

PRE-CONGRESS COURSE 9

**The impact of reproductive
surgery on repeated
implantation failure.**

Special Interest Group Reproductive Surgery
London - UK, 7 July 2013





The impact of reproductive surgery on repeated implantation failure

**London, United Kingdom
7 July 2013**

**Organised by
The ESHRE Special Interest Group Reproductive Surgery**

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Course coordinators

Vasilios Tanos (Cyprus) and Tin-Chiu Li (United Kingdom)

Course description

This advanced course aims to review the aetiology of implantation failure dealing with congenital and acquired pathology as well as the impact of reproductive surgery in diagnosis and treatment. Daily practice problems and dilemmas about implantation failure and how reproductive surgery can solve them will be extensively analysed and discussed. The importance of imaging techniques and endoscopic procedures as diagnostic and treatment tools, improving implantation will be also reported. Presentations of surgical procedures and evidence based data how implantation and endometrial receptivity can be increased will be demonstrated.

Target audience

Gynaecologists, Embryologists, Radiologists

Scientific programme

09:00 - 09:30	Overview of recurrent implantation failure following IVF treatment <i>Zi-Jiang Chen - China</i>
09:30 - 09:45	Discussion
09:45 - 10:15	The role of imaging techniques in the investigation of the pathology affecting implantation TVU 2D / 3D, Hydrosography, MRI <i>Tarek El-Toukhy - United Kingdom</i>
10:15 - 10:30	Discussion
10:30 - 11:00	Coffee break
11:00 - 11:30	New insights of subtle congenital uterine malformation on implantation <i>Marco Gergolet - Italy</i>
11:30 - 11:45	Discussion
11:45 - 12:15	Overview on the uterine congenital anomalies and their impact on implantation failure <i>Gregoris Grimbizis - Greece</i>
12:15 - 12:30	Discussion
12:30 - 13:30	Lunch
13:30 - 14:00	Intramural fibroids and implantation failure <i>Mostafa Metwally - United Kingdom</i>
14:00 - 14:15	Discussion
14:15 - 14:45	Adenomyosis and implantation failure: the oocyte or the uterus? <i>Stephan Gordts - Belgium</i>
14:45 - 15:00	Discussion
15:00 - 15:30	Coffee break
15:30 - 16:00	Surgery of hydrosalpinges and implantation rate (salpigoectomy/salpigostomy/ligation/essure) <i>Vasilios Tanos - Cyprus</i>
16:00 - 16:15	Discussion
16:15 - 16:45	The importance of minor endometrial pathology and endometrial scratching in repeated implantation failure. When a treatment is indicated <i>Tin-Chiu Li - United Kingdom</i>
16:45 - 17:00	Discussion

ESHRE 2013, London

Overview of recurrent implantation failure following IVF treatment

Zi-Jiang Chen

Shandong Provincial Hospital affiliated to Shandong University
Renji Hospital, Shanghai Jiao Tong University School of Medicine

Outline

- RIF definition
- RIF etiology
- Management of RIF

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- Management of RIF

RIF definition

- The definition is controversial
- 2005 ESHRE PGD Consortium defines it as:
“>3 embryo transfers with high quality embryos or the transfer of ≥ 10 embryos in multiple transfers”
- The definition has limitations (*John Rinehart, 2007*)

Limitations of RIF definition

- Time of the first HCG determination (the earlier of the first HCG determination, the lower the failed implantation rate)
- HCG threshold
- The day of embryo transfer (D3 embryo transfer has high implantation failure than blastocyst transfer)
- Age (this will affect implantation rate)

So, John Rinehart defines RIF as “the transfer of ≥ 8 , 8-cell stage embryos or ≥ 5 blastocyst embryos”

John Rinehart. J Assist Reprod Genet (2007)

Outline

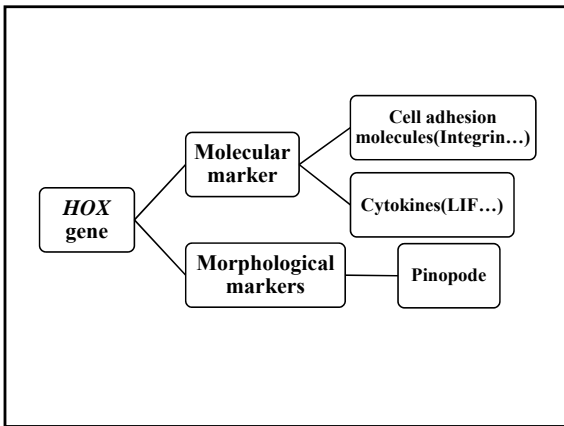
- RIF definition
- RIF etiology
- management of RIF

The etiology of RIF

- Embryos factor (chromosomal abnormality, low quality)
- Endometrium receptivity (endometriosis, hydrosalpinx, leiomyoma, endometrial polyp, PCOS, endometritis)
- Immune factor (Th1 ↓)

Endometrium receptivity

- Window of implantation (menstrual cycle days 20~24)
- *HOX* gene regulates a number of molecular and morphological markers



Endometrium receptivity-*HOX* gene

- Essential for endometrial growth, differentiation by mediating sex steroids
- Regulate target genes important for endometrium receptivity and implantation
- Regulate molecular and morphological markers

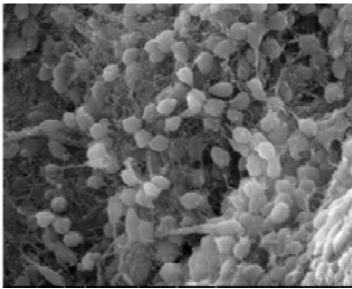
Molecular marker- Integrins

- A family of transmembrane glycoproteins
- $\alpha_1\beta_1$, $\alpha_4\beta_1$, $\alpha_v\beta_3$ are coexpressed on window of implantation
- $\alpha_v\beta_3$ is a potential receptor for embryonic attachment

Molecular marker- LIF

- Leukemia Inhibitory Factor (LIF) is a glycoprotein of the IL-6 family
- Has activities on proliferation, differentiation and cell survival
- Essential for blastocyst development and implantation

Morphological marker-pinopode



Morphological marker-pinopode

- Apical cellular protrusions, visible on menstrual cycle days 20 ~ 21 by scanning electron microscopy
- Not limited to the window of implantation, and the number is equivalent in fertile and infertile
- As a marker of endometrium receptivity remains controversial

Implantation failure-gynecological diseases

- Endometriosis
- Hydrosalpinx
- Leiomyoma
- Endometrial polyp
- PCOS
- Endometritis

Endometriosis

- Prevalent in 6~10% reproductive female, 25~50% women with infertility
- Infertility (altered folliculogenesis, impaired fertilization, defective implantation and poor oocyte quality)
- Women with endometriosis undergoing IVF have low implantation and pregnancy rates

(Kuivasaari P. Hum Reprod.2005)

Hydrosalpinx

Two meta-analysis show that, women with hydrosalpinx undergoing IVF have lower implantation, pregnancy, delivery rate and higher miscarriage rate compared to those do not have hydrosalpinx

Zeyneloglu HB. Fertil Steril. 1998
Camus E, Hum Reprod. 1999

Leiomyoma

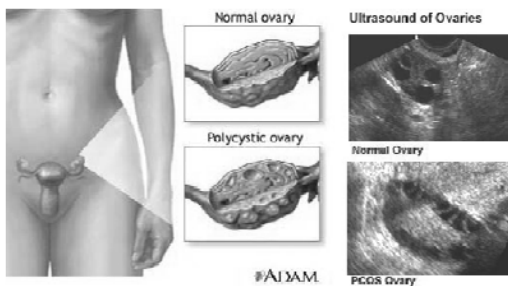
- Distort the uterine cavity
- Impair endometrium receptivity
- Women with leiomyoma have lower IVF pregnancy rate

Pritts EA. Obstet Gynecol Surv. 2001

Endometrial polyp

- Interference sperm transport
- Interference embryo implantation
- Aberrant expression of implantation markers

Polycystic ovarian syndrome

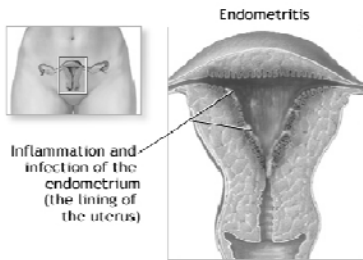


Polycystic ovarian syndrome

- Decrease endometrium receptivity markers
- Dysregulation of steroid expression and activity
- PCOS can further complicate implantation failure achieving pregnancy

Giudice LC. Best Pract Res Clin Endocrinol Metab 2006

Endometritis



Endometritis

- Pathogen
acute endometritis: bacteria
chronic endometritis: bacteria, viruses, parasites
- Women with chronic endometritis have lower clinical pregnancy and implantation rates

Romero R. Fertil Steril 2004

A summary of mechanisms of implantation failure in the diseases

Table 1 Proposed mechanisms of implantation failure in gynecological diseases.

Gynecological disease	Proposed mechanism of implantation failure
Endometriosis	Reduced $\alpha_5\beta_1$ integrin and LIF expressions in the window of implantation Lack of IL-11 and IL-11Ra expressions in secretory phase Absence of HOXA10 and HOXA11 peak in secretory phase Decreased EPIC2 expression Progesterone resistance Alteration in PR A to PR B ratio Decreased HOXA10 expression due to hypomethylation of its promoter region
Hydrosalpinx	Mechanical interference to apposition by bathing of endometrial lining with hydrosalpinx fluid intermittently Reduced $\alpha_5\beta_1$ integrin and LIF expressions Decreased HOXA10 expression
Leiomyoma	Distorting endometrial lining Obstructing the uterine cavity or cervical canal Decreased HOXA10 and BTEB1 expressions
Endometrial polyp	Mechanical interference with sperm transport and embryo implantation Low IGRBP1 and osteopontin levels in secretory phase Low progesterone receptor levels in secretory phase
PCOS	Decreased $\alpha_5\beta_1$ integrin, HOXA10 and IGFBP1 during secretory phase Overexpression of androgen receptors Failure to downregulate estrogen receptor- α in the window of implantation Overexpression of the steroid receptor coactivators SRC1 and SRC2

Hakan Cakmak . Human Reproduction Update, 2011

Outline

- RIF definition
- RIF etiology
- Management of RIF

1. Management of the embryos

- Blastocyst transfer
- Assisted hatching
- PGD/PGS
- Better embryo selection methods

2. Management of uterine receptivity

- Endometriosis
- Hydrosalpinx
- Leiomyoma
- Endometrial polyp
- PCOS
- Endometritis

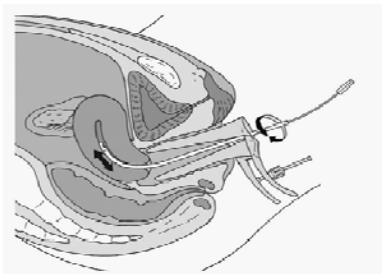
Methods to improve implantation in the diseases

Table II Available methods to improve implantation in gynecological diseases.

Gynecological disease	Therapy methods
Endometriosis	Excision or laser/diathermy ablation of endometriosis implants
Leiomyoma	Myomectomy
Hydrosalpinges	Salpingectomy Proximal tubal occlusion (if salpingectomy is technically difficult or not feasible)
Endometrial polyp	Hysteroscopic polypectomy
PCOS	Weight loss Insulin sensitizers
Adenomyosis	GnRH agonist treatment Surgical excision
Endometritis	Antibiotic therapy
Endometrial dysfunction due to ovarian stimulation	Cryopreservation of embryos Reduced ovarian stimulation

Hakan Cakmak . Human Reproduction Update, 2011

Unexplained RIF-endometrium scratch



Endometrium scratch mechanism

- Enhance endometrium receptivity
- Injury-induced inflammatory reaction
- Cause a pseudo-decidual reaction to enhance implantation
- Eliminate irregular hyperplasia of the endometrium

Endometrium scratch

- RCT
- 115 women with at least two implantation failures
- Endometrial biopsy in the luteal phase of cycle preceding IVF/ICSI

Karimzadeh. Aust NZJ Obstet Gynaecol. 2009

Endometrium scratch

	Biopsy Gp	Control Gp	p
Implantation rate	10.9%	3.4%	<0.05
Pregnancy rate	27.1%	8.9%	<0.05

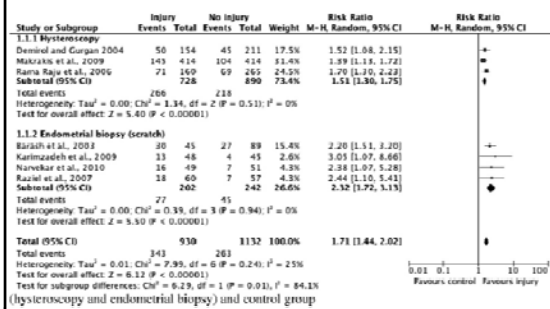
Karimzadeh. Aust NZJ Obstet Gynaecol. 2009

Endometrium scratch

- Meta analysis
- Polling 7 controlled studies (2062 participants)
- Clinical pregnant rate, live birth rate is higher in endometrium scratch group.

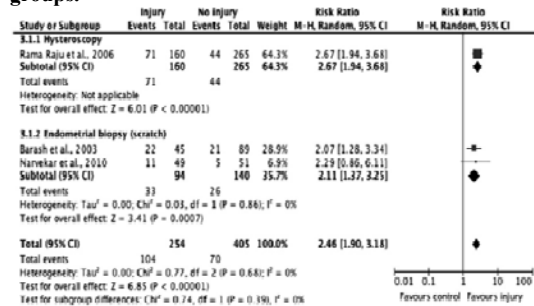
Neelam Potdar. Reproductive BioMedicine Online, 2012

Clinical pregnancy rate in the endometrial injury and control groups.



Neelam Potdar. Reproductive BioMedicine Online, 2012

Live birth rate in the endometrial injury and control groups.



Neelam Potdar. Reproductive BioMedicine Online, 2012

Sequential embryos transfer theory

- Embryos can induce better endometrium receptivity
- Insertion of the catheter in early stage embryo transfer may be a kind of endometrium scratch
- The early stage embryo transfer is co-cultured with endometrium, the environment is better for late stage embryo transfer

Sequential embryos transfer

- A retrospective matched case-control study
- 213 patients with RIF
 - D2/D3 group: 33
 - D3/D5 group: 66
 - D3 control group: 85
 - D5 control group: 29

Cong Fang. Reproductive BioMedicine Online .2013

Sequential embryos transfer

	D2/D3 group	D3 control group	P
Clinical pregnancies per retrieval cycle	16/33 (48.5)	19/85 (22.4)	0.006
Implantation per transferred embryo	17/91 (18.7)	21/227 (9.3)	0.018

Cong Fang. Reproductive BioMedicine Online .2013

Sequential embryos transfer

	D3/D5 group	D3 control group	P
Clinical pregnancies per retrieval cycle	29/66 (43.9)	19/85 (22.4)	0.004
Implantation per transferred embryo	37/160 (23.1)	21/227 (9.3)	<0.001

Cong Fang. Reproductive BioMedicine Online .2013

Unexplained RIF-intracavitary physiotherapy



Intracavitary physiotherapy

- Thermal therapy
- Electrical stimulation and drug conduct

Our study

- 141 participants with ≥ 2 implantation failure were recruited
 - A group (n=21): Endometrium scratch
 - B group (n=5): Intracavitary physiotherapy
 - C group (n=115): Control

Our study

- Low quality embryos, chromosomal abnormality, gynecological diseases that affect endometrium receptivity were excluded
- Age ≤ 40

Clinical pregnancy rate and miscarriage rate in three groups

	A Gp (N=21)	B Gp (N=5)	C Gp (N=115)	P
Clinical pregnancy rate				
Implantation rate	42.42% (14/33)	62.50% (5/8)	33.77% (77/228)	0.16
Miscarriage rate				
Single embryo lost rate	21.43% (3/14)	20.00% (1/5)	6.49% (5/77)	0.12

Clinical characteristics of three groups

	A Gp (N=21)	B Gp (N=5)	C Gp (N=115)	p
age	33.80±3.35	35.27±5.12	34.00±3.39	0.87
BMI	22.94±2.86	22.54±3.76	23.25±3.11	0.45
Infertility year	5.66±3.10	4.73±2.80	5.19±2.91	0.23
Failure cycles	2.47±0.65	2.27±0.47	2.46±0.78	0.68
Basal FSH	6.72±1.41	5.92±1.54	7.06±1.62	0.03
Basal LH	5.46±1.92	3.06±2.16	4.53±2.26	0.002
Basal RovFC	6.65±4.04	5.55±3.93	5.24±2.56	0.01
Basal Lov FC	5.88±2.18	6.91±3.96	4.92±2.57	0.006
Oocyte retrieval	12.00±4.89	—	8.00±5.00	0.004
N of embryos transfer	1.59±0.50	1.55±0.52	1.96±0.56	0.00
N of pregnancy	0.65±0.72	1.00±0.89	0.67±0.84	0.25

3. Management of immune factors

● Leukocyte immunotherapy

(The live birth rate per cycle of leukocyte immunotherapy group is higher than control group. Check. C lin Exp Ob stet Gynecol .2005)

● Intravenous immunoglobulins (IVIg)

(The live birth rate of IVIG group is higher than control group. Clark. J Assist Rep rod Genet.2006)

Summary

- Need for consensus in diagnostic criteria
- Endometrial scratch seems promising
- Intracavitary physiotherapy needs further research
- RIF is an area with significant research potential

Thank You!

The role of imaging techniques in the investigation of pathology affecting implantation



Tarek El-Toukhy, MRCOG
Consultant in Reproductive Medicine
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London

ACU

Conflict of Interest

NONE

Guy's and St. Thomas' NHS Foundation Trust
ACU

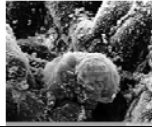
Objectives

- To review the various causes of implantation failure
- To identify the role of imaging in investigation of implantation failure
- To examine therapeutic effectiveness after diagnosis

Guy's and St. Thomas' NHS Foundation Trust
ACU

Definition of RIF

- Absence of implantation (gestational sac seen on scan) after three embryo transfer cycles
- Absence of implantation after replacing 10 or more good quality embryos



Challenges in Management

- Pressure to do/change something
- Heterogeneous/multi-factorial
- Limited evidence for interventions




Predictors of implantation

- Age
- Ovarian reserve
- Presence of pelvic pathology
- Success rate of clinic

Donoso et al, 2007

Pragmatic classification of RIF


- Expected RIF
- Unexpected RIF



Expected RIF

- Advanced maternal age
- Reduced ovarian reserve
- Poor quality embryos
- Atrophic endometrium


Do we need to investigate further?



Unexpected RIF

- Young age
- Adequate ovarian reserve
- Good quality embryos

Investigate



Therapeutic Effectiveness

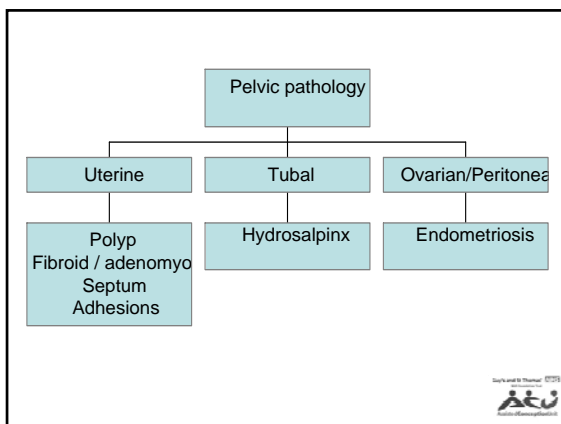
- Studied in relation to a number of pathologies
- Analysis limited to subfertile population
- Effectiveness is measured by restoration of reproductive potential

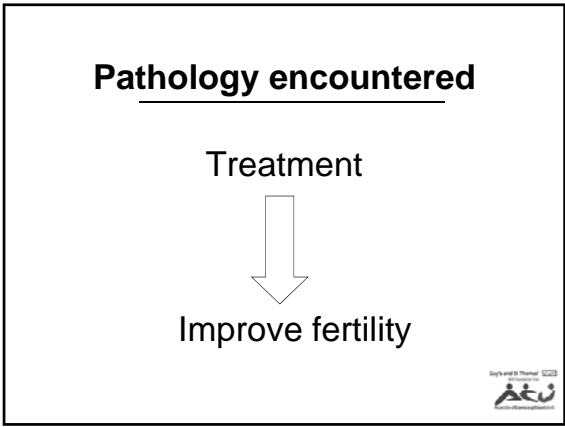


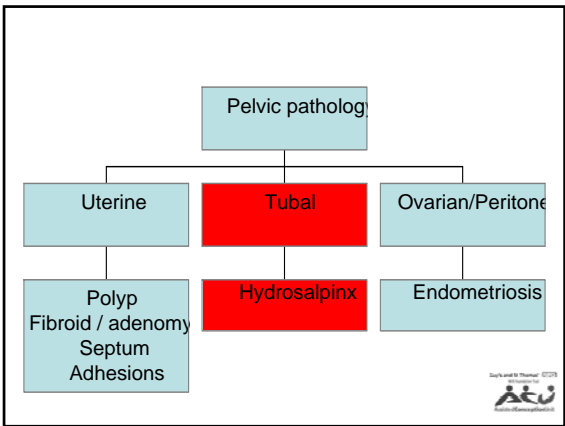
Pathology encountered

- Prevalence in infertile patients 13-40% (4861 cases)
Campo et al, 1999; Hinckley and Milki, 2004; Karayalcin et al, 2010; Al-Mazny et al., 2010; Fatemi et al., 2010
- Commonest findings:
 - Tubal pathology
 - Endometrial polyps - Submucous fibroids
 - Intrauterine adhesions - Septate/subseptate uterus
 - Peritoneal / ovarian endometriosis



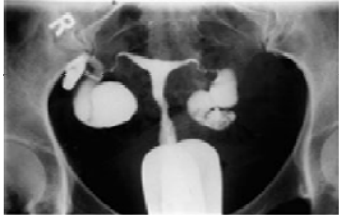







Tubal Pathology:

1- Distal tubal obstruction:

Detailed Imaging

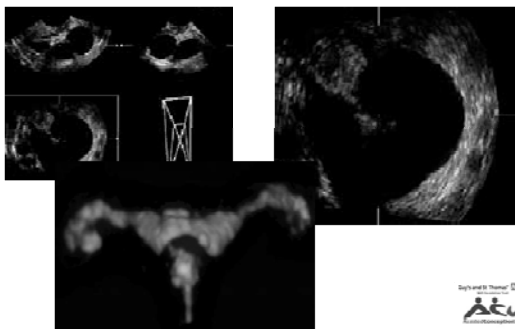
- 2D Transvaginal Scan
- Hystero-contrast sonography
- 3D scan with contrast
- MRI



Hydrosalpinx

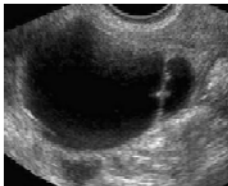


3D image of hydrosalpinx

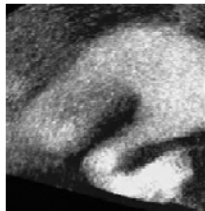


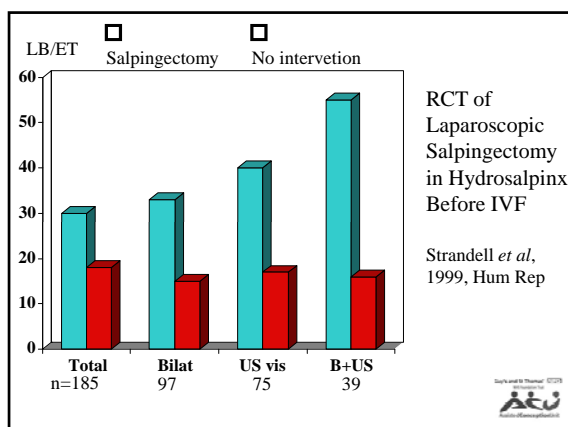
3D assessment of hydrosalpinx

2D view showing possible septated cyst



3D view shows hydrosalpinx (using inverted mode)





Effect of untreated hydrosalpinx

Table VI. Meta-analysis Of 14 studies

Outcome criteria	Group with hydrosalpinx (%)	Group without hydrosalpinx (%)	Odds ratio	Confidence interval
Pregnancy rate	19.67	31.2	0.64	0.56-0.74 ^a
Implantation rate	8.53	13.68	0.63	0.55-0.73 ^a
Delivery rate	13.4	23.44	0.58	0.49-0.69 ^a
Early pregnancy loss rate	43.65	31.11	1.72	1.34-2.20 ^a


^aOdds ratio significantly different from 1 ($P < 0.05$)

Camus *et al.*, 1999

Effect of removal of hydrosalpinx

- Odds of pregnancy = 1.75 (1.1-2.9)
- Odds of ongoing pregnancy = 2.13 (1.2-3.7)
- Embryo implantation = 1.34 (0.9-2.1)
- Ectopic pregnancy=0.42 (0.1-2.1)
- Miscarriage=0.49 (0.2-1.5)


Cochrane review
Johnson et al. 2002

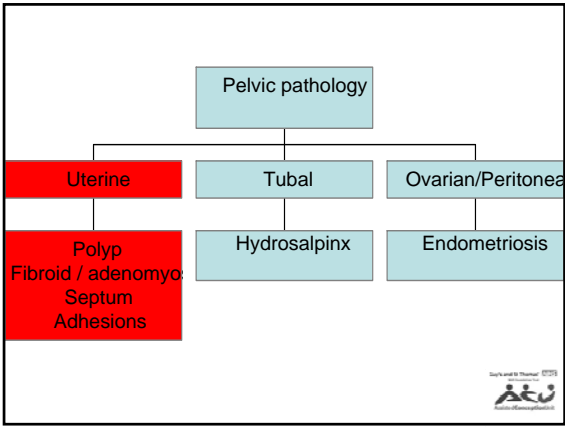


Effect of removal of hydrosalpinx

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- Ectopic pregnancy = 0.42 (0.1-2.1)
- Miscarriage = 0.49 (0.2-1.5)

Cochrane review
Johnson et al. 2002





Uterine Pathology:

- 1- Endometrial polyps
- 2- Uterine fibroids
- 3- Intra-uterine adhesions Up to 45% in subfertile population
- 4- Septate / subseptate uterus
- 5- Adenomyosis



Outpatient hysteroscopy: a routine investigation before assisted reproductive techniques?

