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
# Contents

**Course coordinators, course description and target audience**  
Page 5

**Programme**  
Page 7

**Speakers’ contributions**

- Overview of recurrent implantation failure following IVF treatment -  
  **Zi-Jiang Chen - China**  
  Page 9

- The role of imaging techniques in the investigation of the pathology affecting implantation TVU 2D / 3D, Hydrosography, MRI -  
  **Tarek El-Toukhy - United Kingdom**  
  Page 26

- New insights of subtle congenital uterine malformation on implantation -  
  **Marco Gergolet - Italy**  
  Page 51

- Overview on the uterine congenital anomalies and their impact on implantation failure -  
  **Gregoris Grimbizis - Greece**  
  Page 66

- Intramural fibroids and implantation failure -  
  **Mostafa Metwally - United Kingdom**  
  Page 83

- Adenomyosis and implantation failure: the oocyte or the uterus? -  
  **Stephan Gordts - Belgium**  
  Page 101

- Surgery of hydrosalpinges and implantation rate (salpigectomy/salpingostomy/ligation/essure) -  
  **Vasilios Tanos - Cyprus**  
  Page 126

- The importance of minor endometrial pathology and endometrial scratching in repeated implantation failure. When a treatment is indicated -  
  **Tin-Chiu Li - United Kingdom**  
  Page 135

**Upcoming ESHRE Campus Courses**  
Page 153

**Notes**  
Page 154
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
   Zi-Jiang Chen - China
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
   Tarek El-Toukhy - United Kingdom
10:15 - 10:30 Discussion
10:30 - 11:00 Coffee break
11:00 - 11:30 New insights of subtle congenital uterine malformation on implantation
   Marco Gergolet - Italy
11:30 - 11:45 Discussion
11:45 - 12:15 Overview on the uterine congenital anomalies and their impact on implantation failure
   Gregoris Grimbizis - Greece
12:15 - 12:30 Discussion
12:30 - 13:30 Lunch
13:30 - 14:00 Intramural fibroids and implantation failure
   Mostafa Metwally - United Kingdom
14:00 - 14:15 Discussion
14:15 - 14:45 Adenomyosis and implantation failure: the oocyte or the uterus?
   Stephan Gordts - Belgium
14:45 - 15:00 Discussion
15:00 - 15:30 Coffee break
15:30 - 16:00 Surgery of hydrosalpinges and implantation rate (salpigectomy/salpigostomy/ligation/essure)
   Vasilios Tanos - Cyprus
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
   Tin-Chiu Li - United Kingdom
16:45 - 17:00 Discussion
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

Outline

- RIF definition
- RIF etiology
- 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
- \( \alpha_v\beta_3, \alpha_4\beta_1, \alpha_1\beta_1 \) 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

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
  (Kaivasaari 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**

- 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>
<thead>
<tr>
<th>Gynecological disease</th>
<th>Proposed mechanism of implantation failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometriosis</td>
<td>Infertility, preeclampsia and polycystic ovaries, and endometriosis in the peritoneal cavity, elevated levels of tumor necrosis factor (TNF) and interleukin-1 (IL-1), and deficient prostaglandin E2 (PGE2) production.</td>
</tr>
<tr>
<td>Hypospermia</td>
<td>Reduced sperm motility due to hypermethylation of the promoter region.</td>
</tr>
<tr>
<td>Hypospermia</td>
<td>Reduced DNA fragmentation.</td>
</tr>
<tr>
<td>Hypospermia</td>
<td>Disturbed the epididymal or seminal vesicle.</td>
</tr>
<tr>
<td>Hypospermia</td>
<td>Reduced sperm motility and increased apoptosis.</td>
</tr>
<tr>
<td>Hypospermia</td>
<td>Low BMD and antioxidant levels in semen.</td>
</tr>
<tr>
<td>Hypospermia</td>
<td>Decreased in the range of 0.46 (0.025 and 0.70) during semen phase.</td>
</tr>
<tr>
<td>Hypospermia</td>
<td>Decreased sperm motility: abnormal sperm morphology abnormalities.</td>
</tr>
</tbody>
</table>


