUAL BLEEDING II

↑ Endometrial endothelial cell proliferation

↓ Proliferation of the vascular smooth muscle around spiral artery

↓ Endothelin (↑ fragility)

(The ESHRE Capri Workshop Group, Endometrial bleeding, 2007)

MEDICAL TREATMENTS EMPIRICALLY USED IN PATIENTS WITH ADENOMYOSIS

- GnRH agonists
- Local progestogens
- Aromatase inhibitors

GnRH AGONISTS (1991-1999 – case reports)

1. Grow DR & Filer RB, Obstet. Gynecol, 78, 538-539, 1991.
2. Nelson JR & Corson SL, Fertil. Steril., 59, 441-443, 1993.
3. Hirata JD et al. Fertil. Steril., 59, 444-445, 1993.
4. Silva PD et al. Fertil. Steril., 61, 171-172, 1994.
5. Huang FJ et al. J. Reprod. Med., 44, 741-744, 1999.

- Reduce the lesions
- Improve symptoms
- Severe side effects

LNG-INTRAUTERINE SYSTEM 1997-2005

Fedele L, Bianchi S, Raffaelli R et al. Treatment of adenomyosis-associated menorrhagia with a LNG-IUS. Fertil. Steril., 68, 426-429, 1997.

Fong YF & Singh K. Medical treatment of a grossly enlarged adenomyotic uterus with the LNG-IUS. Contraception, 60, 173-175, 1999.

He SM, Wei MX, Han YH et al. Effect of LNG-IUS in the treatment of adenomyomas. Zhonghua Fu Chan Ke Za Zhi, 40, 536-538, 2005.

LOCAL PROGESTOGEN
(strong uterine concentrations, limited general effect)

LEVONORGESTREL INTRAUTERINE SYSTEM

Induces endometrial gland atrophy and extensive decidual transformation of the stroma

(Critchley et al., HR, 13, 1218-1224, 1998)

LNG-IUS IN PATIENTS WITH MENORRHAGIA DUE TO ADENOMYOSIS

- Patients: 25
- Age: 38-45 yrs
- Levonorgestrel: 20 µg/day

(Fedele et al., Fertil. Steril. 68, 426-429, 1997)

EFFECTIVENESS OF THE LNG-SYSTEM IN PATIENTS WITH MENORRHAGIA DUE TO ADENOMYOSIS

	Before treatment (n=25)	6 months (n=23)	12 months (n=23)
Regular menstrual pattern	0	13	16
Pictorial blood loss	**211±61**	**43±16***	**44±18***
Uterine volume (mL)	348±171	320±152*	314±139*
Endometrial thickness (mm)	**8.8±1.1**	**3.7±0.6***	**3.1±0.5***
Hemoglobin (g/dL)	10.1±1.3	12.3±1.0*	12.5±1.2*

*P<0.01 versus baseline

(Fedele et al., Fertl. Steril. 68, 426-429, 1997)

LNG-IUS: CHANGES IN ANGIOGENIC FACTORS AND FIBRINOLYTIC INHIBITORS

↓ Vascular endothelial growth factor

↑ Fibrinolitic inhibitors (PAI – 1/2)

(Laoag-Fernandez et al., HR, 18, 694-699, 2003; Koh and Singh, Thromb. Haemost, 5, 133-138, 2007)

DANAZOL INTRAUTERINE SYSTEM (300-400 mg Danazol)

- 14 patients
- Inserted for several months
- No systemic side effects
- Normal ovulatory cycles
- Complete remission of dysmenorrhea in 9 patients

(Igarashi et al., FS, 74, 412-413, 2000)

PROGESTOGEN-IUS: FAILURES

- Persistent irregular bleeding
- Spontaneous expulsion

THE FUTURE

- New drugs
- New strategies

AROMATASE INHIBITOR + GnRH AGONIST IN A CASE OF SEVERE SYMPTOMATIC ADENOMYOSIS

- Anastrazole 1-2 mg po/daily x four months
- GnRH agonist one monthly injection

Results:
- uterine volume reduced 60%
- good control of symptoms

(Kimura et al., FS, 2007)

FEATURES COMMON TO BOTH DISEASES: ADENOMYOSIS AND ENDOMETRIOSIS

- Prevalence: reproductive age
- Association: 70-80% of patients with adenomyosis have endometriosis
- Permanent cure: ovariectomy
- Regression of lesions and control of symptoms:
  - GnRH agonists
  - progestogens

(Jo Kitawaki, Best Practice Res., 20, 493,2006)

TREATMENT OF ENDOMETRIOSIS HAS BEEN CHANGED IN THE LAST 10 YEARS

In the past endometriosis was treated primarily by surgery.

- ❖ Invasive
- ❖ 20% non-responders
- ❖ High recurrence rate

(Crosignani et al., HRU, 12, 179-189, 2007)

ENDOMETRIOSIS: MEDICAL TREATMENT OF PELVIC PAIN

- ❖ GnRH agonists (side effects)
- ❖ ↓ estrogen production
- ❖ Progestogen

PROGESTOGENS HAVE BEEN USED WORLDWIDE TO TREAT ENDOMETRIOSIS FOR MORE THAN 40 YEARS (Schweppe, 2001)

- ❖ Suppression of ovarian activity
- ❖ Decidualization and atrophy of endometriotic lesions (ESHRE Capri Workshop Group, 2001)
- ❖ In addition, progestogens inhibit angiogenesis (Blei et al., 1993)

PROGESTOGEN REDUCES THE PAIN SYMPTOMS IN 90% OF PATIENTS WITH ENDOMETRIOSIS

Progestogens alone or in combination (OC) may be an appropriate alternative for the medical management of endometriosis, they are well tolerated, are inexpensive and can be used for years.