Fertility and Sterility Vol. 55, No. 1 January 2011

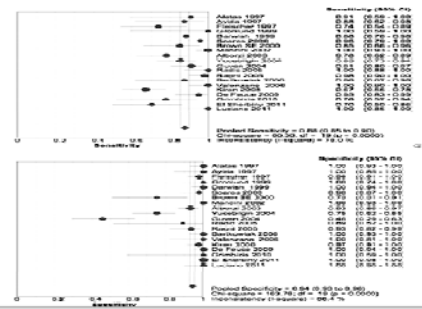
TABLE 3

Hysteroscopic findings according to age distribution and previous ART failure(s).

Hysteroscopic findings	Age < 35 y (n = 67)	Age ≥ 35 y (n = 78)	No previous ART (n = 94)	Previous ART (n = 51)
Cervical stenosis	2 (3.0%)	2 (2.6%)	3 (3.2%)	1 (2.0%)
Endocervicitis	3 (4.5%)	1 (1.3%)	2 (2.1%)	2 (3.9%)
Endocervical polyp	2 (3.0%)	1 (1.3%)	3 (3.2%)	0 (0.0)
Uterine cavity hypoplasia	1 (1.5%)	1 (1.3%)	2 (2.1%)	0 (0.0)
Uterine septum	1 (1.5%)	0 (0.0)	1 (1.1%)	0 (0.0)
Intrauterine adhesions	4 (6.0%)	2 (2.6%)	2 (2.1%)	4 (7.8%)
Intrauterine foreign body	0 (0.0)	1 (1.3%)	0 (0.0)	1 (2.0%)
Endometriosis	2 (3.0%)	1 (1.3%)	1 (1.1%)	2 (3.9%)
Submucous myoma	1 (1.5%)	5 (6.4%)	3 (3.2%)	3 (5.9%)
Endometrial polyp	2 (3.0%)	6 (7.7%)	3 (3.2%)	5 (9.8%)
Polypoid endometrium	1 (1.5%)	3 (3.8%)	3 (3.2%)	1 (2.0%)
Endometrial hyperplasia	0 (0.0)	4 (5.1%)	1 (1.1%)	3 (5.9%)
Blocked ostia	2 (3.0%)	0 (0.0)	1 (1.1%)	1 (2.0%)
Total findings	21 (31.3%)	27 (34.6%)*	26 (27.6%)	25 (50.1%)

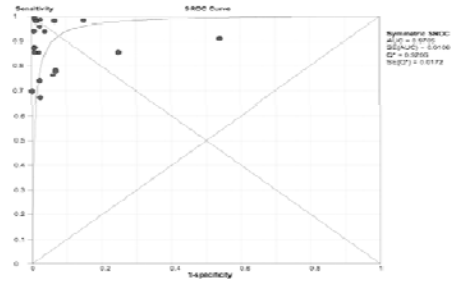
Saline hysterosonography

Figure 4: The sensitivity & specificity of SHS in the detection of all intrauterine abnormalities



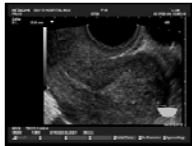
Saline hysterosonography

Figure 5: The summary receiver operating curve (sROC) of SIS in the detection of all intrauterine abnormalities¹⁷

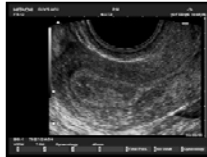


1- Endometrial Polyps

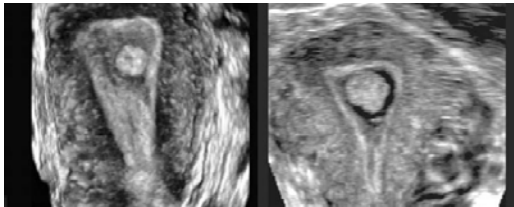
Pre-injection



Post-injection

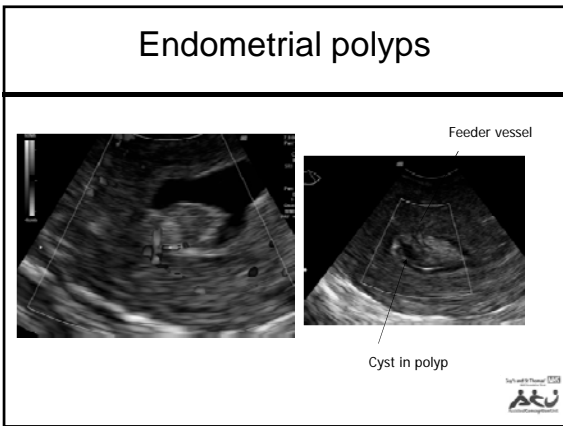


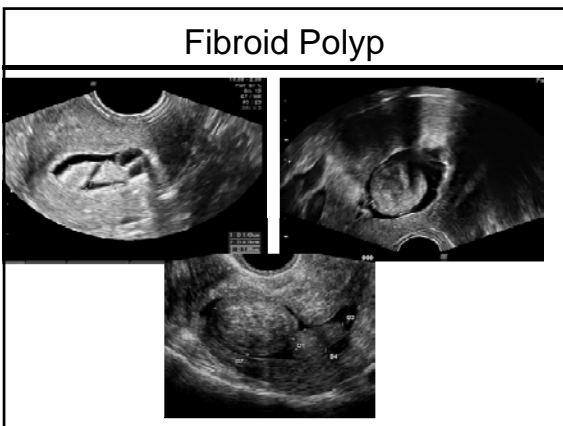
Endometrial polyps



3D scan images







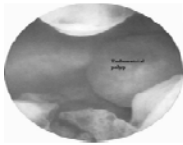
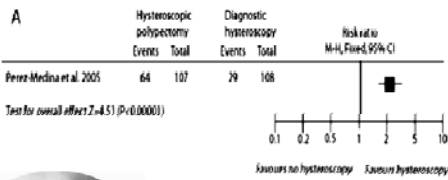
Prevalence of polyps

Table 2 Findings at hysteroscopy in 255 patients

Uterine cavity findings	Group 1		Group 2 (n = 31)
	Primary infertility (n = 121)	Secondary infertility (n = 103)	
Normal	87 (71.9%)	47 (45.6%)	30 (96.8%)
Polyps	18 (14.8%)	16 (15.5%)	1 (3.2%)
Adhesions	11 (9.1%)	34 (33%)	0
Fibroids	4 (3.3%)	3	0 (2.9%)
Adhesions and polyps	0	1	0 (0.97%)
Septa	1 (0.8%)	2 (1.9%)	1 (3.2%)

ATU

Endometrial polyps >15mm



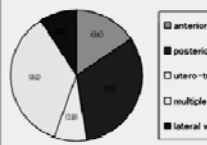
Human Reproduction Update, Vol.16, No.1 pp. 1-11, 2010
 Advanced Access publication on September 10, 2009 doi:10.1093/hropud/dmp033

human
reproduction
update

Locations of polyps

FIGURE 1

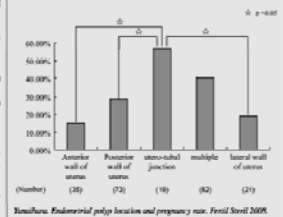
Endometrial polyp location in one of five categories of the endometrial cavity. Data in parentheses are numbers of patients.



Konakova. Endometrial polyp location and pregnancy rate.

FIGURE 2

Pregnancy rate after operation by polyp location. Data in parentheses are numbers of patients.

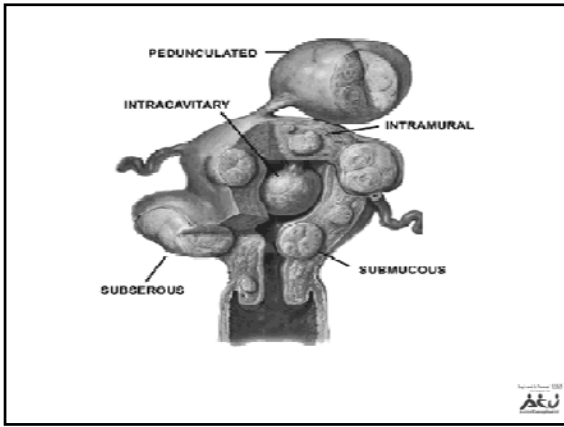


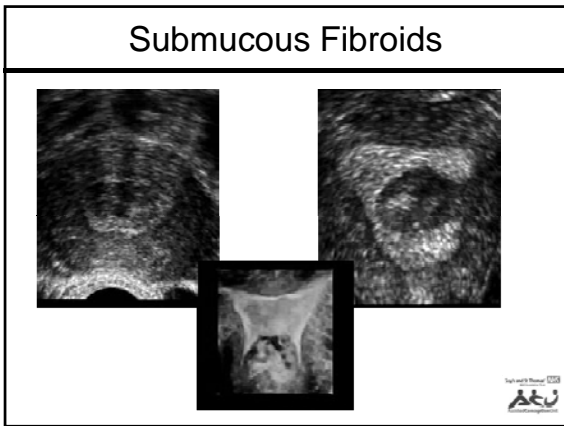
Konakova. Endometrial polyp location and pregnancy rate. Fertil Steril 2009.

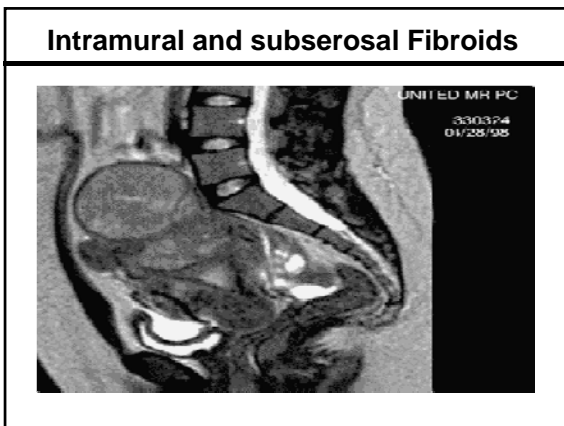


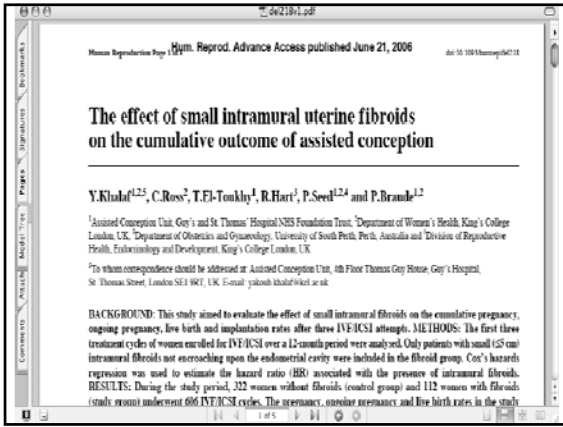
2 - Uterine fibroids

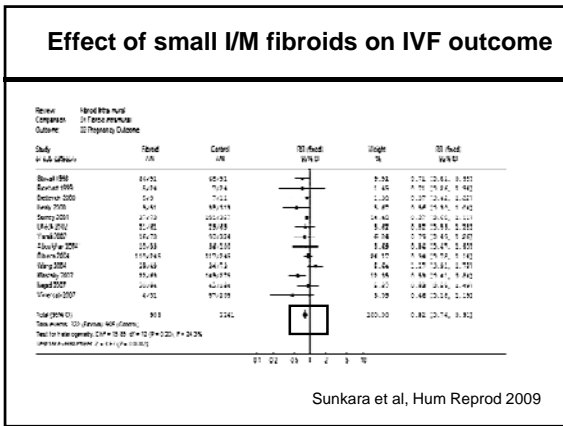


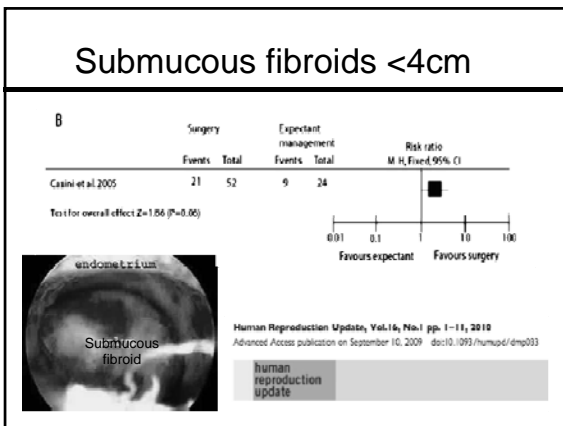




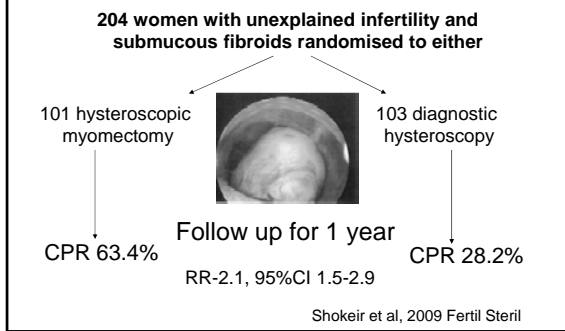




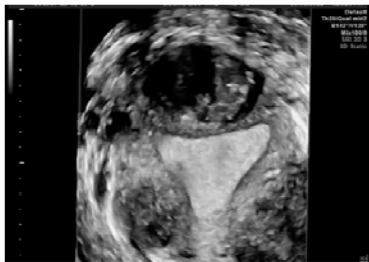




Larger submucous fibroids



Does myomectomy for IM fibroids (not distorting the uterine cavity) improve IVF outcome?



Effect of IM fibroids removal

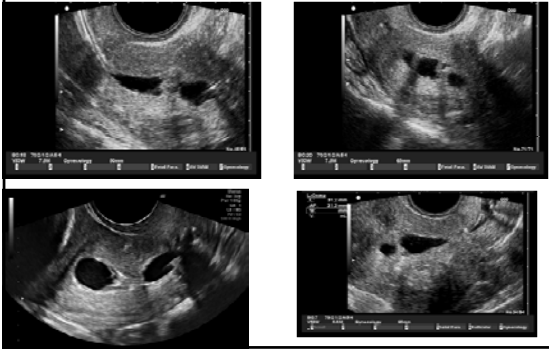
BULLETTI *et al.*: EFFECT OF MYOMA REMOVAL ON IVF 87

TABLE 2. Effect of surgical removal of myomas on IVF success rates

	Cumulative pregnancy rate N (% cases)	Delivery rate N (% cases)	Abortion rate N (% pregnancies)
Group A	28 (34)	21 (25)	8 (7)
Group B	13 (15)	10 (12)	3(4)
<i>P</i>	<.05	<.05	Not significant

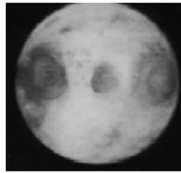
Note: Group A included patients who underwent IVF after surgical removal of their myomas (N=84). Group B included patients who underwent IVF without surgical removal of their myomas (N=84). Subjects with fibroids were those who had one to more than five fibroids subserosal and intramural with at least one larger than 5 cm in diameter.

3-Intra-uterine adhesions



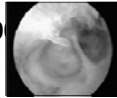
Intra-uterine adhesions

- No randomised trials



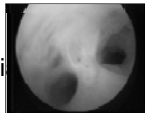
- No controlled trials

- Case series typically with N<10



Intra-uterine adhesions

- Pregnancy rate ranges between 30-50%
- Live birth rate ranges between 10-35%
- Poor prognostic indicators:
 - Adhesions obliterating both ostia
 - Age >35 years
 - Persistence of amenorrhea
 - Reformation of adhesions at 2nd look



Thompson et al,2009; Pabuccu et al, 2008; Yu et al, 2008

4- Mullerian Duct Anomalies

TABLE 1

AFS classification of patients based on the anatomy of the female genital system, especially uterine anatomy.

Class I	Hypoplasia and aplasia	(a) Vaginal, (b) cervical, (c) fundal, (d) tubal
Class II	Unicornuate	(a) Communicating, (b) noncommunicating, (c) no cavity, (d) no horn
Class III	Didelphys	
Class IV	Bicornuate	(a) Partial, (b) complete
Class V	Septate	(a) Partial, (b) complete
Class VI	Arcouate	
Class VII	DES drug-related	

EDITOR'S CORNER

Congenital malformations of the female genital tract: the need for a new classification system

Giuseppe J. Ghezzi, M.D., Ph.D., and Bill Camps, M.D.

TABLE 3

VCAM classification of patients based on the anatomy of the female genital system, more specifically, the independent estimation of each organ's anatomy.

Vagina (V)	<p>0 Normal</p> <p>1 (a) Partial hymenal atresia, (b) complete hymenal atresia</p> <p>2 (a) Incompletely isolated vagina <50%, (b) completely isolated vagina</p> <p>3 Stenosis of the introitus</p> <p>4 Hypoplasia</p> <p>5 (a) Unilateral atresia, (b) complete atresia</p> <p>6 (1) Bicus unperforate fossa clitoridis; (2) bicus unperforate fossae clitoridis; (3) bicus unperforate fossae clitoridis; (4) bicus unperforate fossae clitoridis</p> <p>C Clitoris</p> <p>0 Normal</p> <p>1 Duplex clitoris</p> <p>2 (a) Unilateral atresia/aplasia, (b) unilateral atresia/aplasia</p> <p>Other</p> <p>4 Embryonic</p> <p>5 Normal</p>
Cervix (C)	<p>0 Normal</p> <p>1 (a) Accretion, (b) septate <50% uterine cavity; (c) septate >50% uterine cavity</p> <p>2 Placenta</p> <p>3 Hypertrophy</p> <p>4 (a) Unilaterally rudimentary or aplastic, (b) bilaterally rudimentary or aplastic</p> <p>Other</p> <p>5 Unchanged</p>
Uterus (U)	<p>0 Normal</p> <p>1 (a) Accretion, (b) septate <50% uterine cavity; (c) septate >50% uterine cavity</p> <p>2 Placenta</p> <p>3 Hypertrophy</p> <p>4 (a) Unilaterally rudimentary or aplastic, (b) bilaterally rudimentary or aplastic</p> <p>Other</p> <p>5 Unchanged</p>



Human Reproduction Update, Vol.14, No.5, pp. 415-429, 2008
Advance Access publication June 6, 2008

doi:10.1093/hrop/14.5.415

Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: a critical appraisal

Sotirios H. Saravelos^{1,3}, Karen A. Cocke¹ and Tin-Chiu Li^{1,2}

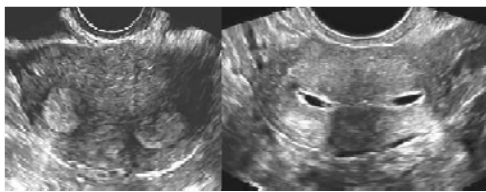
Table III. Congenital uterine anomalies: percentage of subtypes in different population groups.

Population	Hypoplastic, %	Unicornuate, %	Didelphys, %	Bicornuate, %	Septate, %	Arcoate, %
General (total n=225)	-	0.4	0.4	5.0	27.2	68.0
Infertile (n=170)	9.4	0.1	2.9	10.8	46.1	24.7
RM (n=132)	-	2.3	0.8	3.3	29.2	65.2

Data based only on cases in studies using an appropriate classification of the congenital uterine anomaly types.



4- Mullerian duct anomalies



2D ultrasound can suspect Mullerian duct anomalies

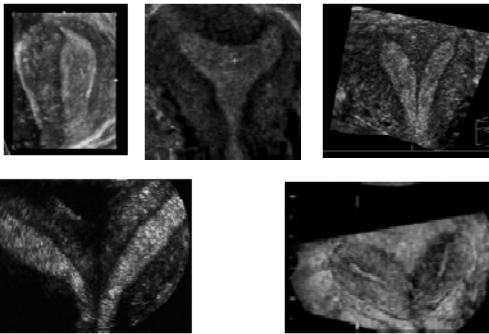


Role of 3D ultrasound

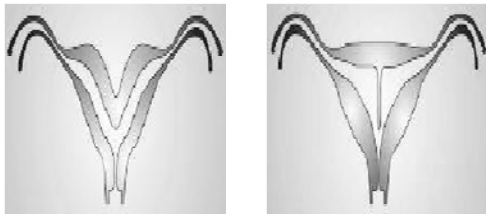
- Investigation of suspected Mullerian duct anomalies
 - Improved cavity and adnexal imaging
 - Volumetric assessment
- Post-operative follow up



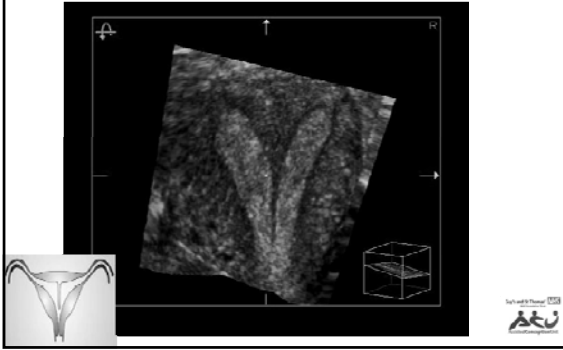
Uterine malformations



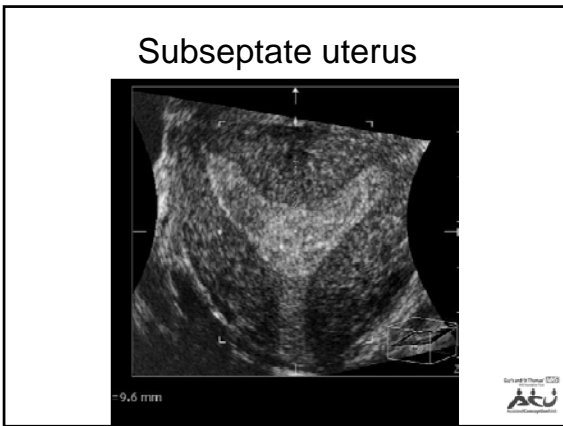
Bicornuate or septate?