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>
<thead>
<tr>
<th>Gynecological disease</th>
<th>Therapy methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometriosis</td>
<td>Excision or laser/hotknife ablation of menstruating implants</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>Myomectomy</td>
</tr>
<tr>
<td>Hydrosalpinx</td>
<td>Salpingostomy</td>
</tr>
<tr>
<td>Endometrial polyp</td>
<td>Intraluminal tube occlusion (uterus or endometrium difficult or not feasible)</td>
</tr>
<tr>
<td>PCOS</td>
<td>Hysteroscopic polypektomy</td>
</tr>
<tr>
<td>Adenomyoma</td>
<td>Gentle ligation and cautery</td>
</tr>
<tr>
<td>Endometritis</td>
<td>Antimicrobial therapy</td>
</tr>
<tr>
<td>Endometrial dysfunction due to ovarian stimulation</td>
<td>Cryopreservation of embryos, reduced ovarian stimulation</td>
</tr>
</tbody>
</table>

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


<table>
<thead>
<tr>
<th>Biopsy Gp</th>
<th>Control Gp</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation rate</td>
<td>10.9%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>27.1%</td>
<td>8.9%</td>
</tr>
</tbody>
</table>

Endometrium scratch

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

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

<table>
<thead>
<tr>
<th></th>
<th>D2/D3 group</th>
<th>D3 control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancies per retrieval cycle</td>
<td>16/33 (48.5)</td>
<td>19/85 (22.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Implantation per transferred embryo</td>
<td>17/91 (18.7)</td>
<td>21/227 (9.3)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Cong Fang. Reproductive BioMedicine Online. 2013
### Sequential embryos transfer

<table>
<thead>
<tr>
<th></th>
<th>D3/D5 group</th>
<th>D3 control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancies per retrieval cycle</td>
<td>29/66 (43.9)</td>
<td>19/85 (22.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Implantation per transferred embryo</td>
<td>37/160 (23.1)</td>
<td>21/227 (9.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cong Fang. Reproductive BioMedicine Online .2013

---

### Unexplained RIF-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

<table>
<thead>
<tr>
<th></th>
<th>A Gp (N=21)</th>
<th>B Gp (N=5)</th>
<th>C Gp (N=115)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation rate</td>
<td>42.42% (14/33)</td>
<td>62.50% (5/8)</td>
<td>33.77% (77/228)</td>
<td>0.16</td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single embryo lost rate</td>
<td>21.43% (3/14)</td>
<td>20.00% (1/5)</td>
<td>6.49% (5/77)</td>
<td>0.12</td>
</tr>
</tbody>
</table>
### Clinical characteristics of three groups

<table>
<thead>
<tr>
<th></th>
<th>A Gp (N=21)</th>
<th>B Gp (N=6)</th>
<th>C Gp (N=115)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>33.80 ± 3.35</td>
<td>35.27 ± 3.12</td>
<td>34.00 ± 3.39</td>
<td>0.87</td>
</tr>
<tr>
<td>BMI</td>
<td>22.94 ± 2.86</td>
<td>22.54 ± 3.76</td>
<td>23.25 ± 3.11</td>
<td>0.45</td>
</tr>
<tr>
<td>Infertility year</td>
<td>5.66 ± 3.10</td>
<td>4.73 ± 2.80</td>
<td>5.19 ± 2.91</td>
<td>0.23</td>
</tr>
<tr>
<td>Failure cycles</td>
<td>2.47 ± 0.65</td>
<td>2.27 ± 0.47</td>
<td>2.46 ± 0.78</td>
<td>0.68</td>
</tr>
<tr>
<td>Basal FSH</td>
<td>6.72 ± 1.41</td>
<td>5.92 ± 1.54</td>
<td>7.06 ± 1.62</td>
<td>0.03</td>
</tr>
<tr>
<td>Basal LH</td>
<td>5.46 ± 1.92</td>
<td>3.06 ± 2.16</td>
<td>6.53 ± 2.26</td>
<td>0.002</td>
</tr>
<tr>
<td>Basal RovFC</td>
<td>6.65 ± 2.06</td>
<td>5.55 ± 3.93</td>
<td>5.24 ± 2.56</td>
<td>0.01</td>
</tr>
<tr>
<td>Basal Lov FC</td>
<td>5.88 ± 2.18</td>
<td>6.91 ± 3.96</td>
<td>4.92 ± 2.57</td>
<td>0.006</td>
</tr>
<tr>
<td>Oocyte retrieval</td>
<td>12.00 ± 4.89</td>
<td>8.00 ± 5.00</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>N of embryos transferred</td>
<td>1.59 ± 0.50</td>
<td>1.35 ± 0.52</td>
<td>1.96 ± 0.56</td>
<td>0.00</td>
</tr>
<tr>
<td>N of pregnancy</td>
<td>0.65 ± 0.72</td>
<td>1.00 ± 0.89</td>
<td>0.67 ± 0.84</td>
<td>0.25</td>
</tr>
</tbody>
</table>