(ESHRE Capri Workshop Group, 2001; Vercellini et al., 2003)

EFFICACY OF CURRENT CONTRACEPTIVE PREPARATIONS

(Vercellini et al., HRU, 9, 387-396, 2003)

Drug	Schedule	Pain relief %	Source
OC (*)	Cyclic administration for 6 months	74	Vercellini et al. (1993) FS 60: 75-79
OC (**)	Cyclic administration for 12 months	70	Parazzini et al. (2000) EJOG Rep Biol 88: 11-14
MPA	150 mg/3 months i.m. for 12 months	90	Vercellini et al. (1996) AJOG 175: 396 - 401

(*) Desogestrel 0.15 mg + ethinyl estradiol 0.02 mg
(**) Gestodene 0.75 mg + ethinyl estradiol 0.03 mg

A GnRH AGONIST OR A LOW-DOSE OC FOR PELVIC PAIN ASSOCIATED WITH ENDOMETRIOSIS

(P. Vercellini, L. Trespidi, A. Colombo, N. Vendola, M. Marchini, P.G. Crosignani FS, 60, 75-79, 1993)

- 57 patients with pelvic pain
  - 29 Goserelin
  - 28 OC (EE 20 μg + DSG 150 μg)
- Changes in severity of baseline symptoms

SYMPTOM SCORES (VERBAL RATING)

SYMPTOM AND TREATMENT	*BASELINE*	*END OF TREATMENT*	*END OF FOLLOW-UP*
DYSMENORRHEA			
Goserelin (26)	5.1 ± 1.6	-	4.8 ± 1.4
OC (24)	5.0 ± 1.1	2.4 ± 1.7 (*)	4.7 ± 1.4
DYSPAREUNIA			
Goserelin (22)	1.7 ± 0.9	1.1 ± 1.0 (*)	1.5 ± 1.0
OC (21)	1.8 ± 1.1	1.2 ± 0.7 (*)	1.6 ± 0.9
NON MENSTRUAL PAIN			
Goserelin (26)	3.0 ± 1.9	1.2 ± 1.3 (*)	2.6 ± 1.9
OC (24)	2.9 ± 2.1	1.6 ± 1.9 (*)	2.6 ± 2.0

(Vercellini et al., FS, 60, 75-79, 1993)

(*) Vs. baseline, P < 0.01

CYCLIC OR CONTINUOUS OC

Patients: Fifty women after surgery for endometriosis, with recurrent dysmenorrhea despite cyclic OC

Intervention: Continuous OC (estradiol 0.02 mg + DSG 0.15 mg) for two years

Changes in dysmenorrhea: 50% reduction in 6 months

(Vercellini et al., FS, 80, 560-563, 2003)

Randomized clinical trial of a LNG-IUS and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis

Carlos a. Petta et al., HR, 20, 1993-1998, 2005

FLOW CHARD FOR THE STUDY

Randomized: 83

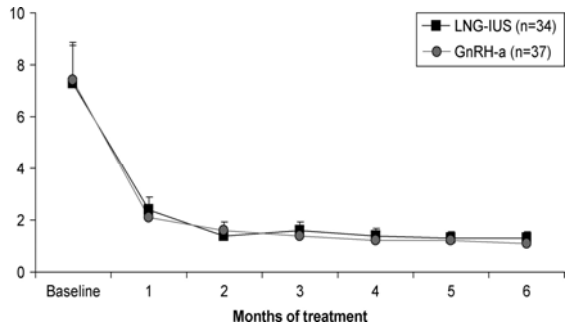
Assigned to receive LNG-IUS: 40
Received LNG-IUS: 39
Did not receive: 1 pregnancy between randomization and study initiation

Assigned to receive GnRH analogue: 43
Received GnRH analogue: 43

Included in primary analysis: 34
Excluded: 5 for not fully completing the pain score diary

Included in primary analysis: 37
Excluded: 6 for not fully completing the pain score diary

CHANGES IN THE PAIN SCORES BETWEEN THE TWO GROUPS



EFFECT OF THE PILL ON MENSTRUAL VOLUME (OBJECTIVE MEASUREMENT OF HEMATIN)

Study	Type	Treatment	Reduction
Nilsson and Sölvel, 1967	random, double-blind (59 ♀)	4 pills EE: 50 µg	69%
Fraser and McCarron, 1991	random. (45 ♀)	EE: 30 µg	44%
Larsson et al., 1992	non-comparative (5 ♀)	EE: 30 µg	44%

Longer cycles are more effective

(Thomas S.L. et al., Lancet, 355, 922-924, 2000)

THE EFFECT OF LEVONORGESTREL-RELEASING INTRAUTERINE SYSTEM USE ON MENSTRUAL BLOOD LOSS IN WOMEN WITH MENORRHAGIA

- 41 patients
- Menorrhagia
  - reduced in 89% of women by 3 months
  - disappeared in all by 6 months
- Amenorrhea: in 39% of the patients after 6 months

(Koh and Singh, J Thromb Haemost, 5, 133-138, 2007)

ADENOMYOSIS: THE PLACE OF MEDICAL TREATMENT

CONCLUSION 1

- Adenomyosis is hard to study because many patients are asymptomatic and diagnosis is still not easy
- Hysterectomy is a simple solution but is invasive and not acceptable to many patients

ADENOMYOSIS: THE PLACE OF MEDICAL TREATMENT

CONCLUSION 2

- There are medical and surgical treatments strategies
- All these methods need to be evaluated by specific randomized controlled trials