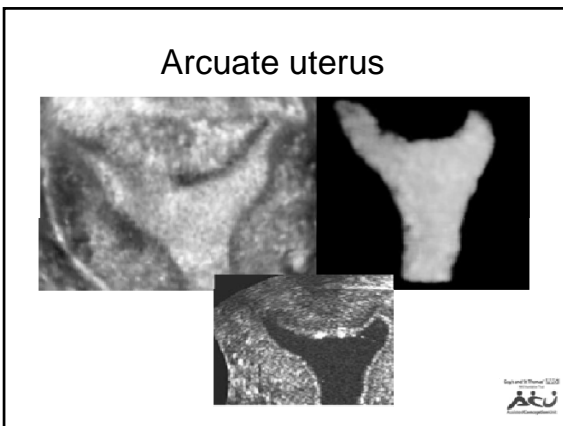
4-Septate uterus



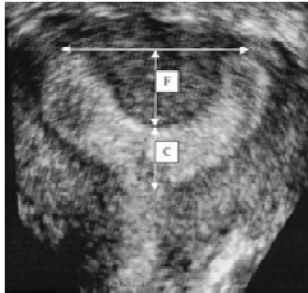
Subseptate uterus



Arcuate uterus



Ratio to quantify cavity distortion

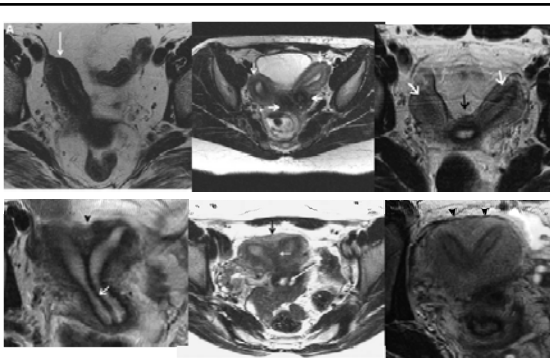


- $F/F+C > 50\%$




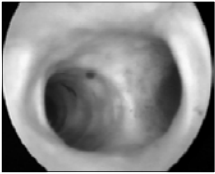
Role of MRI

- Complex Mullerian duct anomalies
- Differentiate Bicornuate from septate uterus
- Detect a rudimentary horn
- Volumetric and adnexal assessment



Intrauterine septum resection

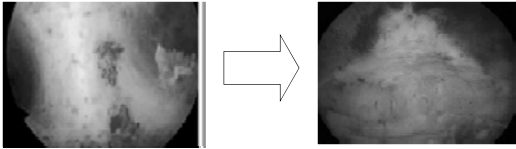
- No randomised trials
- One controlled trial
- Case series typically with N<50





Intrauterine septum resection

Mollo et al, 2009 Fertil Steril

- Controlled study showed higher live birth rate after septal resection (n=44) compared to controls (n=132)
34% vs 19% (P<0.01)



Follow up after septum removal

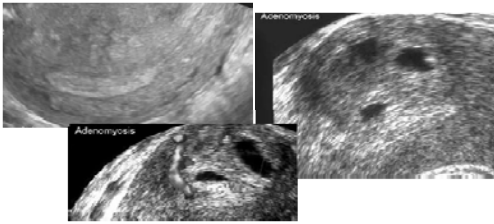


Fertility after septum resection

Table 2: Literature on pregnancy rates and live birth rates after hysteroscopic uterine septoplasty in women with septate uteri

Author	Year	Patient number	Uterine malformation	Patient characteristics	Pregnancy rate	Live birth rate
Hall et al (19)	2005	141	IUS	141 (100%) IUS	22 (15.6%)	24 (17.0%)
Bacalot et al (15)	2005	78	CUIS	21 (27%) IUS, 57 (73%) IUS, 10 (13%) IUS, 10 (13%) IUS	8 (37%)	14 (68%)
Jakovic et al (11)	2004	93	CUIS	93 (100%) IUS	14 (15%)	11 (12%)
Wagner et al (14)	2004	26	CUIS	26 (100%) IUS	11 (42%)	10 (38%)
Fajó et al (16)	2003	78	IUS, CUIS	78 (100%) IUS	21 (27%)	21 (27%)
Catalano et al (22)	2007	135	CUIS	135 (100%) IUS	88 (65%)	83 (61%)
Leong et al (20)	1996	44	IUS, CUIS	44 (100%) IUS	16 (36%)	16 (36%)
Najibi-Nasab et al (17)	2004	90	CUIS	90 (100%) IUS	14 (16%)	14 (16%)
Palacios & Guzmán (24)	2004	67	CUIS	67 (100%) IUS	23 (34%)	18 (27%)
Usher et al (26)	1998	124	CUIS	124 (100%) IUS	10 (8%)	10 (8%)
Stojanović et al (21)	2007	119	IUS	119 (100%) IUS	20 (17%)	20 (17%)
Martikainen et al (18)	1998	40	IUS	40 (100%) IUS	13 (33%)	13 (33%)
Kaplan et al (23)	1998	116	CUIS	116 (100%) IUS	48 (41%)	48 (41%)
Reinhold et al (25)	2000	43	CUIS	43 (100%) IUS	10 (23%)	10 (23%)
Guzmán et al (27)	1999	23	CUIS	23 (100%) IUS	14 (61%)	14 (61%)
Wong et al (28)	2000	25	CUIS	25 (100%) IUS	13 (52%)	13 (52%)
McLennan et al (30)	1999	44	IUS	44 (100%) IUS	14 (32%)	14 (32%)
1587	IUS; CUIS				892 (1,501) (6.0%)	686 (1,501) (4.5%)

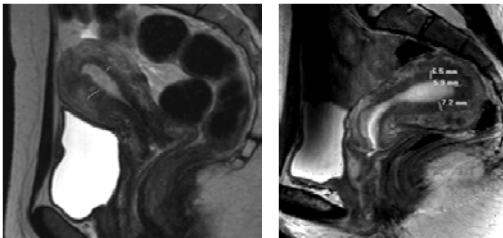
5- Adenomyosis



Asymmetric thickening, irregular cystic spaces and increased vascularity



Uterine junctional zone at magnetic resonance imaging: A predictor of *in vitro* fertilization implantation failure



Uterine junctional zone at magnetic resonance imaging: A predictor of *in vitro* fertilization implantation failure

Table 1 Value of junctional zone thickness in mm according to pregnancy status after *in vitro* fertilization, by patient

	Pregnancy	No pregnancy
Average junctional zone	5.14	6.75
Maximal junctional zone	6.24	9.83
P	<0.001	<0.001

Table 3 Rates of pregnancy or failure in function of a threshold of 10 mm for maximal junctional zone (MJZ)

	MJZ < 10 mm (n = 123)	MJZ > 10 mm (n = 39)
Pregnancy	62.6% (77)	13.8% (4)
No pregnancy	37.4% (46)	86.2% (25)
P	<0.01	

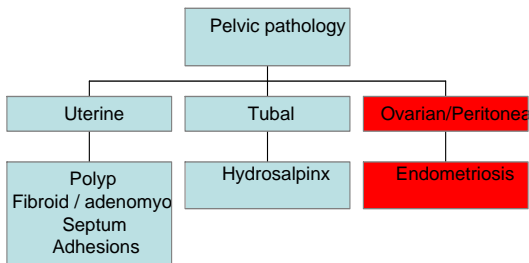


Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes

Abha Maheshwari¹, Sumana Gurunath¹, Farah Fatima²,
and Siladitya Bhattacharya¹

- Both ultrasound and MRI have similar diagnostic accuracy (AUC = 0.88 and 0.91, respectively)
- More studies in infertile population are required to determine the magnitude of its effect on IVF outcome





Does medical treatment of endometriosis improve IVF outcome?

Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis (Review)

Sallam HN, Garcia-Velasco JA, Dias S, Arici A

Arzi Health Team ©2012
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Medical treatment of endometriosis improves IVF outcome

Analysis 01.02. Comparison 01 GnRH agonist versus no agonist before IVF or ICSI, Outcome 01 Clinical pregnancy rate per woman

Review: Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis
Comparison: 01 GnRH agonist versus no agonist before IVF or ICSI
Outcome: 01 Clinical pregnancy rate per woman

Study	GnRH agonist n/N	Control n/N	Odds Ratio (Fixed, 95% CI)	Weight	Odds Ratio (Fixed, 95% CI)
Elder 1992	12/50	2/32	2.02	202	2.02 [1.59, 2.61]
Pines 2002	21/58	8/19	35.4	354	33.1 [24.1, 45.4]
Sills 2002	20/51	4/24	4.04	404	3.41 [1.89, 6.13]
Total (95% CI)	53	77		1000	4.29 [2.09, 7.45]

Total events: 33 (GnRH agonist), 15 (Control)
Test for heterogeneity: chi-square=0.00, df=2, P=0.99
Test for overall effect: z=2.73, P=0.006

0.5 1 5 10
Favours control Favours GnRH agonist

Arzi Health Team ©2012
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Evidence of Clinical Cytology 2012, 46: 441-448
Published online 17 September 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ajoc.11102

Comparison between transvaginal sonography, saline contrast sonovaginography and magnetic resonance imaging in the diagnosis of posterior deep infiltrating endometriosis

Table 1 Performance of clinical examination, transvaginal sonography (TVS), saline contrast sonovaginography (SCSV) and magnetic resonance imaging (MRI) in the detection of posterior deep pelvic endometriosis

Parameter	Clinical examination	TVS	SCSV	MRI
Sensitivity (%)	87.0	73.9	93.3	91.3
Specificity (%)	75.0	87.5	87.5	75.0
PPV (%)	95.2	97.1	97.7	95.5
NPV (%)	59.0	36.8	70.0	60.0
LR+	3.48	5.91	7.47	3.65
LR-	0.17	0.29	0.07	0.11

LR+, positive likelihood ratio; LR-, negative likelihood ratio;
NPV, negative predictive value; PPV, positive predictive value.

Arzi Health Team ©2012
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Conclusions

- Imaging has an important role to play after IVF failure
- All investigations are complementary
- Saline hysterosonography is imaging technique of choice for intra-cavitary pathology
- 3D scan and MRI are helpful in diagnosis of Mullerian duct anomalies and possibly pelvic endometriosis



Thank you



**New insights of subtle congenital
uterine malformation on
implantation**

Marco Gergolet MD
Pre-congress course 9 Special Interest Group
Reproductive Surgery "The impact of reproductive
surgery on repeated implantation failure"
Sunday 7 July 2013

Conflict of interest

- none

Disorders on implantation

- Reproductive failure (RF)
 - Recurrent spontaneous miscarriages
 - Recurrent implantation failure (IVF treatment)
 - » (Farquharson et al., 2005)

Disorders on implantation

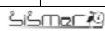
- Decreased embryo quality
- Genetic factors
- Immunological factors
- Thrombophilia
- Uterine causes

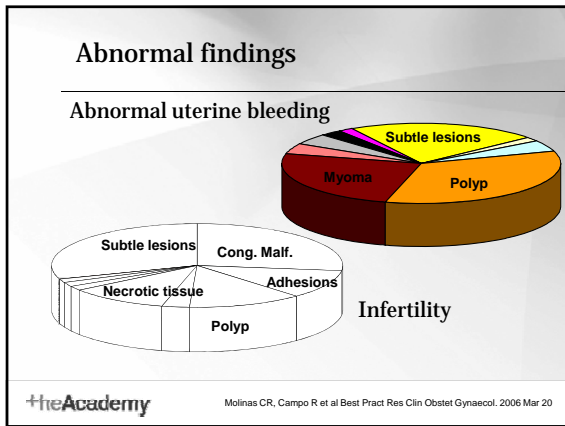
Uterine factor of RF

- Acquired
 - Myoma
 - Adenomyosis
 - Subtle lesions
- Congenital malformations

1526 consecutive diagnostic hysteroscopies

HYSTORY	NEG (group A)	Previous miscarriage (group B)	Previous abortion (group C)	Pprevious delivery (group D)	Total
Number	952	354	97	123	1526
Normal cavity	592 (62%)	196 (55%)	57 (59%)	88 (72%)	933 (61%)
Sub-septum > 1 cm	108 (11%)	49 (14%)	6 (6%)	5 (4%)	168 (11%)
Endometrial polyp	129 (14%)	26 (7%)	6 (6%)	8 (6.5%)	169 (11%)
Adhesions	81 (8.5%)	60 (17%)	24 (25%)	20 (16%)	185 (12%)
Myomas	13 (1.5%)	2 (0.5%)	2 (2%)	0	17 (1.5%)
Malformations	5 (0.5%)	2 (0.5%)	0	0	7 (0.5%)
Combination of more anomalies	24 (2.5%)	19 (5%)	2 (2%)	2 (1.5%)	47 (3%)





MYOMAS EPIDEMIOLOGY

- Most common benign tumors in the female pelvis
- Incidence:
 - 8,9 % among white women
 - 30,6 % among black women

(Marshall et al. 1997)

Uterine leiomyomas

- ✓ Most common benign tumors of the uterus
- ✓ Occur in 25 - 50% in women over the age of 30
- ✓ Frequency increases with age and more common in some ethnic groups especially in Afro Caribbean
- ✓ Affect 25% of women in reproductive age
(Elahi SM & Odejinmi F J ObstGyn 2008)
- ✓ Pathogenesis is unknown
- ✓ Related to Estrogens – occur only after puberty and degenerate after menopause
- ✓ 50% remain asymptomatic
(West PC Repr Med Review 2009)

Impact of Intramural Myomas on Fertility

Greater distance for sperm travel

Encroachment on tubal ostium. Occlusion

Distortion of uterine cavity

Interfere normal rhythmic uterine contractions

Impaired implantation

Alteration on oxytocinase activity

Vascular changes

Abnormal endometrial maturation

Abnormal findings

Abnormal uterine bleeding

Infertility

Myoma

Polyp

Subtle lesions

Subtle lesions

Cong. Malf.

Necrotic tissue

Adhesions

Polyp

Infertility

theAcademy

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

Subtle lesions

Category	Elevation	Hypervascularisation & Strawberry pattern	diffuse polyposis	necrotic tissue	Exophytic	Synechia
Abnormal bleeding	62%	22%				
Infertility	20%	46%	11%	14%	9%	

theAcademy

Prevalence of congenital uterine malformations General population

Author	Method	Anomalies (%)
Raga 1997	HSG, HSC	3.8
Acién 1997	Vag. US, HSG	4.6*, 7.8**, 16.7***
Jurković 1997	3D US	5.4
Maneschi 1995	HSC	10
Nasri 1990	US	2.7

*:Previous term pregnancies, **: previous pregnancies and some miscarriage, *** nulligravidae

Prevalence of congenital uterine malformations Infertile population

Author	Method	Prevalence %
Tulandi 1980	HSG	1.0
Sorensen 1981	HSG	23.9
Raga 1996	HSG, Vag. US, 3D US	26.2
Acién 1997	HSG, Vag. US	16.0

Prevalence of congenital uterine malformations RM population

Author	Method	Prevalence %
Clifford 1994	HSG, Vag US	1.8
Jurković 1995	HSG, Vag. US, 3D US	19.7
Raga 1997	HSG, HSC, LAP	6.3
Acién 1997	HSG, Vag. US	25.4

Congenital uterine malformations

When is necessary to treat?

- When the association with adverse reproductive history is demonstrated
» (Colacurci et al 2001)
- After first miscarriage: conservative approach (80-90% delivery rate in next pregnancy)
» (Homer et al 2000)
- Yes in case of declined fertility (age >35) and before ART
» (Mencaglia and Tantini 1996)

Disorders on implantation

- “...reproductive surgery is recommended as the first step therapy in RIF patients”
- Hysteroscopy and laparoscopy (to exclude endometriosis) is recommended in case of repeated implantation failure
» (B. Toth et al. 2011)

Septate uterus

- “Evaluation of septate uteri is subjective and quantification is lacking”
- Main factor determining fertility after septoplasty are patient’s age and duration of infertility
(Shokeir et al. 2011)

Septate uterus -classification

- “Subjective standards...used to differentiate normal from abnormal...what may be septate for one examiner may be arcuate to another”
» (GS Letterie 2011)
- “Septate uterus ...variably penetrates from **one to two** centimetres..resulting in partial division”

Classification of uterine anomalies



JMIG
The Journal of
Minimally Invasive
Gynecology

Original Article

Metropasty for AFS Class V and VI Septate Uterus Infertility or Miscarriage: Reproductive Outcomes

Sofiane Bendigallah, MD, Fika Fatima, MD, PhD, Xavier Derfieux, MD, PhD, and ... MD, PhD

From Assistance Publique Hôpitaux de Paris, Gynecology and Obstetrics, Hôpital Bicêtre (Dr. Bendigallah, Reprodin, and Remondet); Paris Lodron Universität Salzburg, Department of Perinatology, PERINUM (Dr. Fatima); Hôpital de la Pitié-Salpêtrière (Dr. Derfieux); and Department of Obstetrics and Gynecology, Hôpital Antoine Clémence (Dr. Fatima and Derfieux), France.

...It is also beneficial to offer septoplasty in patients with AFS Va, Vb and VI septate uterus

- From GS Letterie 2011, Management of congenital uterine anomalies



Septate uterus



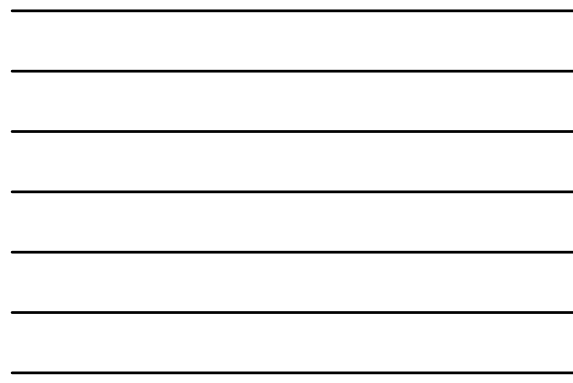
Is it an arcuate uterus??

No clinical relevance of the height of fundal indentation in subseptate or arcuate uterus: a prospective study

Marco Gergolet ^{a,*}, Rudi Campo ^b, Ivan Verdenik ^c, Nataša Kenda Šuster ^c, Stephan Gordts ^b, Luca Gianaroli ^d

^a S.I.F.F.S. d.o.o., Reproductive Surgery, Sedejova 6, 5000 Nova Gorica, Slovenia; ^b I.I.F.F. (Iruven Institute for Fertility and Embryology), Tiensevest 168, 3000 Leuven, Belgium; ^c Department of Obstetrics and Gynaecology, University of Ljubljana, Štajerska 1, 10001 Ljubljana, Slovenia; ^d S.I.S.M.F.R., Reproductive Medicine Unit, Via Mazzini 401 38 Bolzano, Italy

* Corresponding author. E-mail address: marco.gergolet@gmail.com (M. Gergolet).
 Marco Gergolet studied medicine at the University of Trieste, Italy between 1985 and 1991. In 1992 he moved to Ljubljana, Slovenia where in 1998 he became a specialist in obstetrics and gynaecology and senior clinician in the reproductive medicine unit in S.I.S.M.F.R., Bolzano. In 2000 he graduated as Master of Science in Biomedical Sciences at the University of Ljubljana. Between 2005 and 2008 he was the deputy co-ordinator and between 2008 and 2011 co-ordinator of the Special Interest Group on Reproductive Surgery at the European Society of Human Reproduction and Embryology. He started a PhD Fellowship at the University of Ljubljana in 2011.



Outcome	Larger septum (Group 1) n= 204		Smaller septum (Group 2) n= 84	
	Before metroplasty	After metroplasty	Before metroplasty	After metroplasty
Pregnancy seeking Months (median and range)	18 (2-120)	4.9 (0-40)	18 (3-108)	4.4 (1-25)
Pregnancies	157	150 (137 women)	52	59 (55 women)
Deliveries	32 (20.4 %) a	121 (80.7 %) b	6 (11.5 %) c	51 (86.4 %) d
Miscarriages	118 (75.2%)	25 (16.7 %)	39 (75 %)	8 (13.6 %)
Ectopic	7 (4.5%)	4 (2.7 %)	7 (13.4 %)	0

	Group 1, before vs. after metroplasty	Group 2, before vs. after metroplasty	Before metroplasty, Group 1 vs. Group 2	After metroplasty, Group 1 vs. Group 2
Pregnancy seeking duration (Mann-Whitney test)	p < 0.001	p < 0.001	n.s.	n.s.
Pregnancy failure rate (χ ² test)	p < 0.001	p < 0.001	n.s.	n.s.



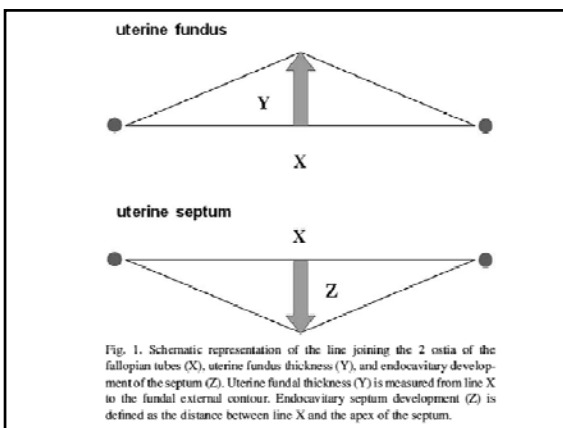
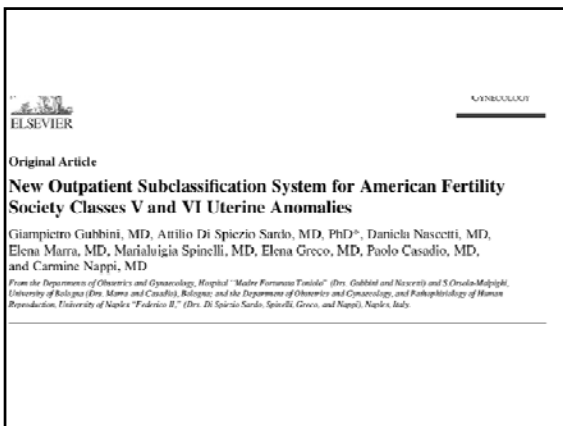
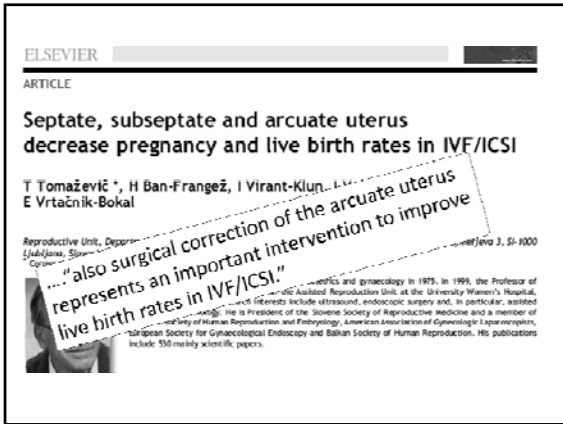
Septate, subseptate and arcuate uterus decrease pregnancy and live birth rates in IVF/ICSI

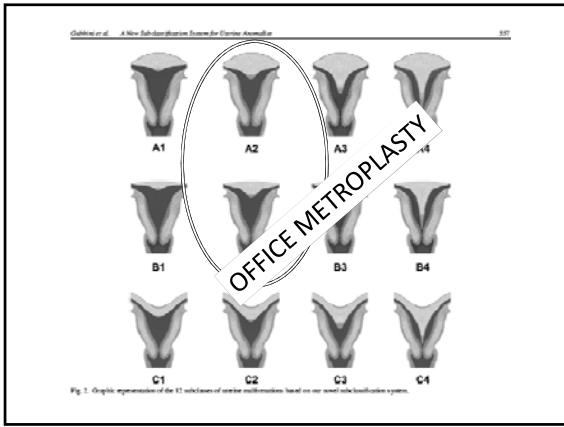
T Tomažević ^a, H Ban-Franjež, I Virant-Klun, I Verdenik, B Požlep, E Vrtačnik-Bokal

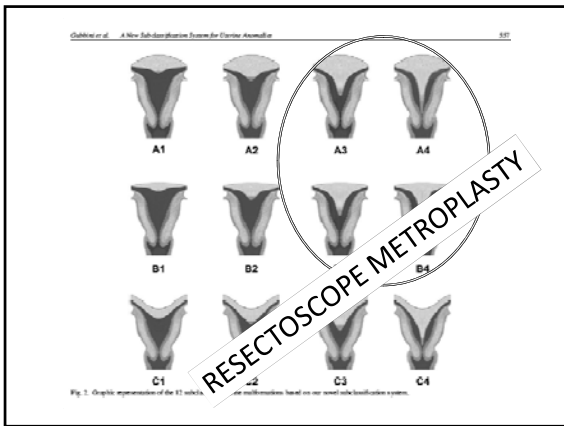
Reproductive Unit, Department of Obstetrics and Gynecology, University Medical Centre Ljubljana, Štajerska 1, SI-1000 Ljubljana, Slovenia
 * Corresponding author. E-mail address: tomasz.tomazevic@ujl.si (T Tomažević).

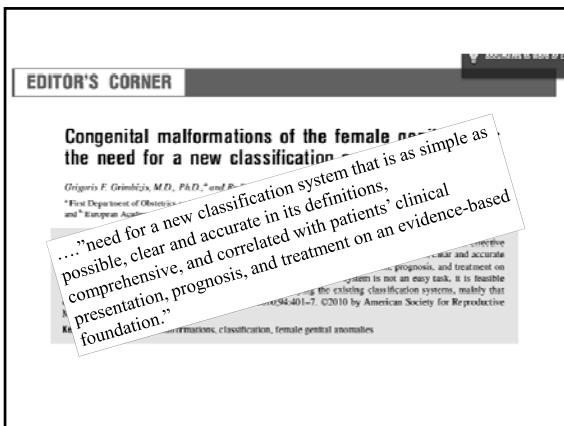
Tomaž Tomažević, Ph.D. began his career in obstetrics and gynaecology in 1975. In 1999, the Professor of Obstetrics and Gynecology and Head of the Assisted Reproduction Unit at the University Women's Hospital, Ljubljana, Slovenia. His research interests include ultrasound, endoscopic surgery and, in particular, assisted reproduction technology. He is President of the Slovene Society of Reproductive Medicine and a member of European Society of Human Reproduction and Embryology, American Association of Gynecologic Laparoscopists, European Society for Gynecological Endoscopy and Balkan Society of Human Reproduction. His publications include 130 mainly scientific papers.