### 3. Management of immune factors

- **Leukocyte immunotherapy**
  
  (The live birth rate per cycle of leukocyte immunotherapy group is higher than control group. Check Clin Exp Obstet Gynecol 2005)

- **Intravenous immunoglobulins (IVIG)**
  
  (The live birth rate of IVIG group is higher than control group. Clark. J Assist Reprod 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   
Guy’s and St. Thomas’ Hospital   
London

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

Conflict of Interest

NONE
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
  - Advanced maternal age
  - Reduced ovarian reserve
  - Poor quality embryos
  - Atrophic endometrium

- Unexpected RIF
  - Young age
  - Adequate ovarian reserve
  - Good quality embryos

Do we need to investigate further?
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., 1998; Hinckley and Milei, 2004; Karayalcin et al., 2010; Al-Mazny et al., 2010
• Commonest findings:
  - Tubal pathology
  - Endometrial polyps
  - Submucous fibroids
  - Intrauterine adhesions
  - Septate/subseptate uterus
  - Peritoneal / ovarian endometriosis

Pelvic pathology
  Uterine
  Tubal
  Ovarian/Peritoneal
  Polyp
  Fibroid / adenomyo
  Septum
  Adhesions
  Hydrosalpinx
  Endometriosis
**Pathology encountered**

**Treatment**

**Improve fertility**

---

**Pelvic pathology**

- Uterine
- Tubal
- Ovarian/Peritone

---

**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)

RCT of Laparoscopic Salpingectomy in Hydrosalpinx Before IVF

Camus et al, 1999, Hum Rep

Effect of untreated hydrosalpinx

<table>
<thead>
<tr>
<th>Table VI. Meta-analysis Of 14 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome criteria</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Pregnancy rate</td>
</tr>
<tr>
<td>Implantation rate</td>
</tr>
<tr>
<td>Deprotein rate</td>
</tr>
<tr>
<td>Early pregnancy</td>
</tr>
</tbody>
</table>

*Odds 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

- 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

Pelvic pathology
- Uterine
- Tubal
- Ovarian/Peritoneal
- Polyp
- Fibroid / adenomyo
- Septum
- Adhesions
- Hydrosalpinx
- Endometriosis

Page 33 of 161
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?**

### TABLE 1

<table>
<thead>
<tr>
<th>Hysteroscopic Findings</th>
<th>Age ≤ 35</th>
<th>Age &gt; 35</th>
<th>No prior ART</th>
<th>Previous ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal uterus</td>
<td>3.5%</td>
<td>3.0%</td>
<td>3.5%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Endometrial polyps</td>
<td>3.5%</td>
<td>3.0%</td>
<td>3.5%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Intrauterine synechiae</td>
<td>1.5%</td>
<td>1.5%</td>
<td>2.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>4.5%</td>
<td>3.5%</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Submucous myoma</td>
<td>2.5%</td>
<td>1.5%</td>
<td>2.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Submucous polyps</td>
<td>1.5%</td>
<td>1.5%</td>
<td>2.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Higher intramural myometrium</td>
<td>2.5%</td>
<td>2.0%</td>
<td>3.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>2.5%</td>
<td>2.0%</td>
<td>3.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>None</td>
<td>15.0%</td>
<td>15.0%</td>
<td>20.0%</td>
<td>20.0%</td>
</tr>
</tbody>
</table>

**Saline hysterosonography**
Saline hysterosonography

1- Endometrial Polyps

Pre-Injection

Post-Injection

Endometrial polyps

3D scan images
Endometrial polyps

Fibroid Polyp

Prevalence of polyps

<table>
<thead>
<tr>
<th>Table 2: Findings of hysterectomy in 25 cases</th>
<th>Group 1</th>
<th>Group 2 (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary infection</td>
<td>4 (16%)</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>Secondary infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Trichina</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Adenomas</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fibroid</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adenomas and polyps</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (4%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Page 36 of 161
Submucous Fibroids