Gynecol Surg
DOI 10.1007/s10297-011-0724-2


PERSPECTIVE

Clinical approach for the classification of congenital uterine malformations


Grigoris F. Grimbizis · Rudi Campo ·
On behalf of the Scientific Committee of the Congenital Uterine Malformations (CONUTA) common ESHRE/ESGE working group; Stephan Gordts, Sara Brucker, Marco Gergolet, Vasilios Tanos, T.-C. Li, Carlo De Angelis, Attilio Di Spicchio Sardo

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Delphi procedure



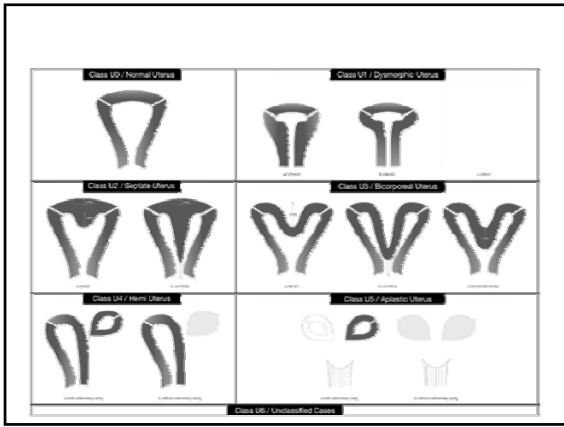
- interactive forecasting method which relies on a panel of experts
- the experts answer questionnaires in two or more rounds
- experts are encouraged to revise their earlier answers in light of the replies of other members of their panel.
- during this process the range of the answers will decrease and the group will converge towards the "correct" answer
- finally, the process is stopped and the mean or median scores of the final rounds determine the results

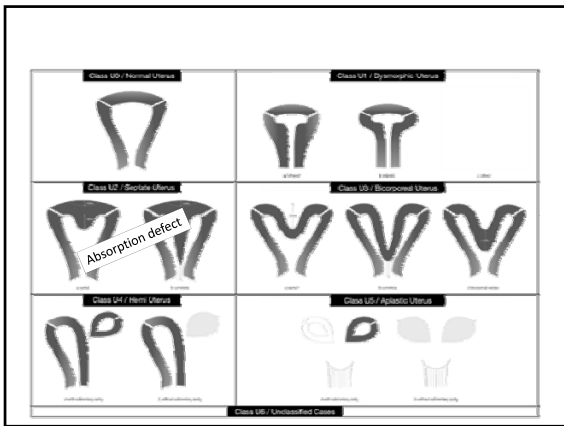


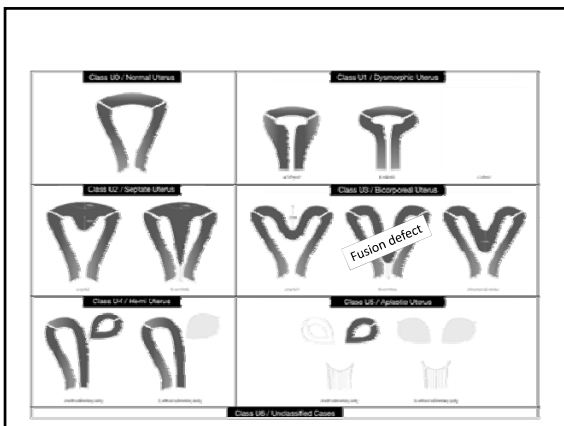
"The ESHRE-ESGE consensus on the classification of female genital tract congenital anomalies".

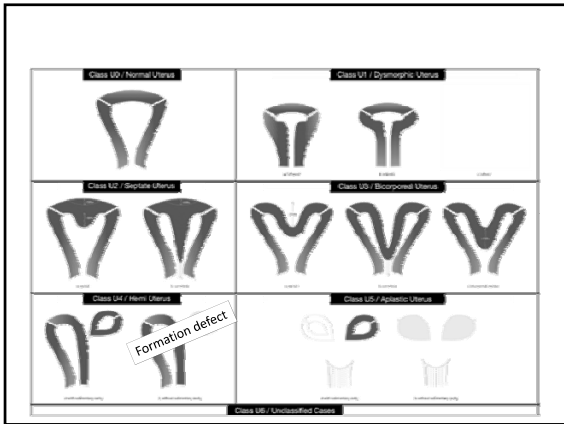
Grigoris F. Grimbizis, Stephan Gordts, Attilio Di Spicchio Sardo, Sara Brucker, Carlo De Angelis, Marco Gergolet, Tzu-Chia Li, Vasilios Tanos, Hans Drißmann, Luca Gianaroli, Rudi Campo

Congenital Uterine Malformations (CONUTA) common ESHRE / ESGE Working Group
Human Reproduction In press





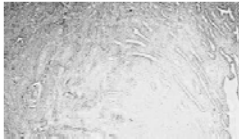




Septate uterus and infertility

- Which malformation is detrimental for conception and pregnancy and which is not?
- Why we cannot postulate that metroplasty is mandatory in women who are not yet child willing?

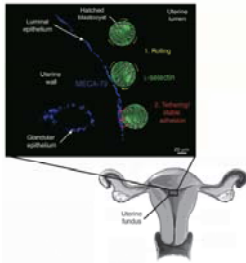
ENDOMETRIUM COVERING SEPTUM



- Fedele described a morphological alteration of mucosa covering the septum (Fedele et al. 1996).

SIEES
Società Italiana di Endometriosi e Chirurgia Riproduttiva

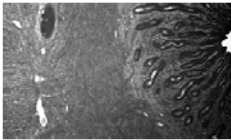
ROLLING AND TETHERING



The mechanism of the trophoblast invasion has analogies with the rolling and tethering of leucocytes on blood vessels. (Red-Horse et al. 2004). Could be that septum covering endometrium cannot express ligands such MECA 79 recognized antibodies that recognize L selectin expressed on blastocyst surface (Red-Horse et al. 2004)

Ukoner Institute of Fertility and End of Life Surgery **SIFES**

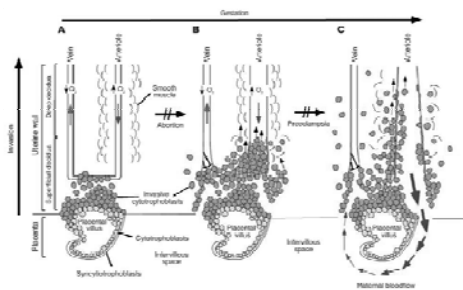
VASCULARIZATION



- Increased miscarriage rate could be consequence of a disrupted vascular architecture within septa (Fayez et al 1986)

Ukoner Institute of Fertility and End of Life Surgery **SIFES**

INVASION OF UTERUS



Gembocz et al. 2004

CONCLUSIONS

- The complex dialogue between the embryo and his mother should be studied in order to understand which uterine anomaly should be treated and why some septa behave benignly, whereas others are detrimental for pregnancy.



Overview of uterine congenital anomalies and their impact on implantation failure

Grigoris F. Grimbizis
Associate Professor
1st Department of Obstetrics & Gynecology
Medical School, Aristotle University of Thessaloniki



Female Genital Tract Malformations Definition & Clinical Comments

• *Miscellaneous deviations from normal anatomy resulting from embryologic maldevelopment of Müllerian or paramesonephric ducts*

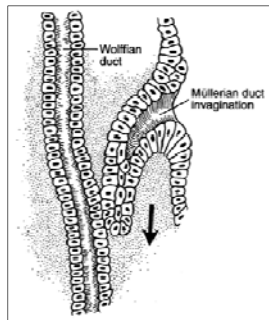
- *High prevalence in the general population (although not absolutely known) and even higher in women with pregnancy losses and implantation failures*

- *They are associated with reproductive problems (infertility and poor pregnancy outcome) and, more infrequently, with severe health problems (e.g. obstructive anomalies)*

Female genital tract: Embryogenesis

Step 1 (6th week of gestation)
Formation and canalization of the paramesonephric or Müllerian ducts

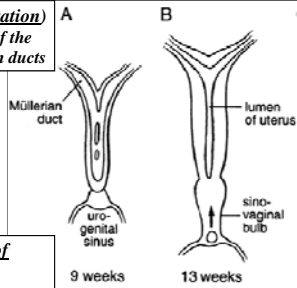
Schematic diagram of the Müllerian duct invagination into the coelomic epithelium following the course of the existing Wolffian ducts



Female genital tract: Embryogenesis

Step 2 (7th – 9th week of gestation)
Fusion of the caudal parts of the paramesonephric or Müllerian ducts

Diagram showing the fusion of the caudal portions of the Müllerian ducts and their subsequent formation of the uterine horns

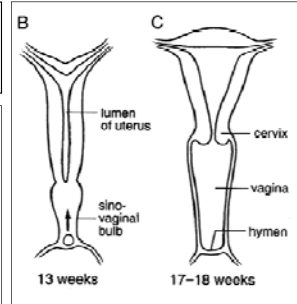


Step 3 (9th– 13th week of gestation)
Absorption of the midline septum and formation of cavity

Female genital tract: Embryogenesis

Formation of the vagina
Fusion of the cavity coming from the Müllerian to that from the sinovaginal bulb

Diagram shows the formation of the vagina from 9 weeks at 17–18 weeks of gestation. Sinovaginal bulb progresses cephalad, fuses with the cavity coming from the caudal part of the Müllerian ducts to form the vaginal lumen



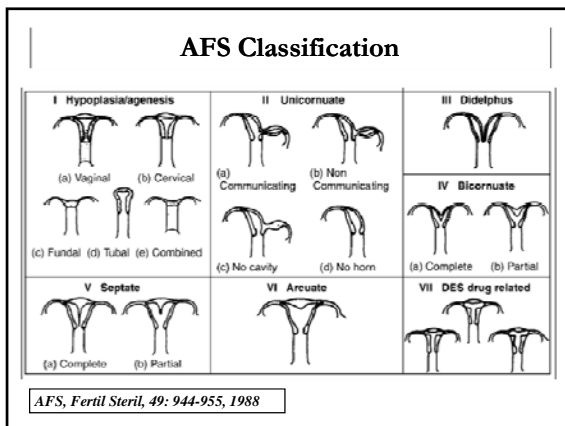
Female genital malformations: Embryogenesis

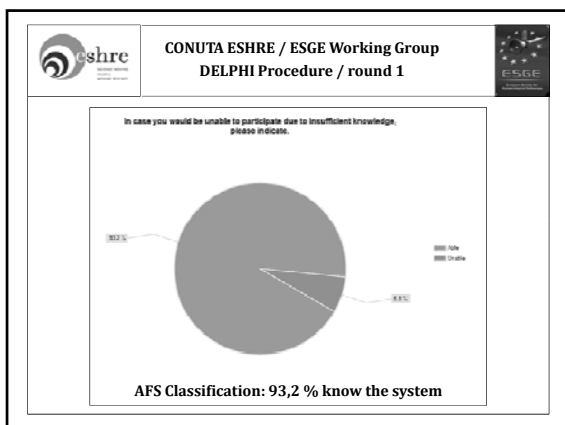
Failure of Müllerian ducts' development

Failure of Müllerian ducts' canalization

Failure of or abnormal fusion of the ducts

Failure of midline's septum absorption





AFS Classification: Limitations

- *Should arcuate uterus be placed as a separate class?*
- *Definitions of the classes are not clear enough for the needs of differential diagnosis between them*
- *It is not comprehensive: a lot of anomalies are not included in the categories of the system*
- *Place of all aplasias in the first class of the system (different clinical significance depending on the affected organ)*
- *Obstructive anomalies are not clearly represented in the classes of the system*

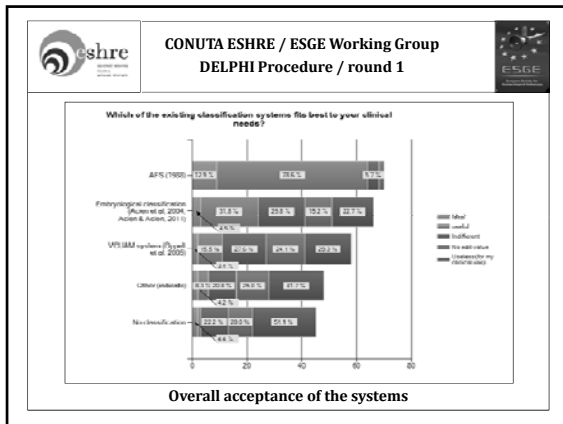
Grimbiz and Campo, Fertil Steril, 94: 401-407, 2010

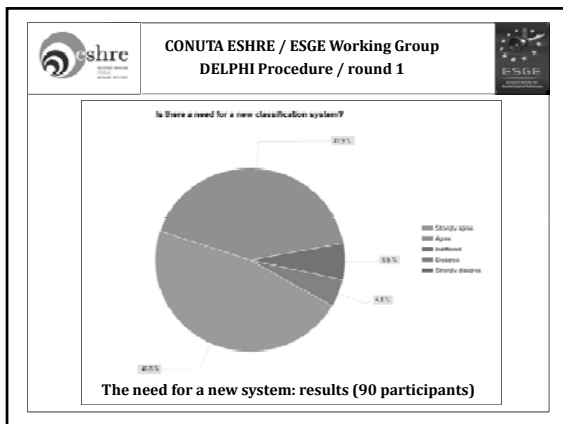
AFS Classification: Comments

The inability of the AFS classification system to effectively classify "complex" anomalies has as a result

two other proposals for a different classification system

subdivisions proposed for certain categories of genital malformations



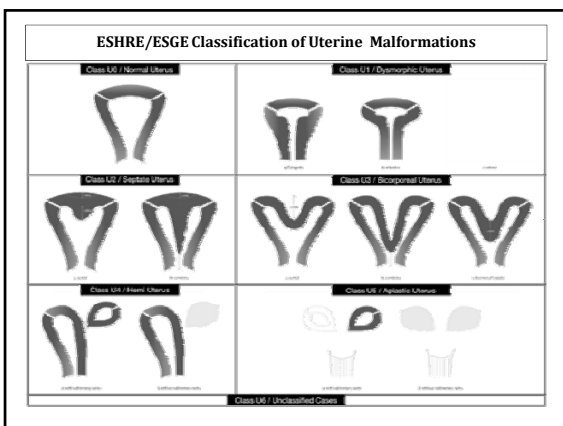


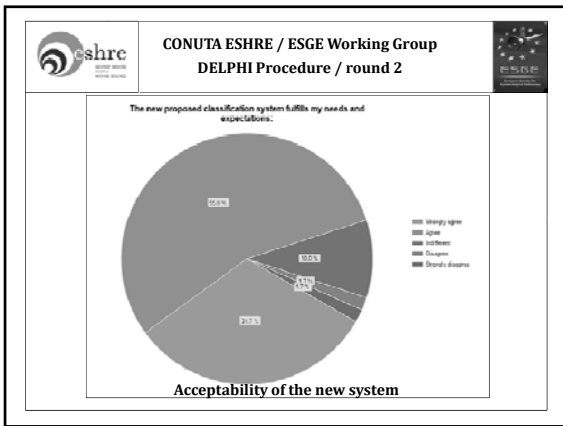
ESHRE **ESHRE / ESGE Working Group**

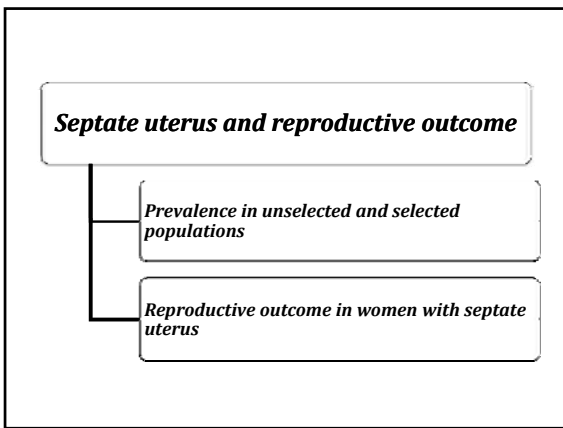
- ESHRE & ESGE recognizing the importance of female genital malformations have established a common initiative on that issue under the code name CON(genital) UT(erine) A(nomalies)
- Following the previous scientific work done by EAGS, the CONUTA group has initiated the Delphi procedure with the ultimate aim to create consensus between the experts on:
 - A new classification system
 - Guidelines on congenital anomalies diagnostic work-up
 - Guidelines on congenital anomalies treatment
- *Where we are?*
 - The new ESHRE/ESGE classification system is now ready!

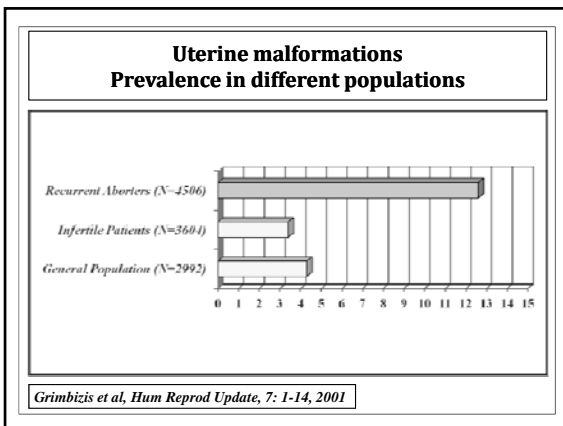
ESHRE/ESGE Classification of Female Genital Malformations

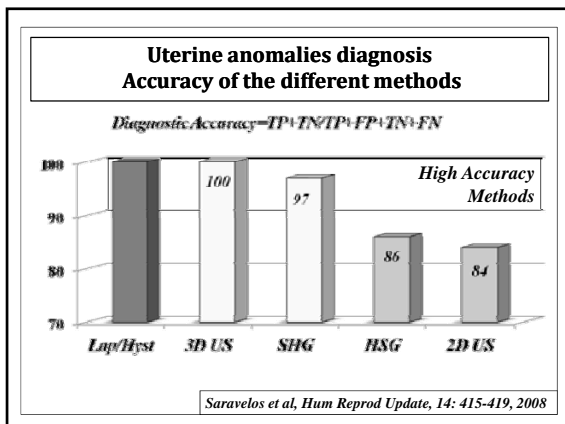
Uterine anomaly		Cervical / Vaginal anomaly	
Main class	Sub-class	Co-existent class	
U0	Normal uterus	C0	Normal cervix
U1	Dysmorphic uterus a. T-shaped b. Infundibulic c. Others	C1	Septate cervix
		C2	Double "normal" cervix
		C3	Unilateral cervical aplasia
U2	Septate uterus a. Partial b. Complete	C4	Cervical Aplasia
U3	Bicorporeal uterus a. Partial b. Complete c. Bicorporeal septate	V0	Normal vagina
		V1	Longitudinal non-obstructing vaginal septum
		V2	Longitudinal obstructing vaginal septum
U4	Horned uterus a. With rudimentary cavity (communicating or not horn) b. Without rudimentary cavity (horn without cavity / no horn)	V3	Transverse vaginal septum and/or imperforate hymen
		V4	Vaginal atresia
U5	Aplastic		
U6	Unclassified Malformations		
U		C	V

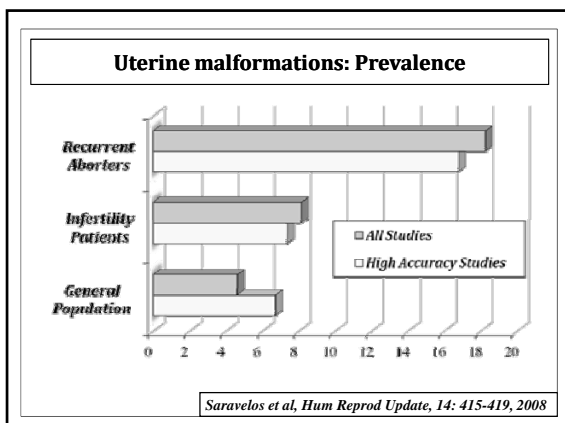












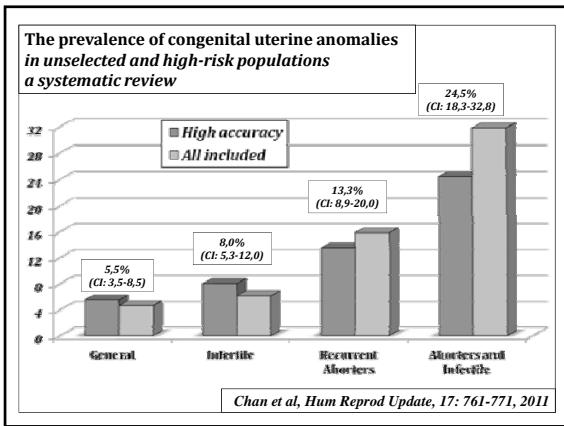
Uterine malformations and reproductive outcome

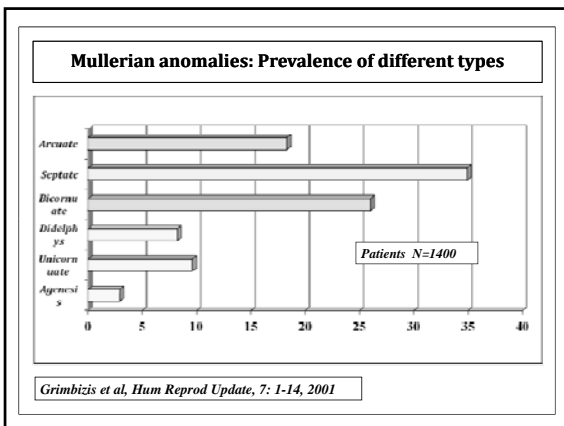
Malformations and pregnancy outcome: preliminary conclusion
The prevalence of uterine malformations is higher in patients with poor pregnancy outcome

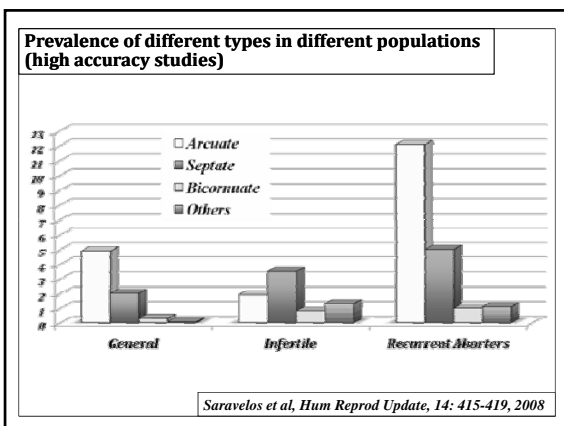
Malformations and fertility: preliminary conclusion
The prevalence does not seem to be different in infertile patients despite the common sense between experts that uterine malformations are found more commonly in infertile population

Are these conclusions final?
Are there changes that might elucidate more objectively this relation?

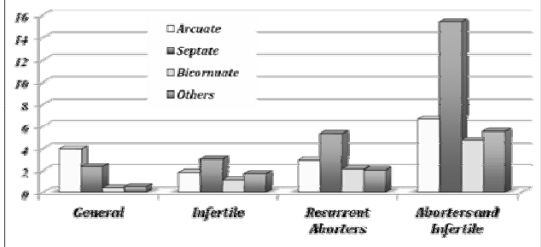
1. Greater awareness in the estimation of uterine anatomy
2. Increasing availability in every day practice of non-invasive, high accuracy diagnostic methods
3. Increasing experience with non-invasive high accuracy methods





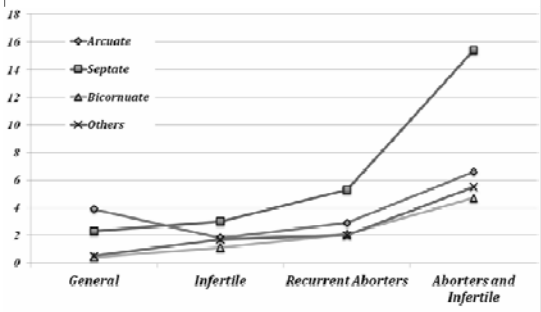


The prevalence of congenital uterine anomalies in unselected and high-risk populations a systematic review



Chan et al, Hum Reprod Update, 17: 761-771, 2011

The prevalence of congenital uterine anomalies in unselected and high-risk populations: a systematic review



Chan et al, Hum Reprod Update, 17: 761-771, 2011

Septate uterus and reproductive outcome

Prevalence in unselected and selected populations

Reproductive outcome in women with septate uterus

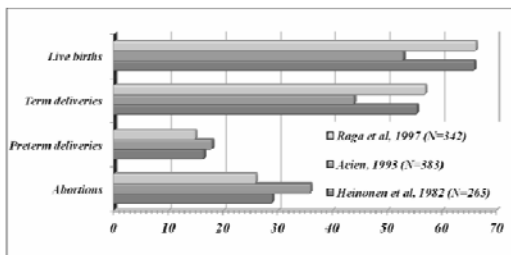
Clinical implications of uterine malformations and hysteroscopic treatment results

Grimbizis et al, Hum Reprod Update, 7: 1-14, 2001

Design: systematic review of retrospective cohort studies
Aim: to determine the pregnancy outcome in patients with untreated uterine malformations
Limitations: retrospective design of the studies included, not standard diagnostic method, no control group

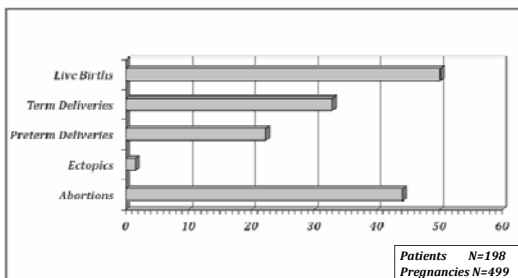
Study population: women with untreated uterine malformations

**Pregnancy outcome / Cohort studies
 Unselected population with uterine malformations**

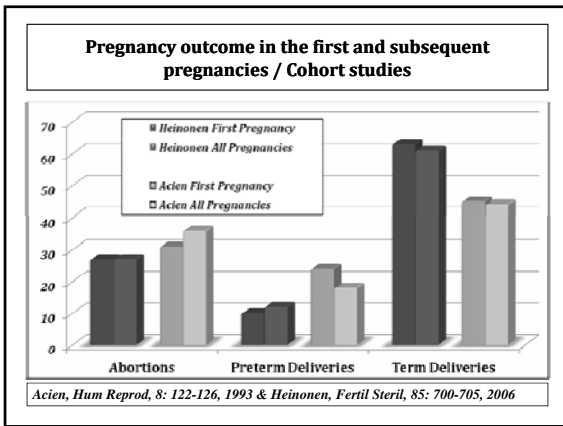


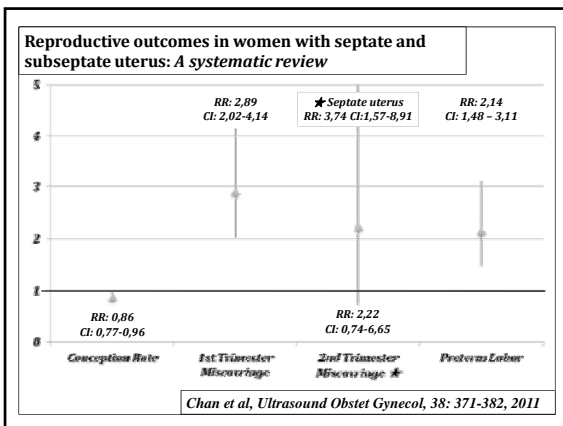
Grimbizis et al, Hum Reprod Update, 7: 1-14, 2001

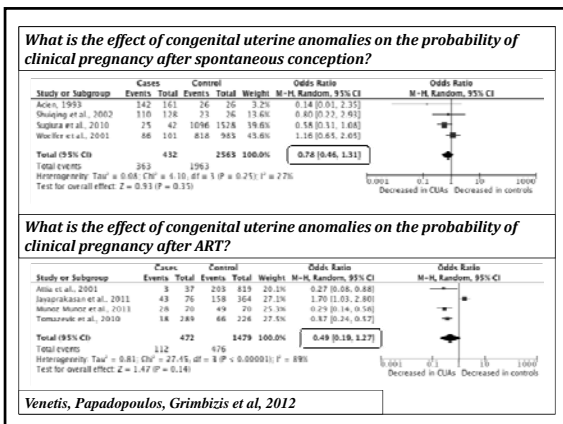
**Pregnancy outcome / Cohort studies
 Unselected patients with septate uterus**

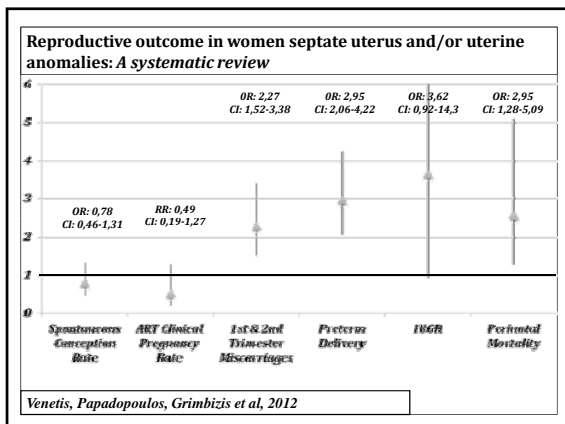


Grimbizis et al, Hum Reprod Update, 7: 1-14, 2001









Septate uterus seems to be associated with infertility and poor pregnancy outcome...

The more severe the degree of the anatomy defect, the more the possibility to impair woman's reproductive outcome...

... clinical problems associated with septate uterus support the need for hysteroscopic treatment

Uterine malformations and implantation failure
Pathophysiology: altered endometrial receptivity?

Redefining receptivity

Once the epithelial barrier has been overcome....

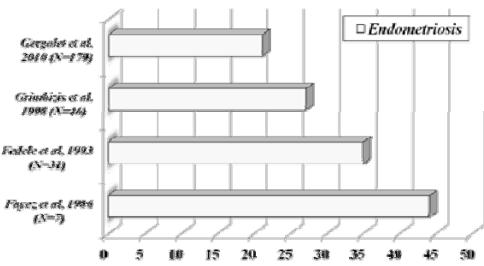
.....it may be that the uterine vasculature and stroma carry out subsequent barrier (or 'interrogative') functions towards the implanting conceptus

John Aplin

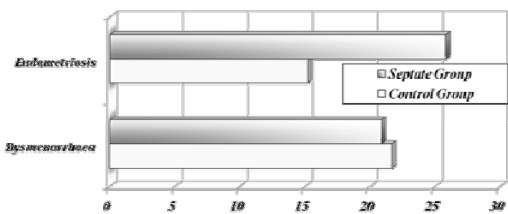
Uterine malformations and implantation failure
Pathophysiology: altered endometrial receptivity?

- ⊙ *Infertility and pregnancy losses in patients with uterine anomalies may be associated with abnormalities in the later vascular stages of implantation*
- ⊙ *Different vascular beds differ in receptivity to invading trophoblast*
- ⊙ *Uterine septum and/or uterine defective walls represent locations with alterations of endometrial vascularization indicating an impaired vascular bed*

Incidence of endometriosis in patients with septate uterus



Is there an association between septate uterus and endometriosis?
 Nawroth et al, Hum Reprod, 21: 542-544, 2006



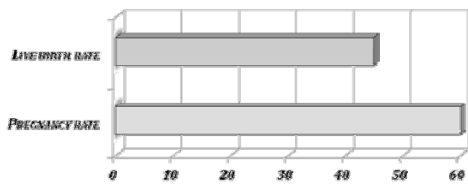
Design: Case-control study, retrospective; Aim: to determine the incidence of endometriosis in patients with septate uterus; Diagnostic method: hysteroscopy / laparoscopy
Cases: 120 patients (29,4 ± 4,7 years) with septate uterus
 51 primary, 36 secondary infertility / 33 recurrent abortions
Controls: 486 consecutive infertile patients (30,8 ± 6,3 years) with normal uterus
 252 primary & 234 secondary infertility

Does hysteroscopic treatment makes any difference on reproductive outcome?

Is there any treatment effect on fertility?

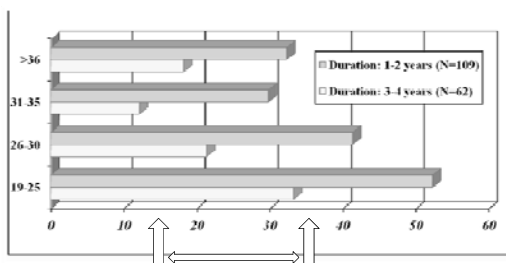
Does hysteroscopic treatment restore pregnancy outcome?

Reproductive outcome after hysteroscopic septoplasty in patients with septate uterus. A systematic review of the literature
Nouri et al, Reprod Biol Endocrinol, 8: 52, 2010



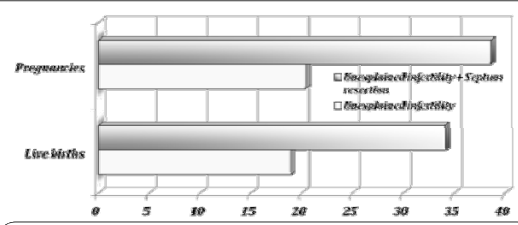
Design: systematic review, retrospective cohort longitudinal studies included
 Aim: to determine the effect of hysteroscopic treatment on reproductive outcome
 Study population: 1501 mainly infertile women with septate uterus
 Primary outcome: pregnancy and live birth rate after treatment
 Limitations: retrospective studies, no control group

Untreated patients with primary unexplained infertility
Cumulative pregnancy rates in the first year



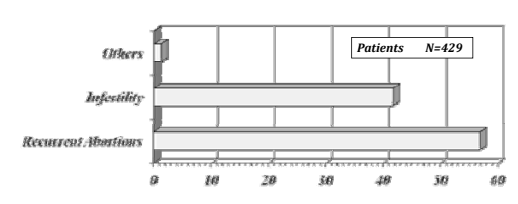
The ESHRE Capri Workshop, Hum Reprod, 11: 1779-1807, 1996

Hysteroscopic resection of the septum improves the pregnancy rate of women with unexplained infertility: a prospective control trial
 Mollo et al, Fertil Steril, 91: 2628-2631, 2009



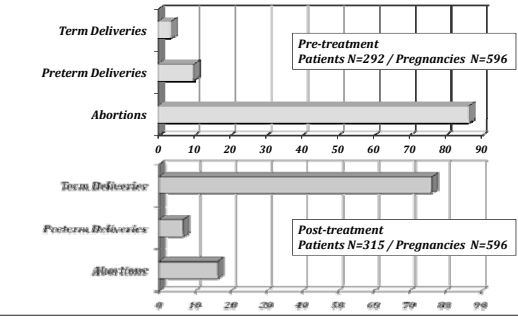
Study design: case-control, prospective
Aim: to assess fecundity of infertile women after surgical correction of uterine septum
Cases: 44 patients with septate uterus and otherwise unexplained infertility
Controls: 132 patients with normal uterus and unexplained infertility
Intervention: hysteroscopic metroplasty, IVF/ET

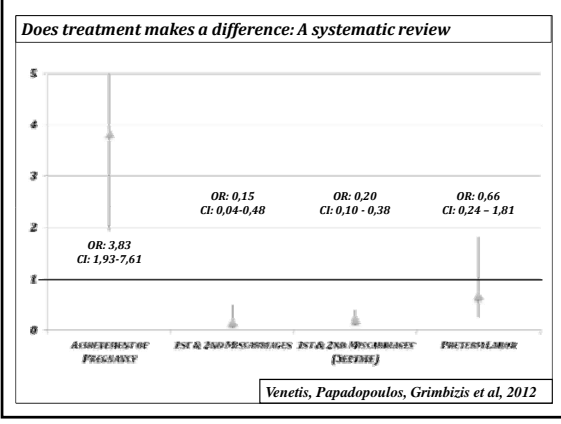
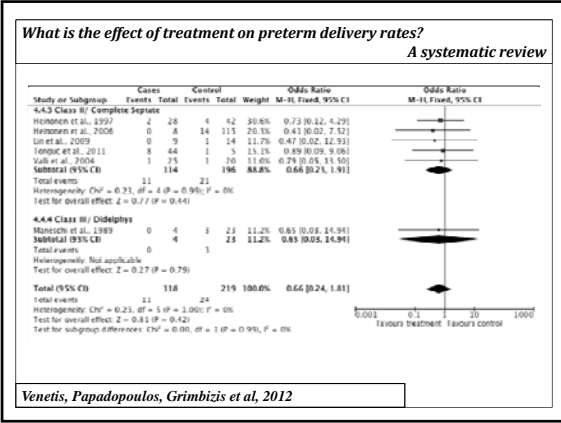
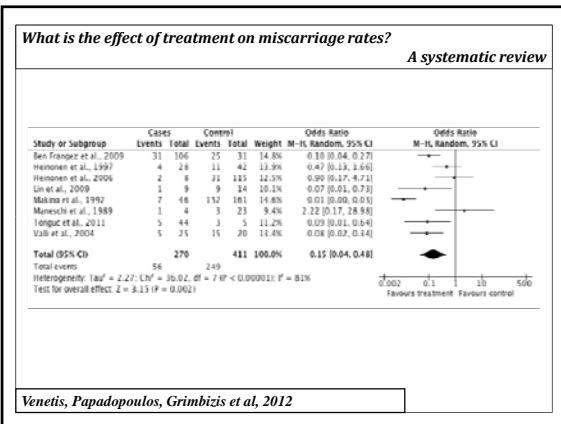
Clinical implications of uterine malformations and hysteroscopic treatment results
 Grimbizis et al, Hum Reprod Update, 7: 1-14, 2001



Design: systematic review, retrospective cohort longitudinal studies included
Aim: to determine the effect of hysteroscopic treatment on pregnancy outcome
Study population: 429 women with septate uterus
 596 pregnancies before treatment / 366 pregnancies after treatment
Limitations: retrospective studies, women served as their own controls, treatment effect might be explained as a "tendency to the mean"

Clinical implications of uterine malformations and hysteroscopic treatment results
 Grimbizis et al, Hum Reprod Update, 7: 1-14, 2001





Conclusions

- *Uterine anomalies are associated with impaired*
 - *fertility*
 - *pregnancy outcome*
- *Hysteroscopic metroplasty seems to be associated with an improvement*
 - *in the achievement of pregnancy*
 - *in pregnancy outcome*
- *Hysteroscopic treatment is indicated in patients with septate uterus*



Invitation

ESHRE Campus Workshop



“Female genital tract congenital malformations: new insights in an old problem”



Thessaloniki, 27 & 28 September 2013
Main Auditorium, “Papageorgiou” General Hospital

**Intramural fibroids
and implantation failure**

Mostafa Metwally MD MRCOG
Consultant in Reproductive Medicine and Surgery
The Royal Hallamshire Hospital, Sheffield, UK

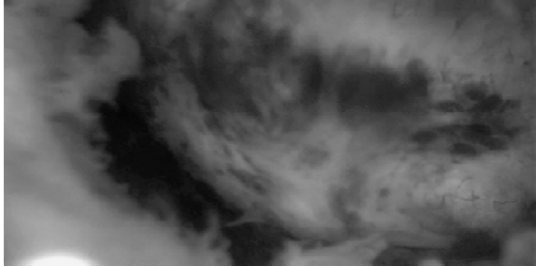
Learning Objectives

- Do intramural fibroids have an effect on implantation and fertility?
- Should intramural fibroids be removed to improve fertility?

Declaration

No conflict of interest

Fibroids and fertility
Submucous



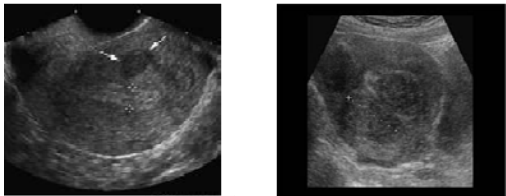
Fibroids and fertility
Subserous



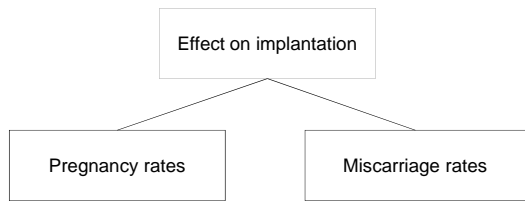
Fibroids and fertility
Intramural



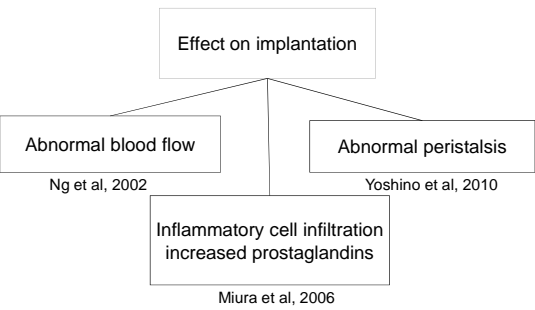
Intramural fibroids
a common finding




Intramural fibroids




Intramural fibroids



**Intramural fibroids
not a single entity**



Site




Size


Inconsistent
management

Number

**Intramural fibroids
not a single entity**



Site



Size

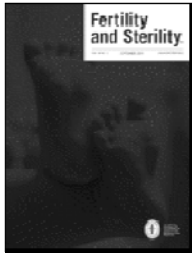
Inconsistent
management

Number

UTERINE FIBROIDS

**Fibroids and infertility: an updated systematic review
of the evidence**

Elizabeth A. Pritts, M.D.,¹ William H. Parker, M.D.,^{2} and David L. Olive, M.D.^{3*}*



UTERINE FIBROIDS				
Fibroids and infertility: an updated systematic review of the evidence				
Elizabeth A. Pritts, M.D., ¹ William H. Parker, M.D., ² and David L. Olive, M.D. ³				
Effect of fibroids on fertility: intramural fibroids.				
Outcome	Number of studies/substudies	Relative risk	95% confidence interval	Significance
A. All studies				
Clinical pregnancy rate	12	0.810	0.686-0.941	$P=0.006$
Implantation rate	7	0.684	0.587-0.796	$P<.001$
Ongoing pregnancy/live birth rate	9	0.703	0.583-0.849	$P<.001$
Spontaneous abortion rate	8	1.747	1.226-2.489	$P=0.002$
Preterm delivery rate	1	6.000	0.309-116.606	Not significant
B. Prospective studies				
Clinical pregnancy rate	3	0.708	0.437-1.146	Not significant
Implantation rate	2	0.682	0.391-0.781	$P=0.01$
Ongoing pregnancy/live birth rate	2	0.465	0.291-0.744	$P=0.019$
Spontaneous abortion rate	2	2.384	1.110-5.122	$P=0.02$
Preterm delivery rate	0	—	—	—
C. Studies using hysteroscopy in all subjects				
Clinical pregnancy rate	2	0.846	0.666-1.071	Not significant
Implantation rate	1	0.714	0.547-0.931	$P=0.013$
Ongoing pregnancy/live birth rate	2	0.733	0.363-1.405	Not significant
Spontaneous abortion rate	2	1.215	0.301-3.774	Not significant
Preterm delivery rate	1	6.000	0.309-116.606	Not significant

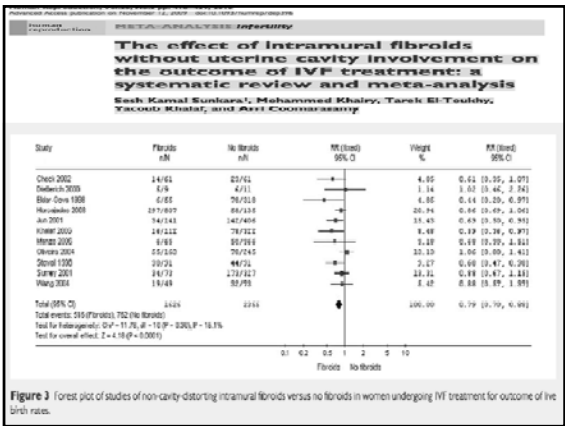
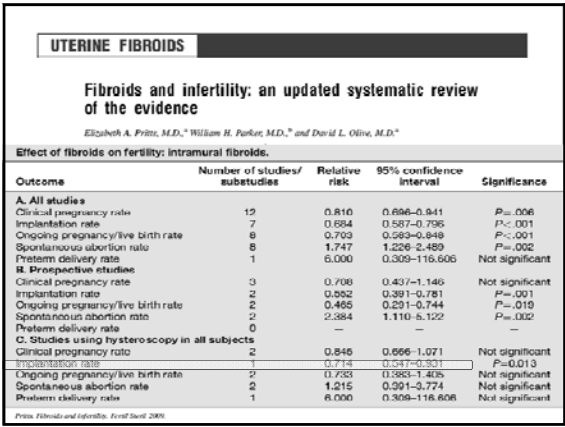
Pritts, Fibroids and Infertility, Fertil Steril 2005

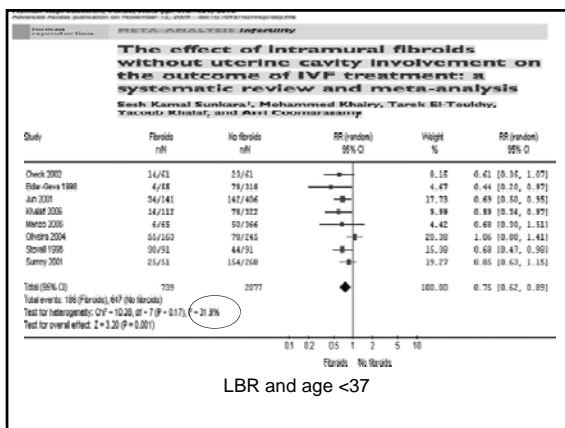
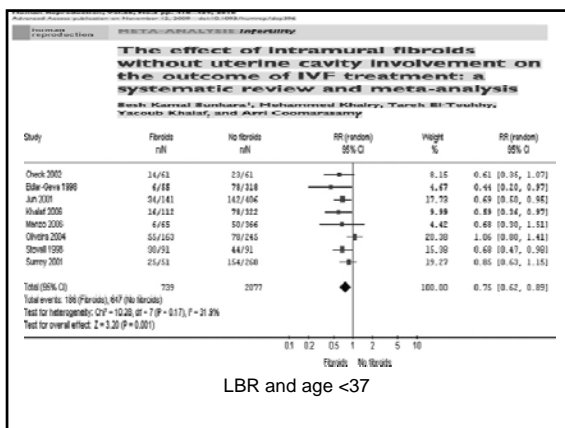
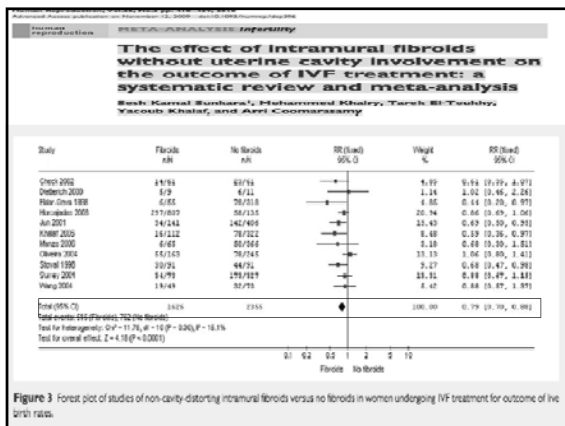
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Pritts, Fibroids and Infertility, Fertil Steril 2005

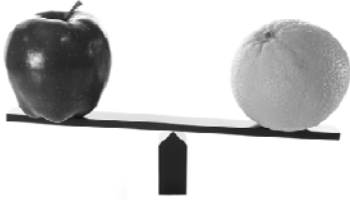
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Pritts, Fibroids and Infertility, Fertil Steril 2005





Heterogeneity



How to decrease heterogeneity?

- Intramural fibroids only
- Exclude cavity involvement
- Number, size and site
- Account for confounding factors: Age
- Ongoing pregnancy rate vs. LBR

The image shows the cover of a medical journal article. At the top, it features the Elsevier logo and the text 'www.elsevier.com' and 'www.reproductive.com'. Below this, it says 'SYMPOSIUM: REPRODUCTIVE SURGERY REVIEW'. The main title of the article is 'Is another meta-analysis on the effects of intramural fibroids on reproductive outcomes needed?'. The authors listed are 'Mostafa Metwally ^{a,*}, Cynthia M Farquhar ^b, Tin Chiu Li ^c'. The cover also features a graphic of a globe with a grid of dots, and the text 'Reproductive BioMedicine Online'. At the bottom, it says 'www.elsevier.com'.

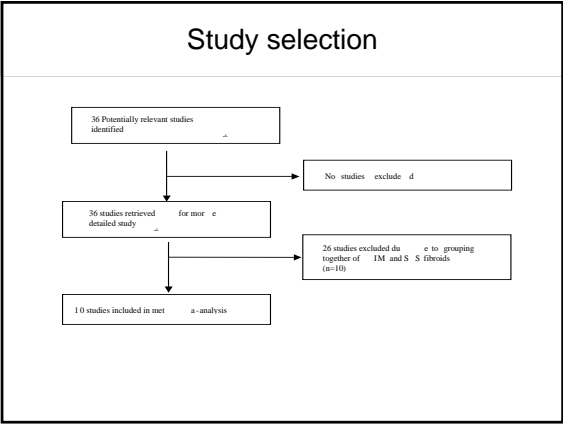
What is new?

- Strictly intramural fibroids
- Sensitivity analysis:
 - Age
 - Hysteroscopy/sonohysterography
 - Low risk of bias studies

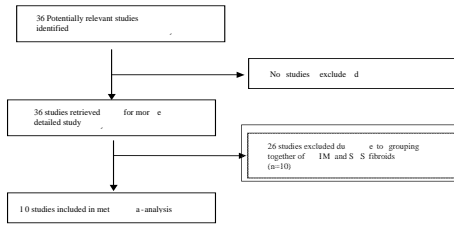
What is new?

- Strictly intramural fibroids
- Sensitivity analysis:
 - Age
 - Hysteroscopy/sonohysterography
 - Low risk of bias studies

**Decrease
heterogeneity**



Study selection



Study quality

Study	Prospective design	Cavity involvement adequately excluded	Age possible confounding factor	Sample size calculation	Uterine anomalies excluded	Subserous fibroids present
Bodag et al. (2009)	No	Yes	No	No	Yes	No
Cavini et al. (2006)	Yes	Yes	No	No	No	No
Dietterich et al. (2000)	No	No	Yes	No	Yes	Yes
Hart et al. (2001)	Yes	Yes	Yes ^a	Yes	No	Yes
Horcajadas et al. (2008)	No	Yes	Yes	No	No	No
Khalaf et al. (2006)	No	Yes	Yes ^a	Yes	No	Yes
Klatzky et al. (2007)	No	No ^b	Yes	Yes	Yes	No
Ng et al. (2005)	Yes	No	No	No	No	No
Sarney et al. (2001)	No	Yes	No ^b	No	Yes	No
Vimercati et al. (2007)	No	Yes	No	No	No	No

Study quality

Clinical pregnancy rate

Study or Subgroup	Fibroids		Control		Weight	Odds Ratio		Odds Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI	
Bodag et al. 2009	22	61	167	444	13.8%	0.64	[0.54, 1.61]	
Dietterich et al. 2000	5	9	7	31	5.4%	0.73	[0.12, 4.32]	
Hart et al. 2001	7	117	90	322	10.7%	0.17	[0.03, 0.34]	
Horcajadas et al. 2008	431	807	80	325	16.9%	0.79	[0.54, 1.14]	
Khalaf et al. 2006	27	112	106	322	14.9%	0.65	[0.40, 1.04]	
Klatzky et al. 2007	22	69	149	275	13.8%	0.40	[0.23, 0.69]	
Ng et al. 2005	11	48	7	47	7.6%	1.70	[0.60, 4.84]	
Sarney et al. 2001	27	51	70	114	12.1%	0.71	[0.58, 1.58]	
Vimercati et al. 2007	4	31	57	205	7.2%	0.38	[0.13, 1.15]	
Total (95% CI)		1300		1875	100.0%	0.69	[0.42, 0.87]	
Total events	516		733					
Heterogeneity: Tau ² = 0.17, Chi ² = 20.67, df = 8 (P = 0.008), I ² = 61%								
Test for overall effect: Z = 2.71 (P = 0.007)								

Clinical pregnancy rate

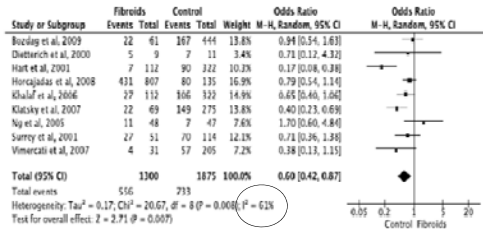
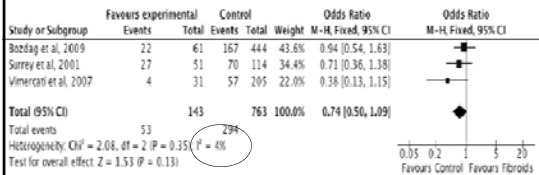


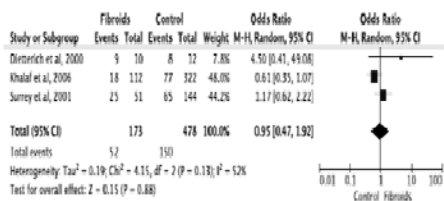
Figure 3 The effect of presence of intramural fibroids on the clinical pregnancy rate after assisted conception.

Clinical pregnancy rate

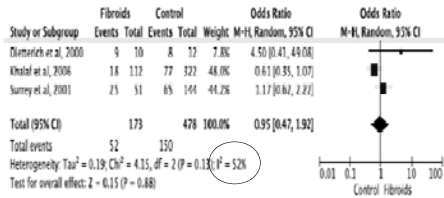
Sensitivity analysis



Live birth rate

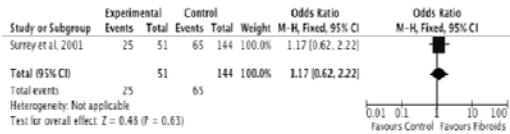


Live birth rate

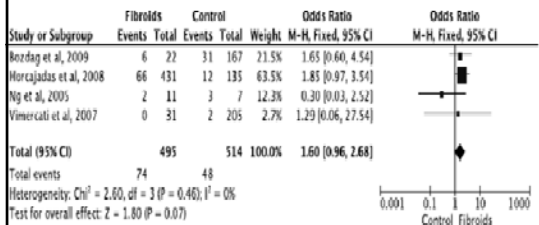


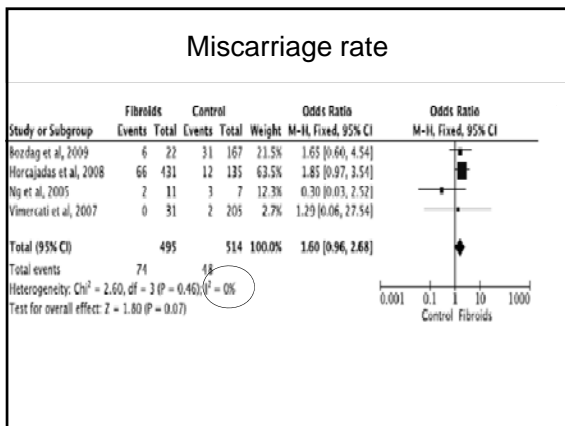
Live birth rate

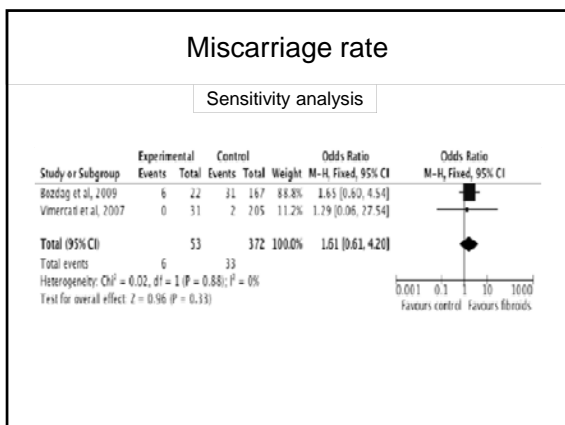
Sensitivity analysis



Miscarriage rate







Intramural fibroids

insufficient evidence that
Intramural fibroids decrease
pregnancy rates

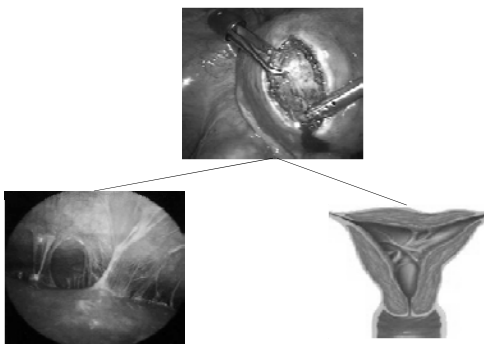
Intramural fibroids

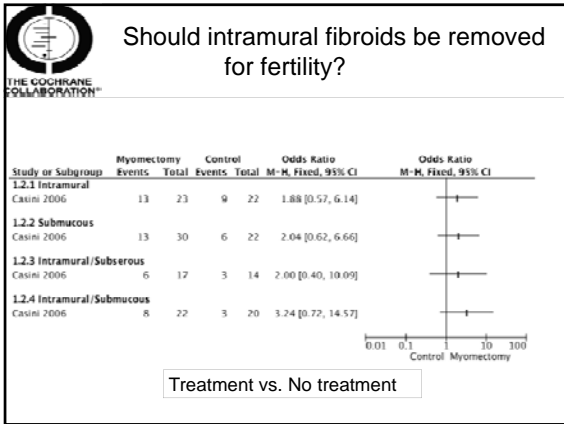
insufficient evidence that
Intramural fibroids decrease
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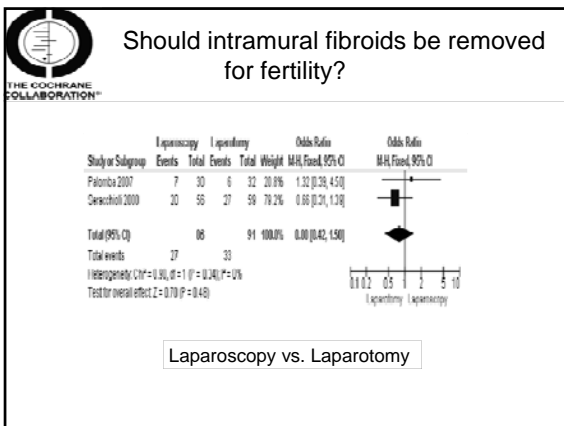
Do not increase miscarriage
rates

Should intramural fibroids be
removed for fertility?









Should intramural fibroids be removed for fertility?

insufficient evidence that myomectomy improves pregnancy rates

Should intramural fibroids be removed for fertility?

insufficient evidence that myomectomy improves pregnancy rates

No difference between laparoscopy and laparotomy

Summary of evidence

- The effect of intramural fibroids on implantation and fertility is uncertain

Summary of evidence

- The effect of intramural fibroids on implantation and fertility is uncertain
- Treatment should be individualized

Summary of evidence

- The effect of intramural fibroids on implantation and fertility is uncertain
- Treatment should be individualized
- Intramural fibroids do not cause miscarriage

Summary of evidence


- The effect of intramural fibroids on implantation and fertility is uncertain
- Treatment should be individualized
- Intramural fibroids do not cause miscarriage
- Consider hysteroscopy

Summary of evidence

- The effect of intramural fibroids on implantation and fertility is uncertain
- Treatment should be individualized
- Intramural fibroids do not cause miscarriage
- Consider hysteroscopy
- Consider other factors:
 - Site, size, number
 - Combination with other fibroids
 - Cause of Infertility

Bibliography

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- Pritts EA, Parker WH, Olive DL: Fibroids and infertility: an updated systematic review of the evidence. *Fertil Steril*. 2009 91(4):1215-23.
- Sunkara SK, Khairy M, El-Toukhy T et al: The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. *Hum Reprod*. 2010; 25(2):418-29.
- Yoshino O, Hayashi T, Osuga Y et al: Decreased pregnancy rate is linked to abnormal uterine peristalsis caused by intramural fibroids. *Hum Reprod*. 2010 Oct;25(10):2475-9.



**Adenomyosis and implantation failure:
the oocyte or the uterus?**

Stephan Gordts

*ESHRE 2013
London, 7 – 10 July*

Adenomyosis
BE
Endometriosis

L.I.F.E.
Leuven Institute for Fertility & Embryology

Conflict of interest: cons. Storz

**Publications on Adenomyosis and
Endometriosis**

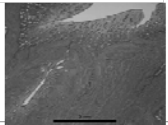
	<u>Aden'osis</u>	<u>End'osis</u>
2000-today	1.387	10.718
80s & 90s	845	9.853
60s & 70s	174	2.988
Before	58	651
	1077	

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Adenomyosis - Pathogenesis

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

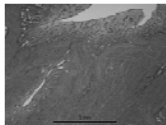
It is a myoproliferative disease of the inner myometrium and is further characterized by an altered local paracrine and immune microenvironment




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Adenomyosis - Incidence

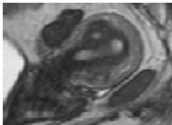
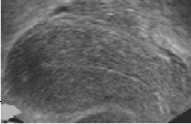
No real clinical diagnosis
common histological diagnosis



Incidence: 5- 70 %
retrospective studies



Clinical entity
TVS and MRI

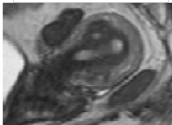



LIFE
Leuven Institute for Fertility & Embryology

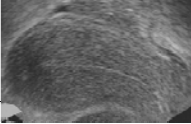
Adenomyosis - Incidence

subfertility
dysmenorrhea
menorrhagia

Incidence: 28/56 (50%)



Clinical entity
TVS and MRI



Brosens J et al.1995 Lancet,346

LIFE
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Adenomyosis and reproduction

New:

clinical entity: diagnosis by US/ MRI/ hysteroscopy

increased age of women wishing to conceive

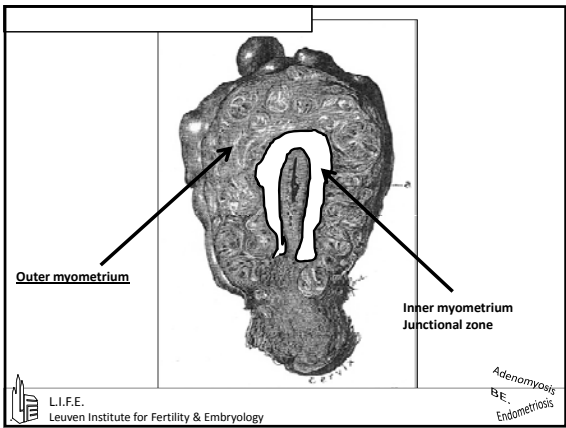
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Adenomyosis
B.E.
Endometriosis

Adenomyotic Lesion
Cullen, 1920

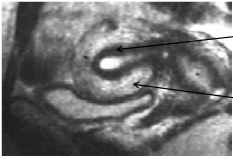
- Defined as endometriosis with predominantly fibromuscular tissue
- Locations :
 - uterus
 - rectovaginal space
 - tubal isthmic segment
 - round ligament
 - ovarian fossa
 - uterosacral ligament
 - sigmoid
 - abdominal wall and umbilicus

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MRI
clinical significance of the myometrial architecture

Myometrium has 2 structural and functional different entities



Junctional zone
small central zone of increased density
IMPORTANT IN REPRODUCTION

Outer myometrium
Larger outer hypodenser zone

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Leuven Institute for Fertility & Embryology

The Myometrial Junctional zone

JZ myometrium is a distinct uterine structure

More akin to the endometrium than outer myometrium

Like the endometrium, the JZ is of Müllerian origin, while the outer myometrium is of non-müllerian, mesenchymal origin (Noe et al. 1999)

The JZ but not outer myometrium undergoes cycle-dependent changes

Uterine peristaltic activity originates exclusively from the JZ while the outer myometrium remains quiescent throughout the cycle

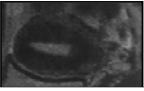
L.I.F.E.
Leuven Institute for Fertility & Embryology

Adenomyosis
BE
Endometriosis

Junctional Zone Myometrium
Important role in Reproduction

Functional important entity in reproduction

- Early changes from time of implantation
- Decidualization and trophoblast invasion
- Defective transformation of JZ spiral arteries in spectrum of pregnancy complications
- Preterm rupture membranes
- Preterm delivery



L.I.F.E.
Leuven Institute for Fertility & Embryology

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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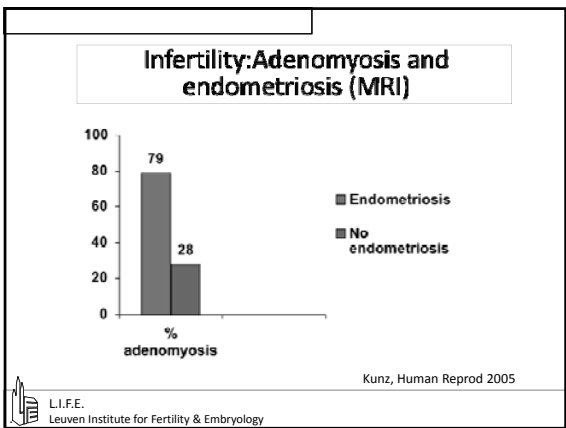
ADENOMYOSIS AND REPRODUCTION

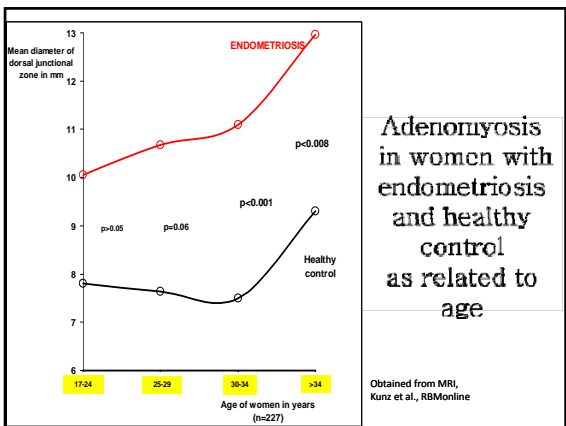
Relation ?

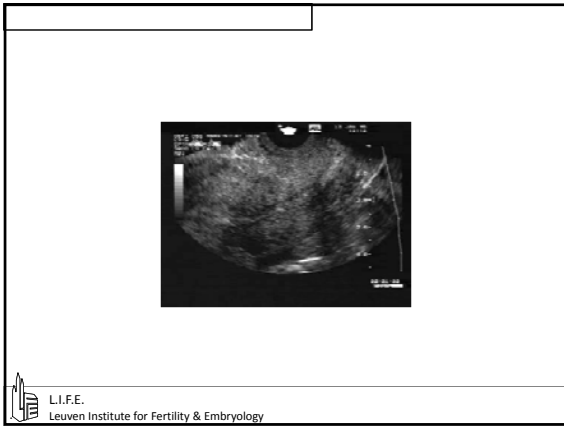
Impairing probability spontaneous conception?

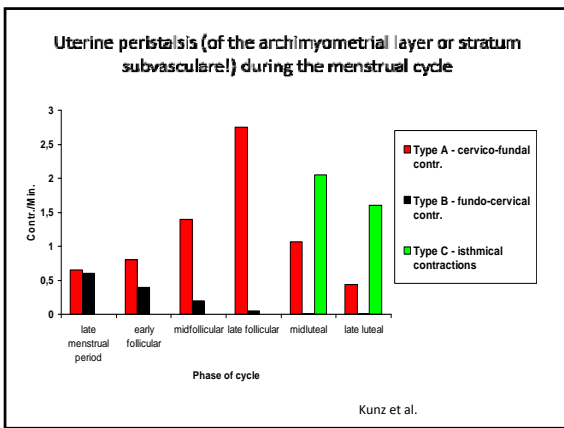
Disturbed JZ activity (Kunz et al, Brosens J et al)

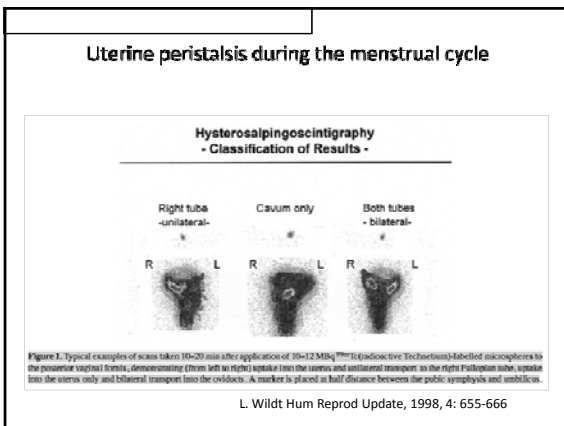
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Uterine peristalsis during the menstrual cycle

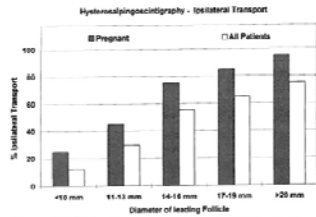
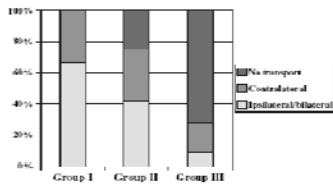


Figure 4. Lateralization of transport of labeled microspheres and size of the leading follicle. With increasing diameter of the dominant follicle, the proportion of patients exhibiting ipsilateral transport to the ovulated follicle increased progressively. The proportion of patients with ipsilateral transport was higher in those who became pregnant after timed intercourse or insemination than in those who did not conceive after this treatment (treatment duration leading up to six cycles). Up to a follicle size of 13 mm, ipsilateral transport could be diagnosed only in retrospect, at the time when a dominant follicle did appear on the side where radioactivity was concentrated.

L. Wildt Hum Reprod Update, 1998, 4: 655-666



Group I: Patients with endometriosis but no evidence of adenomyosis : highest % ipsilateral transport.
Group II: Endometriosis plus at least one feature of focal adenomyosis
Group III: Endometriosis plus widespread diffuse adenomyosis

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Uterine peristalsis and pregnancies

Table II. Result of hysterosalpingoscintigraphy and pregnancy rates (no. of pregnancies/no. of patients treated). Values in parentheses are percentages

	Ipsilateral transport	No transport
Pregnant ^a (Sp + IUI)	78/360 (21.7)	4/200 (2)
Pregnant ^b (IVF + ICSI)	25/110 (22.7)	48/198 (24.5)

^aIncludes pregnancy after normal and timed intercourse.
^bIncludes pregnancies after transfer of cryopreserved pronucleus cells.
IUI = intrauterine injection; ICSI = intracytoplasmic sperm injection; IVF = in-vitro fertilization.


L. Wildt Hum Reprod Update, 1998, 4: 655-666

ADENOMYOSIS AND REPRODUCTION

Impairing probability spontaneous conception?

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

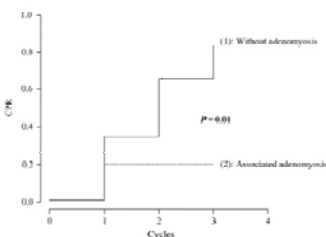
Impairing probability spontaneous conception?

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

Occurrence of pregnancies after reductive treatment


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Impact of adenomyosis on CPR in patients with colorectal endometriosis.



Cycles	1	2	3
Patients (n)	73	21	0
CPR(1)(95%CI)	33.3% (19.5-44.8)	64.7% (40-79)	82.4% (47.3-94)
CPR(2)(95%CI)	19% (0.5-34)	19% (0.5-34)	19% (0.3-34)


Balaster M et al. Hum. Reprod. 2012;27:1043-1049

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ADENOMYOSIS AND REPRODUCTION

Impairing probability spontaneous conception?

Yes: reduced fertility in patients with adenomyosis dysperistalsis JZ and disturbed uterine transport.

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Adenomyosis and IVF..


The Controversy...

Impact of ultrasound diagnosis of adenomyosis on IVF-ET in recipients of oocytes from the same donor.

	Adenomyosis recipients	Without adenomyosis recipients	P value
No. of patients	40	60	
No. of cycles	60	60	
Age (mean ± SD)	38.7 ± 6.5	37.9 ± 5.9	N.S
No. of oocytes/cycle (mean ± SD)	9.9 ± 2.3	9.5 ± 1.8	N.S
MII oocytes (%) (ICSI)	80.1	81.2	N.S
Transferred embryos (mean ± SD)	2.7 ± 1.5	2.7 ± 1.6	N.S
Implantation/embryo transferred (%)	27/160 (16.9)	40/161 (24.8)	N.S
Clinical pregnancy/cycle (%)	18/60 (30)	23/60 (38.3)	N.S
Miscarriage (%)	3/18 (16.7)	5/23 (21.7)	N.S
Ongoing/term pregnancies (%)	15/40 (37.5)	18/60 (30)	N.S

N.S = not significant.

Camargo, F., Gaytan, J., Caligaris, C., Simon, C. and Pellicer, A. (2001) Impact of ultrasound diagnosis of adenomyosis on recipients of sibling oocytes. *Fertil Steril*, 76, Abstract P-111.

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The effect of adenomyosis on in vitro fertilisation and intra-cytoplasmic sperm injection treatment outcome.

Costello MF et al. Eur J Obstet Gynecol Reprod Biol.. 2011 Oct

To investigate the effect of uterine adenomyosis diagnosed by transvaginal ultrasound on IVF/ICSI treatment outcome

A retrospective cohort study of all women aged ≤42
 A total of 201 patients

- 37 patients in Group A
- 164 patients in group NA


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The effect of adenomyosis on in vitro fertilisation and intra-cytoplasmic sperm injection treatment outcome

Costello MF, Lindsay K. et al. Eur J Obstet Gynecol Reprod Biol 2011; 158: 229-34.


	Adeno	Control
Number	37	164
Fertil.%	66.7 %	71.4 %
Implant %	28.3 %	31.6 %
Abortion %	15.4 %	27.1 %
Live Birth %	29.7 %	26.1 %

Long term down regulation protocol

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RESULTS:

- No difference in live birth rate per patient (cycle) between the two groups with both raw and logistic regression adjusted data (29.7%V 26.1%; p=0.395; OR 1.45 with 95% CI 0.61-3.43).
- No other differences in ovarian response, embryological parameters or clinical outcomes between the two groups

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IVF/ET outcomes in relation to myometrial thickness

Hyun Sik Youm et al
J Assit Reprod Genet. 2011 Sept 24

Three groups according to maximum myometrial thickness:

- group A (<2.00 cm: 302 patients, 397 cycles)
- group B (2.00–2.49 cm: 63 patients, 81 cycles)
- group C (≥2.50 cm: 48 patients, 73 cycles).



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Hyun Sik Youm et al J Assit Reprod Genet. 2011

Table 2 Response to ovarian stimulation and clinical outcomes

	Group A (397 cycles)	Group B (81 cycles)	Group C (73 cycles)	P-value
E ₂ level, hCG day (pg/mL) ^a	1990±1319.1	1725.3±1314.9	2017.0±1306.7	NS
Endometrial thickness, hCG day (cm) ^b	1.1±0.2	1.3±0.2	0.9±0.2 ^c	0.001
No. of oocytes retrieved ^d	11.4±5.2	11.8±8.2	10.2±5.0	NS
No. of fertilized oocytes ^e	8.2±5.6	8.3±6.4	7.5±3.9	NS
Fertilization rate per retrieved oocyte (%) ^f	82.2±18.7	81.7±17.9	82.1±18.6	NS
No. of embryos transferred ^g	3.1±0.8	3.2±0.8	3.1±0.8	NS
Implantation rate (%)	38.4 (158/412) ^h	38.281 (14/37)	39.238 (13/33) ⁱ	0.002
2000-2004 (200 cycles)	133/267 (21.2)	25/25 (20.3)	11/102 (10.8) ^j	0.04
2005-2009 (261 cycles)	13/30 (12.4) ^k	30/28 (23.4)	17/126 (13.5) ^l	0.03
Clinical pregnancy cycle (%)	37.1/397 (9.4) ^m	40.8/81 (50.3)	37.7/73 (51.5) ⁿ	0.02
2000-2004 (200 cycles)	122/219 (55.7)	28/42 (55.8)	8/28 (28.6) ^o	0.02
2005-2009 (261 cycles)	102/178 (57.3)	19/38 (50.0)	15/95 (15.3) ^p	0.02
Abortions/clinical pregnancy (%)	29/224 (12.9) ^q	3/42 (7.1) ^r	12/22 (55.2) ^s	<0.001
2000-2004 (200 cycles)	16/122 (13.1)	5/24 (20.8)	5/10 (50.0) ^t	0.009
2005-2009 (261 cycles)	13/102 (12.7)	4/19 (21.1)	7/12 (57.8) ^u	0.001
Ectopic pregnancy/clinical pregnancy (%)	9/224 (4.0)	1/42 (2.3)	0/23 (0.0)	NS
2000-2004 (200 cycles)	5/122 (4.1)	1/24 (4.2)	0/10 (0.0)	NS
2005-2009 (261 cycles)	4/102 (3.9)	0/19 (0.0)	0/13 (0.0)	NS
Live birth/cycle (%)	186/397 (46.9)	33/81 (40.7)	11/73 (15.1) ^v	<0.001
2000-2004 (200 cycles)	161/219 (46.1)	18/42 (41.9)	8/28 (28.6) ^w	0.017
2005-2009 (261 cycles)	85/178 (47.8)	15/38 (39.5)	6/95 (6.3) ^x	<0.001

	Group B (81 cycles)		P-value	Group C (73 cycles)		P-value
	B-1 (52 cycles)	B-2 (29 cycles)		C-1 (21 cycles)	C-2 (52 cycles)	
Implantation rate (%)	44/162 (27.2)	11/89 (12.4) ^y	0.001	9/64 (14.0)	8/104 (7.6)	NS
Clinical pregnancy cycle (%)	33/52 (63.5)	10/29 (34.5) ^z	0.012	9/21 (42.9)	14/52 (26.9)	NS
Abortions/clinical pregnancy (%)	4/33 (12.1)	5/10 (50.0) ^{aa}	0.01	4/9 (44.4)	8/14 (57.1)	NS
Live birth/cycle (%)	29/52 (55.8)	5/29 (17.2) ^{ab}	0.001	5/21 (23.8)	6/52 (11.5)	NS

B-1: Group B without myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial-myometrial junction
 B-2: Group B with myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial-myometrial junction
 C-1: Group C without myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial-myometrial junction
 C-2: Group C with myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial-myometrial junction

Hyun Sik Youm et al
J Assit Reprod Genet. 2011 Sept 24



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Conclusions

- Myometrial thickening of more than 2.50 cm exerts overall adverse effects on IVF-ET outcomes.
- Even with mild thickening (2.00–2.49 cm), the presence of sonographic findings suggestive of adenomyosis is associated with adverse outcomes of IVF-ET.

Hyun Sik Youm et al
J Assit Reprod Genet. 2011 Sept 24



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Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation

In vitro fertilization outcomes in recipients of oocytes from donors with and without ultrasound diagnosis of adenomyosis or endometriosis (Fedele [7] and Reinoldi [8]) or levels of transvaginal ultrasonographic diagnosis of adenomyosis.

	Adenomyosis group		Endometriosis group		Control group		P value
	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	
Donated oocyte	10.6	10.2-11.0	11.0	10.8-11.6	11.0	10.8-11.7	NS
Blastomeres (1 day 3)	7.6	7.5-7.8	7.5	7.3-7.8	7.4	7.2-7.7	NS
ET day							NS
Day 2	4 (1.2%)		3 (1.2%)		6 (1.8%)		
Day 3	292 (81.7%)		161 (67.8%)		256 (77.6%)		
Day 5	58 (17.7%)		40 (16.5%)		47 (15.7%)		
Day 6	34 (10.4%)		35 (14.5%)		79 (25.9%)		
No. of transferred embryos	1.97	1.93-2.04	1.93	1.88-1.98	1.90	1.89-1.96	NS
Implantation rate	22.6%	22.5-26.7	23.9%	18.3-35.7	20.6%	25.5-34.3	NS
Clinical pregnancy rate	10.0% (n = 121)	9.4-10.2	14.2% (n = 127)	17.8-20.4	14.4% (n = 147)	10.2-16.8	NS
Clinical miscarriage	13.1% (n = 43)	9.4-16.7	0.1% (n = 1)	3.1-6.2	7.2% (n = 24)	6.4-10.0	<.05
Multiple pregnancy	13.1% (n = 43)	8.5-16.7	15.3% (n = 37)	10.7-19.8	12.4% (n = 41)	8.8-15.0	NS
Term pregnancy rate	20.5% (n = 59)	22.3-31.8	30.0% (n = 92)	31.9-44.7	27.1% (n = 123)	31.5-42.4	<.05

Note: NS = not significant.
Martinez-Conejero: Adenomyosis and implantation in ART. Fertil Steril 2011.

Martinez-Conejero et al Fertil Steril. 2011 Oct

Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation.

Martinez-Conejero JA, Morgan M Fertil Steril 2011; 96: 943-50

	I: Adeno	II: Endom	III: control
Number	152	144	147
OD cycles	328	242	331
Age	40.5	37.3	40.9
Implant %	29.6%	33.3%	30.8%
Abortion %	13 %	6.1 %	7.2%
Term pregn %	26.8 %	38 %	37.1 %



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- Implantation rate in OD did not differ among the three groups.
- Miscarriage was significantly higher in the adenomyosis group vs. the adenomyosis + endometriosis and control groups.
- Term pregnancy rate was also significantly lower in the adenomyosis group compared with others.

CONCLUSION(S):

- Clinical and molecular data
 - Implantation is not affected
 - Higher miscarriage rates
 - Lower term pregnancy rates
- → a clear negative effect on the final outcome of OD

Ultrasound diagnosed adenomyosis has a negative impact on successful implantation following GnRH antagonist IVF treatment
V. Thalluri and K.P. Tremellen Hum Reprod 2012; 27: 3487-92

Retrospective study: 213 patients; no other interfering factors

	Adeno positive	Control
Number	38	175
Mean age	35 (32,7-37,3)	33 (30 -36)
Fertilization %	66.7%	66.7%
Estradiol	2100	3200
Clin. Pregnn.%	23.6%	44.6%
Abortion%	25%	10.3%

Adenomyosis reduces pregnancy rates in infertile women undergoing IVF
Behan Salim, Salon Riris, et al. RBM online 2012; 25: 273-7

	Adeno pos.	Control
Number	19	256
Clin. Pregn. %	22.2%	47.2%
Ongoing pregn. %	11.7%	45.9%
Abortion %	50%	2.86%

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Adenomyosis has no adverse effects on IVF/ICSI outcomes in women with endometriosis treated with long-term pituitary down-regulation before IVF/ICSI.
Mijatovic V, Florijn E et al. Eur J Obstet Gynecol Reprod Biol 2010; 151: 62-5.

74 pat with surgical endometriosis III – IV adeno 27 %

5.35 months down regulation

Fertil % 43.6 %
 Implant % 26.3 %
 Abortion % 24.3 %
 Clin Pregn % 31.7 %

No differences between groups

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NMR JZ thickness predicts IVF failure

Predictive value for implantation failure is 97 %
Odds ratio per patient is 39
Odds ratio per transfer is 39

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

Piver P. et al. J. Gynecol Obstet Biol reprod 34, 2005

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Adenomyosis and IVF

	Normal uterus	Adenomyosis
N	197 (91.7%)	18 (8.3%)
Age	37.2 (SD +/- 6.2)	37.7 (SD +/- 9.3)
Oocytes	8.3 (SD +/- 2.4)	9.1 (SD +/- 3.7)
MII oocytes	80.5%	78.9%
CPR	47.5%	28%
Miscarriage	11%	20%
Ongoing pregnancy rate	40%	16%

Paul Serhal

Adenomyosis and IVF

- Adenomyosis is found in a significant number of women undergoing IVF/ICSI
- Adenomyosis may have a significant negative impact on the outcome of IVF/ICSI; need for further research

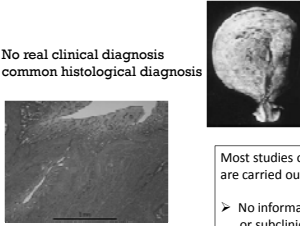
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Adenomyosis and the endometrium

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Endometrium and adenomyosis

**No real clinical diagnosis
common histological diagnosis**



Most studies on endometrium & adenomyosis are carried out on hysterectomy specimens:

- No information exists on endometrium in initial or subclinical forms of the disease.
- No epidemiological data on the incidence

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**Adenomyosis does not affect implantation,
but is associated with miscarriage
in patients undergoing oocyte donation**

To evaluate the effect of adenomyosis on endometrial gene expression and its correlation with oocyte donation outcome.

After identifying the 25 window of implantation genes strongly related with endometrial receptiveness and the implantation process

Martinez-Conejero et al Fertil Steril. 2011 Oct

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DESIGN:

- Transcriptomic analysis of the endometrium of women with adenomyosis during the window of implantation.
- The gene expression profile of the samples obtained on LH +7
- Endometrial samples were analyzed using microarrays in women with adenomyosis and healthy controls.(diagnosed by TVU; 6 patients in each group)

Martinez-Conejero et al Fertil Steril 2011 Oct

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RESULT(S):

- Similar endometrial gene expression pattern in both the adenomyosis group and controls
- 34 dysregulated genes in adenomyosis patients were identified but none belonged to the group of window of implantation genes.

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The distribution of immune cells and macrophages in the endometrium of women with recurrent reproductive failure: adenomyosis and macrophages.
Tremellen KP, Russell P I.Reprod Immunol 2012; 93:58-63

64 women with diffuse adenomyosis / adenomyoma
Endometrium biopt late luteal phase:
increase of macrophages
increase of natural killers

Adenomyosis and infertility.
Campo S, Campo V, Benagiano G
RBM online 2012;24: 35-46

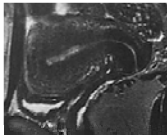
Altered decidualisation
Increase in intra uterine free radicals
Uterine dysperistalsis

Leukemia inhibitory factor is dysregulated in the endometrium and uterine flushing fluid of patients with adenomyosis during implantation window
Xiao Y, Sun X. Fertil Steril 2010; 94:85-9

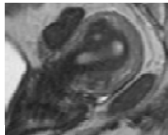
LIF, mRNA LIF & protein: decreased in patients with adenomyosis in endometrial tissue and flushing

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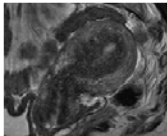
Adenomyosis - Characteristics



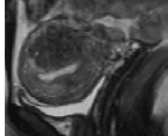
Diffuse lesion



Focal lesion



Hyperplasia




Adenomyoma

MRI
New challenges to uterine diagnosis

MRI has demonstrated the importance of JZ pathology.

Uterine diagnosis should implement the evaluation of the JZ myometrium.

HOW ?
 As MRI can not be implemented as a screening procedure we explore the value of US and HSC ?


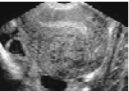
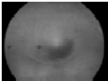

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Adenomyosis : Minimal invasive diagnosis ?

Magnetic Resonant Imaging
 MRI

Ultrasound

Hysteroscopy

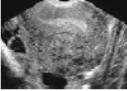

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The Myometrial Junctional zone
Adenomyosis : Minimal invasive diagnosis ?


2D TVS
 Accuracy: 83%
 Sensitivity: 75%

Ultrasound

3D TVS (coronal view)
 Accuracy: 89%
 Sensitivity: 91%

Evacuatus Ultrasound Obstet Gynecol 2011; 37: 44-48

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Adenomyosis
SE
Endometriosis

MRI objective parameters in diagnosing adenomyosis by 3DTVS

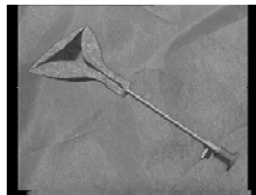
- JZ > 12mm
- ratio of maximum thickness of JZ (JZ max/total maximum myometrial thickness) > 40%
- difference between the JZ max and the minimum thickness of the JZ (JZ max - JZ min = Jzdif) > 5mm

Exacoustos Ultrasound Obstet Gynecol 2011; 37: 471-479



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**Hysteroscopy
Natural access to JZ myometrium**



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Subtle lesions sign of JZ Pathology?

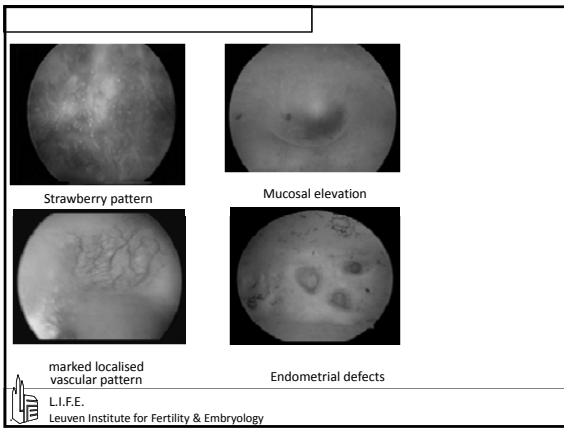
Abnormal endometrial images with an unclear clinical significance

Subtle lesions possibly related to adenomyosis

- Strawberry pattern
- Cystic mucosal elevation
- Focal or general hypervascularisation
- Endometrial defects



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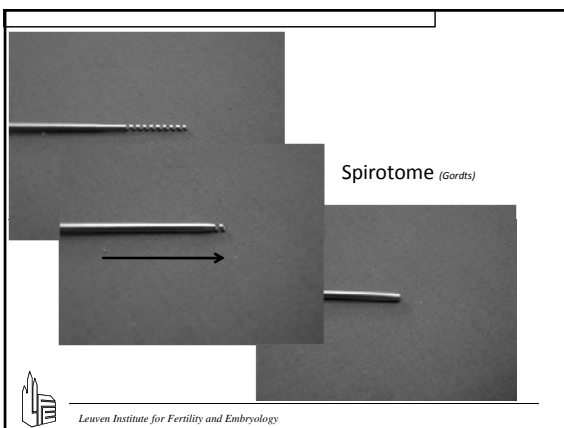
New Tools for Myometrial Exploration

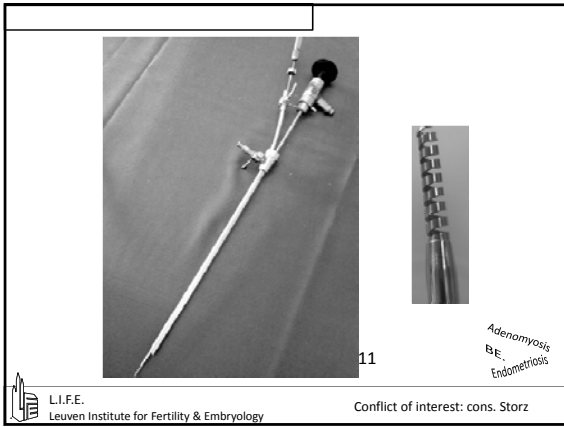
Spirotome

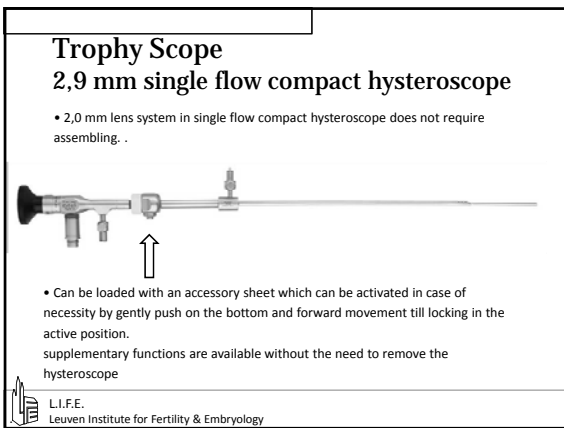
A device made to harvest high quality samples from soft tissues.

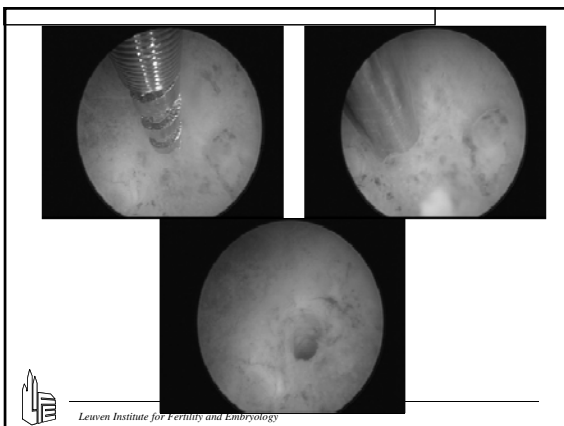
It is built on the pioneering concept of a cutting helix on a cutting canula well identified by Ultrasound.

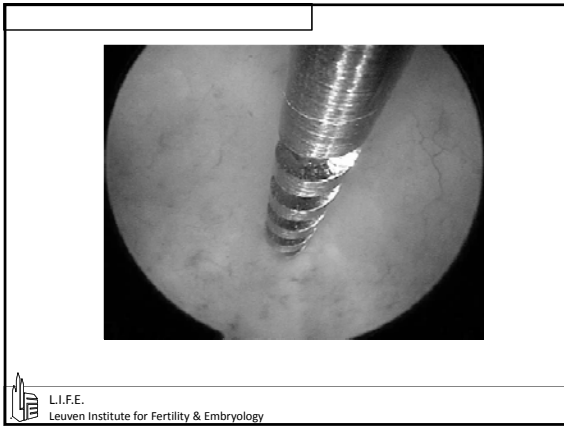
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Spirotome (*Gordts*)

The sample is harvested by turning the helix into the diseased area under ultrasound guidance. The cannula turns subsequently over the helix to free the sample from the surroundings.

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ADENOMYOSIS and REPRODUCTION CONCLUSIONS

- Limited number available date
- TVS/MRI made from adenomyosis a clinical entity
3D TVS, coronal view , high accuracy, high cost/ effectiveness
- Decreased fertility through involvement of junctional zone
- Cyto reductive treatment results in amelioration of fertility

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ADENOMYOSIS and REPRODUCTION CONCLUSIONS

- Uterine hyper- and dysperistalsis with impeded sperm transport
- Alterations of the eutopic endometrium
- Archimetrial infiltrations into the neometra (adenomyosis and its early manifestations)
- No available data of impaired oocyte quality

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Adenomyosis
BE
Endometriosis

ADENOMYOSIS and REPRODUCTION CONCLUSIONS

Endometriosis/ adenomyosis are primarily a disease of the uterus

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Uterine adenomyosis and surgery

C. Wood Hum Reprod update 1998, 4

“ if junctional zone hypertrophy is present without endometrial penetration of the myometrium, it may deserve a new name, or the definition of adenomyosis could be changed to include a pre-invasive stage to describe the junctional zone hypertrophy, adenomyosis, stage 0


L.I.F.E. Leuven Institute for Fertility & Embryology

Adenomyosis
BE
Endometriosis

**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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Aetiology of adenomyosis

Trauma by chronic peristalsis and hyperperistalsis
autotraumatization

How long does it take before
pathology of junctional zone results in
adenomyosis and/or
endometriosis?

Management

Women with symptomatic severe endometriosis
should prior to surgery be investigated for the
presence of adenomyosis

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Uterine Disorder Triad
Larsen et al 2011

Endometriosis <i>Associated with</i>	Adenomyosis 34.6% <i>Increased in stage IV</i> 42.8%
--	--

The E & JZ Disorder
39.9%

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Uterine Endo-Myometrial dysfunction

Endometrium & Junction Zone Disorder

Endometriosis Adenomyosis

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Ivo Brosens
Rudi Campo
Patrick Puttemans
Sylvie Gordts
Marion Valkenburg

L.I.F.E.
Leuven Institute for Fertility & Embryology

Surgery of hydrosalpiges and implantation rate
(salpingectomy / salpingostomy / ligation /essure)

<p>Frequency of tubal pathologies in infertility Causes of tubal occlusion – Chlamydia Diagnosis of DTO - infertility problems</p> <p>Endo-lumen / Ampulary / Fibril - lesions Diagnosis: HSG / and 3D hydrososonography Trans Vaginal Endoscopy / Laparoscopy</p> <p>Treatment and success rates: Salpingectomy / Salpingostomy Tubal ligation / micro-insert -Essure</p>	<p>ESHRE SIG Reproductive Surgery</p> <p>7 - 10 July 2013 29th Annual Meeting Pre-Congress Course 9</p> <p>London – United Kingdom</p>
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Vasilios Tanos, MD, PhD.
Professor in Obstetrics and Gynaecology

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Causes of tubal factor Infertility
Risks and Statistics

- Tubal and pelvic Pathology 30 - 40%
- Tubal factor increases with age and infertility duration
(Am.Soc.ReprMed A Practice Com Report 2000)
- Risk of subsequent tubal infertility after PID is
 - 10 -12% after 1 episode
 - 23 -35% after 2 episodes
 - 54 -75% after 3 episodes
 (Westrom LV et al Sex Transm Diseases 1994)
- Mucosal subtle adhesions value has not yet fully validated by prospective studies and it is difficult to interpret and compare
(Al-Inany H Acta Obs Gynec Scand 2001)

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Distal Tubal Occlusion
a wide spectrum of severity

- Agglutinated fibrina - Adherent fibril folds,
- Various degrees of phimosis
partial up to severe form
- Complete obstruction
- Hydrosalpinges

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Chlamydia and tubal cause of infertility

- Chlamydia Ab test as accurate as HSG in detecting tubal pathology (Rowland AS et al Epidemiology 2002) (Mol BW ASRM Birmingham, AL 2001)
- Chlamydia antibody tests: Immunofluorescence, Microimmunofluorescence ELISA Immunoperoxidase
- Source of antigen: Genus –specific major outer membrane proteins
Inactivated organism, Whole cell inclusion

Some methods are highly specific for the chlamydia species do not distinguish antibodies between C trachom., C pneumonia or C psirlaci (Jones CS et al J Clin Pathol 2003) (Land JA et al Hum Reprod 1998)



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Chlamydia test as a selective criteria to send patients for endoscopic surgery

- Select patients likely to benefited most by laparoscopy
- If applied as screening test tool early in a evaluation a positive chlamydia antibody test might alert one to the possibility of tubal factors although it may be unjustified for all infertile patients
(Johnson NP et al BJOG 2000)
- May be recommended for unexplained infertility, with normal HSG, those suspected to have tubal factor



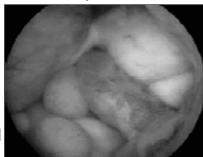
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Diagnosis of tubal pathologies

- 2D and 3D US + Hydrosonography
- HSG / Sono – cannot reliably detect or accurately define lesser degrees of disease when the tubes are still open
- Trans vaginal Endoscopy
Excellent for subtle tubal lesions
Hysteroscopic microinsert for PTO
- Laparoscopy – salpingoscopy
Provides the definitive diagnosis and
Treatment options



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Hydrosalpinges adversely affect fertility & IVF outcomes

- Mechanical interference with implantation
- Toxic affects on the embryo
- Toxic affects on the endometrium

(Beyler SA et al. *Hum Reprod* 1997)
 (Meyer WR et al. *Hum Reprod* 12:1393, 1997)
 (Strandell A et al. *Hum Reprod* 16:2403, 2001)



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Hydrosalpinx and IVF outcome:

a prospective randomized multicentre trial in Scandinavia on salpingectomy prior to IVF

Group	Patient	PR	Miscarriage	Live birth
Salpingectomy	112	36.6%	16.2%	28.6%
NO salpingectomy	92	23.9%	26.3%	16.3%

PR, p= 0.067 LBR, p=0.045

Strandell et al 1999 Human Reprod 14:2762



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Surgical treatment for tubal disease in women due to undergo in vitro fertilisation

Johnson N, van Voorst S, Sowter MC, Strandell A, Mol BW, *Cochrane Database Syst Rev*:CD002125, 2010.

- 2010 review, 5 RCTs, overall 646 patients
- Double PR in women underwent
- Salpingectomy (OR = 2.14, CI= 1.23 – 3.73)
- Tubal Ligation (OR = 4.66, CI= 2.47 – 10.01)
- Neither of the procedures was superior to the other
- **Conclusion:** Data clearly demonstrates that laparoscopic salpingectomy or tubal occlusion increases IVF success rates by 2-fold and should be recommended to all women with hydrosalpinges planning IVF



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Women with DTO - Fertility Management

- Younger women with mild DTO – Reconstructive Surg
 - Laparoscopic surgery
 - Wait for spontaneous pregnancy for the 1st pop year if not then IVF
- Older women ... IVF more effective and efficient
 - Significant degree of DTO (irreversible forms ... BTL, microinsert , salpigectomy, etc)
 - Cycle fecundability after DTO is 1 -2%
- Time is limited (Marana R, Quagliarello J, Distal tubal occlusion: microsurgery versus IVF—a review, *Int J Fertil* 33:107, 1988)



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Hydrosalpinges and treatment options

- Fibrinolysis – separation of adherent fibria
- Fibrinoplasty – correction of phimotic but patent fibria
- Neosalpingostomy – reopening of a completely obstructed tube
- Tubal ligation
- Salpingectomy – excision of the tube
 - Complete ... close to the cornua (endanger compromising vascular network)
 - Partial below isthmus ?? (increased risk of recurrency)
- Micro-insert proximal end occlusion by hysteroscopy
(The microinsert –Essure, consists of stainless steel inner coil, a Nitinol expanding, super-elastic outer coil, a polyethylene terephthalate fibers)



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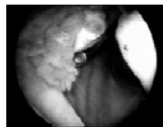
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Laparoscopic Fimbrioplasty

- 35 women with DTO
- Laparoscopic Fimbrioplasty, follow up 2 years

- Intrauterine PR 51%
- Live birth rate 37%
- Ectopic PR 23%



Audebert AJ, Pouly JL, Von Theobald P
Hum Reprod 13:1496, 1998



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Pros & Cons of Tubal Ligation

- In general it's a simple operation
- Decreased risk to destroy blood supply to ovary and ovarian stimulation in ART cycle
- Increased risk to ligate the tube in cases with severe adhesions

- Risk of pain aggravation ... persistence of Hydrosalpingis
- Risk of recurrent infection, eventually pyosalpinx
- Risk of additional surgery (salpingectomy at a later stage)
- Pregnancy rate chance is less than that after salpingectomy
- Higher risk of an ectopic pregnancy



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Important characteristics leading to salpingostomy as treatment option

The extent and character of the lesions affect the prognosis

1. Size of the HS / preferable small hydrosalpingis
2. Partial occlusion is preferable
3. Peri – tubal / ovarian adhesions
4. Tubal thickness / normal is thin wall
5. Endolumen mucosal architecture (severity of adhesions)
6. Internal ampullary mucosal architecture

(Winston RM, *J Assist Reprod Genet* 9:309, 1992)
(Dubuisson JB et al. *Hum Reprod* 10:1145, 1995)



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General Surgical success after salpingostomy

- The majority of pregnancies occurs within the first 2 years after surgical treatment
- an evaluation of 35 cases, (Audebert AJ et al. *Hum Reprod* 13:1496, 1998)
- Pop tubal patency success rates far exceed PR
 - patency is more easily restored than function
- Mucosal regeneration is slow and often fails altogether (Kitchin JD et al. *Am J Obstet Gynecol* 1986. (Daniell JF et al *Fertil Steril* 1986)
- For the milder forms of DTO pop live birth rate > 50%
(Donnez J, Casanas-Roux F, *Fertil Steril* 1986)
- For severe forms of DTO pop live birth rate is 10 -35%
(Taylor RC, Berkowitz J, McComb PF, *Fertil Steril* 2001)
- Risk for ectopic pregnancy is 5 -20%



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Unilateral Hydrosalpings with a Contra-Lateral Patent Tube

- 23 women with unilateral hydrosalpinx treated with salpingostomy
- Intrauterine pregnancy rate 43.5 %

Conclusion: unilateral salpingostomy in women with a contra-lateral patent tube improves fertility

McComb & Taylor 2001 Fertil Steril 2001



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Salpingectomy impairs regional vascular network

- Retrospective study
- 40 women had salpingectomy
- 25 women had proximal tubal ligation

Conclusion:

Salpingectomy appears to reduce ovarian response to stimulation
No difference in pregnancy rate and miscarriage rate

Gelbaya et al Ferti Steril 2006,85:1464



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Proximal tubal ligation Vs Salpingectomy

Randomized Control Trial

	Number of patients	Ongoing PR / transfer
Tubal occlusion	45	37.8 %
Salpingectomy	47	48.9 %
No treatment	14	7.1 %

Kontoravdis et al, Fertil Steril 2006



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Salpingostomy technique

1. Clear adhesions and mobilize fimbrial end
2. Locate and stabilize blocked ostium
3. Incise and open blocked ostium
4. Inspect lumen – salpingoscopy
Evaluate mucosal architecture, degree of adhesions versus healthy tissue
5. Eversion of fimbrial mucosa
6. Secure stoma with suturing



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Hysteroscopic treatment of hydrosalpinges

Micro-insert proximal end occlusion by hysteroscopy

The microinsert –Essure, consists of stainless steel inner coil, a Nitinol expanding, super-elastic outer coil, a polyethylene terephthalate fibers



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Micro-inserts seem promising

- 7 studies published on the topic with generally positive results. [Sonigo C et al Gynecol Obstet Fertil.(French) 2013]

Thebault N et al. J Gynecol Obstet Biol Reprod (Paris) 2012

- 13 infertile women with hydrosalpinges, essure placement prior to IVF
- Easy placement in all patients
- 1 pop complication (pyosalpinx)
- 64 % rate of pregnancy,
- 18 % rate of normally ongoing pregnancies
- with no Essure related complication during pregnancy and delivery



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Micro insert (Essure) treatment of Hydrosalpinges in patients could not undergo salpingectomy prior to IVF

Reference	Study type	Patients	Comments	PR	BR
Hitkari JA et al Fertil Steril 2007	Descriptive	5	2/5 bil successful application		
Mijatovic V et al Fertil Steril 2010	Prospective single arm	10	PTO achieved at 9/10 pts	40	20
Mijatovic V et al EJOGR Rep Biol 2012	Prospective single arm	20	1 case amnionitis 2 nd trim	36	27
Thebault N et al 2012 JGO Biol Rep (Paris)		13	1 pyosalpinx	64	18
Sonigo C et al 2013 GyneObsteFertil (Fr)	Review 7 studies		All 7 studies show +ve results and no complications		

Conclusion: The placement of Essure in ambulant setting, is feasible and safe alternative to laparoscopic approach with encouraging fertility results



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Micro-insert Essure application Pros & Cons

- Ambulant setting by office Hysteroscopy
- Fast procedure
- Alternative treatment when extensive pelvic adhesions
- The vascularity of the ovary is not compromised

- Risk to perforate the tube
- Delayed occlusion up to 3 months
- Need of X-ray confirmation of occlusion
- Risk of the insert-spiral hanging in the endometrial cavity
- The tube wall remains
- Safety, efficiency are under research
- Cost effectiveness ? Expensive for some health systems



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Surgery of Hydrosalpinges and Implantation rates

Summary of hydrosalpinges treatment options prior to IVF except salpingostomy that gives the chance for a spontaneous conception

	No treatment	Micro-insert	Tubal Ligation	Salpingostomy	Salpingectomy
Pregnancy rate	7-10%	27 - 40% ?? Very small series	25 -37%	mild DTO >50% severe DTO 10-40 %	25 - 35%
Procedure Effort	0	++ need good Hysteroscopy skills	++	+++++ very high skill level surgery	+++ high skill level surgery
Complications	+++ infection recurrence	Under research perforation of the tube	++ failure to ligate tube	+ risk of ectopic 20%	++++ compromised ovarian function



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Conclusion

- Hydrosalpinges reduce pregnancy rates
- Unilateral Hydrosalpinges also reduce PR and should be treated
- Age, past history and tubal health status will indicate the treatment option
- Mild forms DTO ... salpingostomy gives chance for spont pregn
- Severe forms DTO ... salpingectomy (balance your decision according to surgery radicality to be accomplished)
- Severe forms of adhesions and tubal deformities
 - tubal ligation PTO
 - micro insert hysteroscopic PTO



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The importance of minor endometrial pathology and endometrial scratch in Repeated Implantation Failure (When a treatment is indicated)

Prof T C LI
Professor of Reproductive Medicine & Surgery
Sheffield, England

London, 7 July, 2013

Outline

- Minor endometrial pathology which affects implantation
- Endometrial scratch in Repeated Implantation failure

Outline

- Minor endometrial pathology which affects implantation
- Endometrial scratch in Repeated Implantation failure

Levels of evidence

- Level 1+ : high quality meta-analyses of RCTs or RCT with a low risk of bias
- Level 1- : meta-analyses or RCTs or RCT with a high risk of bias
- Level 2 : systematic review of case-control or cohort studies or well conducted case-control or cohort studies
- Level 3: case reports or case series
- Level 4: expert opinion

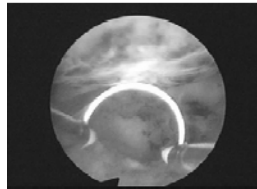
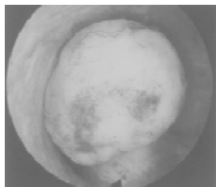
Endometrial pathology

- Obvious or significant
- Subtle or minor

Significant endometrial pathology

Submucus fibroid

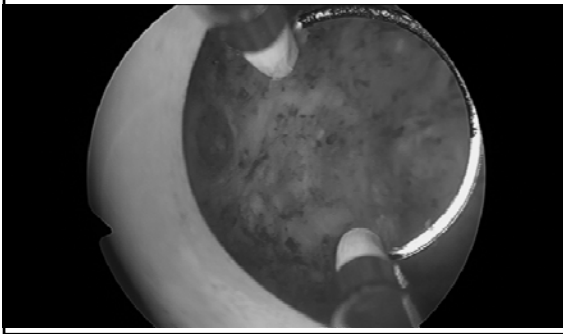
Endometrial polyp



Subtle Endometrial Pathology

- Adenomyosis
- Intra-mural fibroid
- Uterine septum
- Intra-uterine adhesions
- Chronic endometritis
- Thin endometrium

1. Adenomyosis



Expression of integrin $\beta 3$ and osteopontin in the eutopic endometrium of adenomyosis (n=28) was significantly lower than controls (n=27) during the implantation window

Xiao, Li et al, 2013
European J Obst Gynae Reprod Bio

Adenomyosis is a potential cause of recurrent implantation failure during IVF treatment
Tremellen & Russell, 2011
Aust N Z obstet Gynaecol 51:280

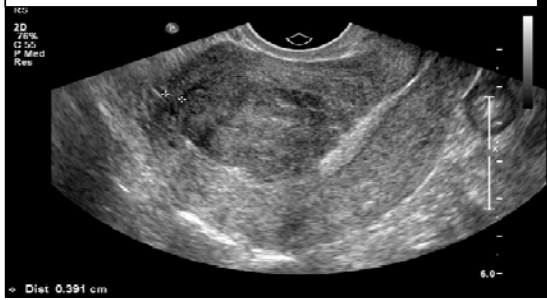
Surgery is of no benefit

Ultra-long protocol in women with adenomyosis may improve outcome

Level 3 evidence

2. Intra-mural fibroid

Not apparently distorting the cavity

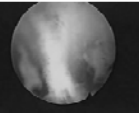


There is insufficient evidence that removal of intra-mural fibroids improves implantation rate

Metwally M, Farquhar C, Li TC (2011)
Is another meta-analysis on the effects of intramural fibroids on reproductive outcome needed?
RBM Online 23: 2-14

In women with recurrent implantation failure, intra-mural fibroids of >5cm should be removed

Level 3 evidence



3. Uterine septum


Retrospective Control Study

Outcome of singleton pregnancies after IVF/ICSI in women before and after hysteroscopic resection of a uterine septum compared to normal controls
Ban-Franquez et al, Euro J Obstet Gynae & Reprod Biol 2009

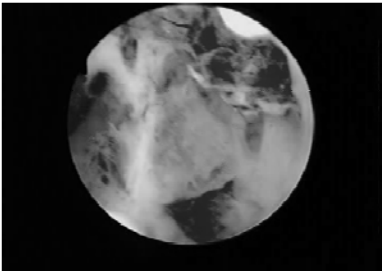
	Miscarriage rate	Miscarriage rate in matched controls	P value
Large septum, not removed	83.3%	16.7%	<0.001
Small septum, not removed	78.9%	23.7%	<0.001
Large septum removed	30.6%	20.4%	NS
Small septum removed	28.1%	19.3%	NS

Level 2 evidence

SEPTUM TRANSECTION



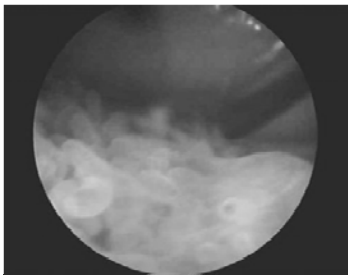
4. Intra-uterine adhesion



4. Intra-uterine adhesion

- There is no firm evidence to show treatment of this condition improves outcome, but it seems logical to remove the adhesions covering the endometrium

5. Chronic Endometritis



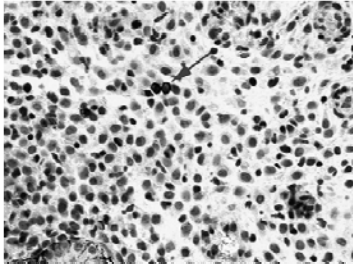
Chronic endometritis is a frequent finding in women with recurrent implantation failure after IVF

Johnston-MacAnanny et al 2010 Fertil Steril 93:437-41

1. Present in 30% of women with RIF
2. In women with RIF, the IR in those with chronic endometritis (11.5%) is significantly lower than those without the condition (32.7%)

Chronic Endometritis

Diagnosis: mast cells in endometrial biopsy



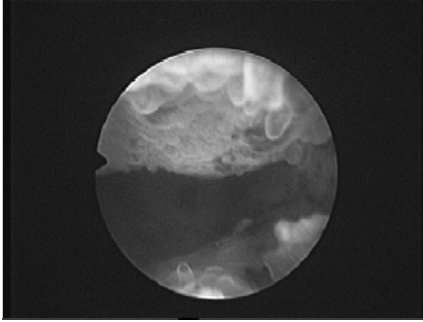
Chronic Endometritis

- Often clinically silent
- Often subtle
- Prevalence in infertile population up to 19% (Polisseni et al 2003, Gynecol Obstet Invest 55:205)
- May contribute to increased inflammatory markers in uterine cavity (Inagaki et al 2003, Human Reprod 18:608)
- Culture does not always isolate organism

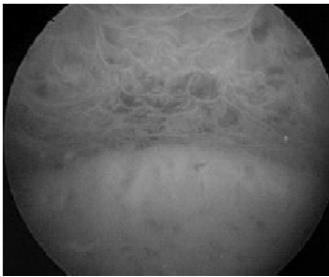
Chronic Endometritis

Hysteroscopy features

5. Chronic Endometritis



5. Chronic Endometritis



Chronic Endometritis Treatment

- Effectiveness of antibiotic treatment not proven
- Doxycycline 100mg bd for one week
- Ciprofloxacin 500mg bd and metronidazole 400mg tds for two weeks

6. Thin endometrium

- Previous intra-uterine surgery
- Infection
- Genetic: Turner syndrome
- Congenital: T-shape uterus
- Previous radiotherapy
- unexplained

6. Thin endometrium

- Hysteroscopy essential
- Modified long protocol with high dose estrogen priming

Modified long protocol

- Aim – increase the duration of estrogenic priming of the endometrium prior to hCG trigger
- Start GnRH agonist in the mid-luteal phase of the cycle preceding IVF treatment
- Start high dose estrogen therapy (estradiol valerate 8mg per day) two days after menstruation
- Monitor endometrial thickness with serial ultrasonography after 7 days of estrogen therapy
- Start gonadotrophins after endometrium has grown to more than 6mm; continue estrogen therapy

Level 4 evidence

Thin endometrium

- Hysteroscopy essential
- Modified long protocol with high dose estrogen priming
- Sildenafil?

Outline

- Minor endometrial pathology which affects implantation
- Endometrial scratch in Repeated Implantation failure

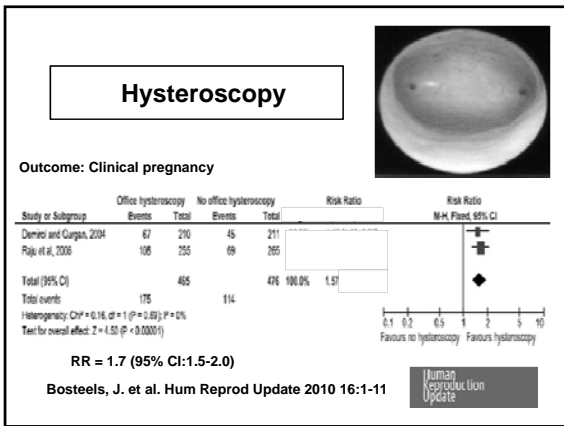
How often is there an endometrial pathology for RIF?

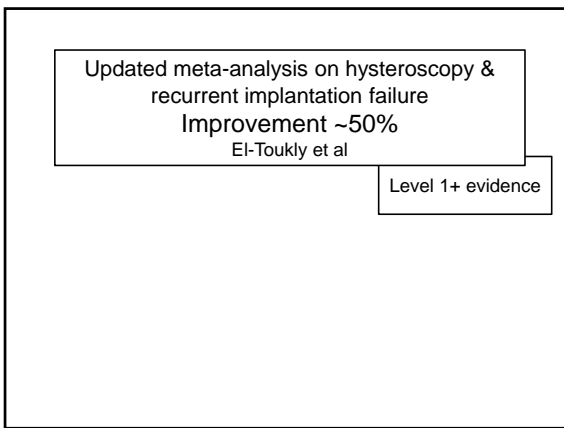
~20%

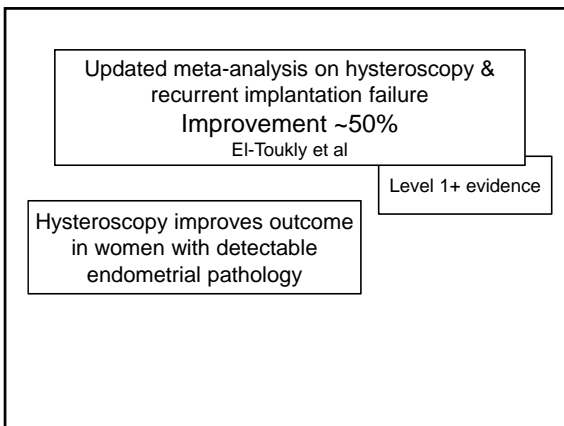
~80% no obvious pathology

The clinical characteristics of women with recurrent implantation failure
Coughlan et al, submitted

Level 3 evidence





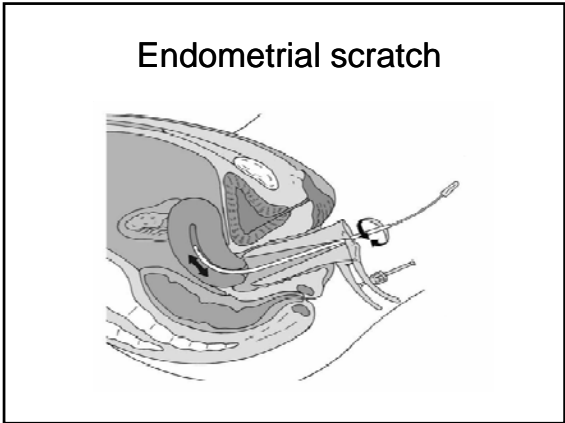


Updated meta-analysis on hysteroscopy & recurrent implantation failure
Improvement ~50%
El-Toukly et al

Level 1+ evidence

Hysteroscopy improves outcome in women with detectable endometrial pathology

Hysteroscopy also improves outcome in women with no detectable pathology



Endometrial scratch

Three meta-analyses

Questions

- What is it?
- Does it work?
- How to do it?
- When to do it?
- Who should have it?
- How does it work?



Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta-analysis.

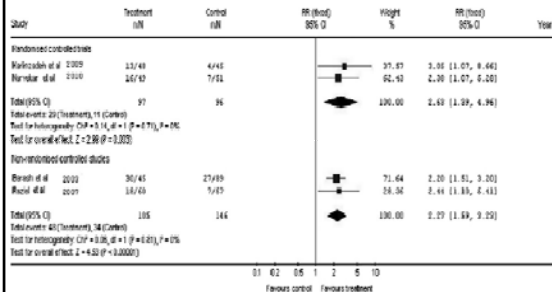
Table 3 Implantation rates in the intervention and control groups.

Study	Design	Endometrial injury (%)	Control (%)	P-value ^a
Barash et al. (2003)	NR	27.7	14.2	0.0001
Karimzadeh et al. (2009)	RCT	10.9	3.38	0.039
Narvekar et al. (2010)	RCT	13.07	7.1	0.04
Raziel et al. (2007)	NR	11.0	4.0	0.02

NR = non-randomized; RCT = randomized controlled trial.
^aSignificance level of <0.05.

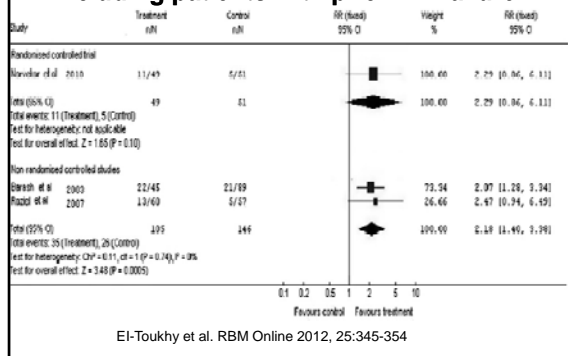
Potdar et al. 2012. RBM Online 25:561-571

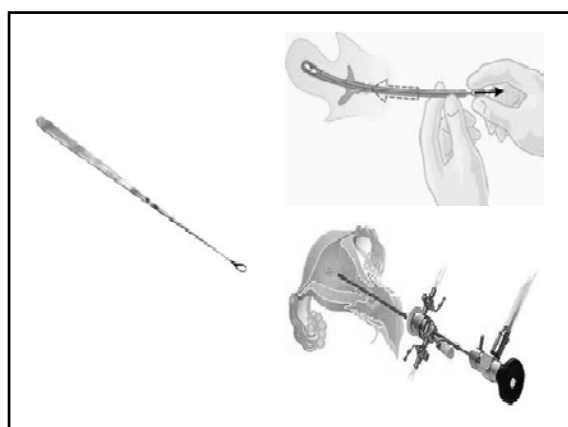
Clinical pregnancy rate for studies which included patients with prior IVF failure

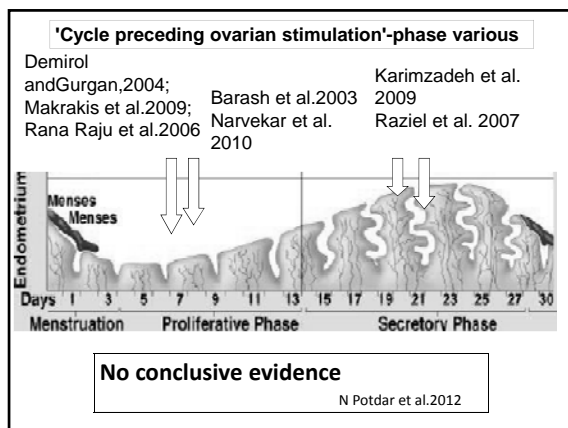


El-Toukhy et al. RBM Online 2012, 25:345-354

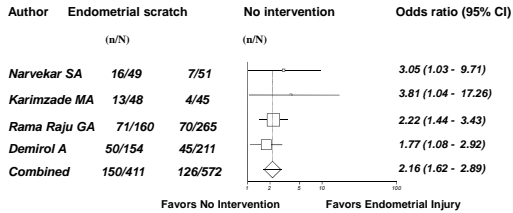
Live birth/ongoing pregnancy rate for studies including patients with prior IVF failure







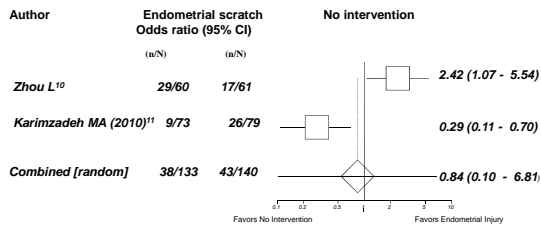
Luteal Phase Endometrial Injury versus No Intervention on CPR



Non-combinability of studies: Cochran Q = 1.99 (df = 3) P = 0.57
 Random effects (DerSimonian-Laird): Chi² (test odds ratio differs from 1) = 27.44 (df = 1) P < 0.0001

Level 1- evidence

Follicular Phase Endometrial Injury versus No Intervention on CPR



Non-combinability of studies: Cochran Q = 13.72 (df = 1) P = 0.0002
 Random effects (DerSimonian-Laird): Chi² (test odds ratio differs from 1) = 0.03 (df = 1) P = 0.87

Level 1- evidence

Endometrial scratch: timing

1. Doubling in LBR and CPR when endometrial injury is performed in the luteal phase of menstrual cycle preceding repeat IVF treatment.
2. No such benefits were demonstrated when performed in the follicular phase of the same treatment cycle.

Level 1- evidence

- Endometrial injury on OPU day was detrimental to the IVF success rate.

Karimzade et al.2010

- Ⓢ Endometrial requires ~2 weeks to achieve complete repair after mechanical injury.

Li et al. 2011

- Ⓢ Endometrial changes following injury are sustained, and possible even increased, in the following menstrual cycle.

Kalma et al.2009; Gnainsky et al.2010

Sheffield study

Who benefits from endometrial scratch?

- A retrospective analysis on the factors affecting the success of endometrial scratch
- 55 subjects with RIF
- Age below 40 years
- All had endometrial scratch by the use of the pipelle sampler in mid-luteal phase of the cycle preceding IVF treatment

Factors affecting the outcome of endometrial Scratch

Sheffield data

FSH	Pregnancy Rate after scratch
≤ 10 or less	29/45 = 64%
> 10	3/10 = 30%

Coughlan et al, in press

**Endometrial Scratch Retrospective Study
Conclusion**

1. Endometrial scratch is less likely to work if FSH level is high
2. Endometrial scratch does not work for everybody. Patient selection is important.
3. Do not scratch everyone having IVF treatment – it won't work!

Level 3 evidence

How does it work?

How does it work?

No one knows

Summary

- Subtle endometrial pathology may adversely affect implantation; treatment should be considered in women with repeated implantation failure
- In the absence of any recognisable endometrial pathology, endometrial scratch appears to improve outcome in those with repeated implantation failure

THANKYOU

Acknowledgement

Dr Xiao YU, Fuxing Hospital, Beijing
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You can now register for these upcoming ESHRE Campus events:

- Application and challenges of emerging technologies in preimplantation and prenatal diagnosis
12-13 September 2013 - Prague, Czech Republic
- Female genital tract congenital malformations: new insights in an old problem
27-28 September 2013 - Thessaloniki, Greece
- Introducing new techniques into the lab
4-5 October 2013 - Barcelona, Spain
- Polycystic ovary syndrome: A new look at an old subject
25-26 October 2013 - Rome, Italy
- Infections from conception to birth: role of ART
7-8 November 2013 - Berlin, Germany
- Endoscopy in reproductive medicine
20-22 November 2013 - Leuven, Belgium
- From early implantation to later in life
28-29 November 2013 - Brussels, Belgium

Mark your calendar for:

- Premature ovarian insufficiency
6-7 December 2013 - Utrecht, The Netherlands

www.eshre.eu
(see "Calendar")

Contact us at info@eshre.eu



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