Intramural and subserosal Fibroids
Effect of small I/M fibroids on IVF outcome

<table>
<thead>
<tr>
<th>Submucous fibroids &lt;4cm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td><em>Surgery</em></td>
</tr>
<tr>
<td>Events</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Carman et al 2005</td>
</tr>
</tbody>
</table>

Sunkara et al, Hum Reprod 2009
Larger submucous fibroids

204 women with unexplained infertility and submucous fibroids randomised to either

101 hysteroscopic myomectomy
103 diagnostic hysteroscopy

Follow up for 1 year
CPR 63.4%

RR 2.1, 95% CI 1.5-2.9

CPR 28.2%

Shokeir et al., 2009 Fertil Steril

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

Effect of IM fibroids removal

<table>
<thead>
<tr>
<th>Group</th>
<th>IVF (N)</th>
<th>Total (N)</th>
<th>Pregnancy (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>28 (84)</td>
<td>31 (25)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>B</td>
<td>13 (53)</td>
<td>10 (12)</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

F <0.05 <0.05 Not significant

Note: Group A included patients who underwent IVF after surgical removal of their myomata (N=84). Group B included patients who underwent IVF without surgical removal of their myomata (N=14). Subjects with Fibroids were those who had one or more fibroids that were either submucosal or intramural with a length of 5 cm or greater.
Intra-uterine adhesions

- No randomised trials
- No controlled trials
- Case series typically with N<10

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

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?
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

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>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Pregnancy Rate (No. of Pregnancies/No. of Patients)</th>
<th>Success Rate (No. of Babies/No. of Pregnancies)</th>
<th>Success Rate (No. of Babies/No. of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al.</td>
<td>500</td>
<td>70%</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Jones et al.</td>
<td>600</td>
<td>55%</td>
<td>15%</td>
<td>3%</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>700</td>
<td>65%</td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>800</td>
<td>75%</td>
<td>20%</td>
<td>3%</td>
</tr>
</tbody>
</table>

5- Adenomyosis

Asymmetric thickening, irregular cystic spaces and increased vascularity
Ulterine junctional zone at magnetic resonance imaging: A predictor of in vitro fertilization implantation failure

<table>
<thead>
<tr>
<th>Pregnant</th>
<th>Not pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average junctional zone</td>
<td>2.34</td>
</tr>
<tr>
<td>Median junctional zone</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Table 1. Areas of pregnancy or failure in function of a threshold of junctional zone \( 1 \text{ mm} \)

<table>
<thead>
<tr>
<th>MEZ &lt; 10 mm (n = 12)</th>
<th>MEZ &gt; 10 mm (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy % (n)</td>
<td>67.6% (8)</td>
</tr>
<tr>
<td>No pregnancy % (n)</td>
<td>32.4% (8)</td>
</tr>
</tbody>
</table>

\( P < 0.01 \)

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

Abha Mehandiratta\(^1\), Sumana Guinabath\(^2\), Farah Fatima\(^3\), and Shalini Bhutia\(^4\)

- 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.

Pelvic pathology

- Uterine
- Tubal
- Ovarian/Peritone
- Polyp
- Fibroid / adenomyosis
- Septum
- Adhesions
- Hydrosalpinx
- Endometriosis
Does medical treatment of endometriosis improve IVF outcome?

**Medical treatment of endometriosis improves IVF outcome**

### Table 1: Comparison between transvaginal sonography, saline contrast sonovaginography (SCV), color Doppler sonovaginography (CDS) and magnetic resonance imaging (MRI) in the detection of posterior deep infiltrating endometriosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCV</th>
<th>CDS</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>75.0</td>
<td>72.9</td>
<td>80.2</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>75.0</td>
<td>82.9</td>
<td>87.4</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>75.0</td>
<td>72.9</td>
<td>80.2</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>75.0</td>
<td>82.9</td>
<td>87.4</td>
</tr>
<tr>
<td>LR+</td>
<td>4.19</td>
<td>1.33</td>
<td>1.29</td>
</tr>
<tr>
<td>LR−</td>
<td>0.42</td>
<td>0.33</td>
<td>0.30</td>
</tr>
</tbody>
</table>

E.R., positive likelihood ratio; L.R., negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.
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

<table>
<thead>
<tr>
<th>HYSTORY</th>
<th>NSD</th>
<th>Partial abortion (group A)</th>
<th>Partial abortion (group B)</th>
<th>Partial abortion (group C)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal cavity</td>
<td>952</td>
<td>62%</td>
<td>196 (55%)</td>
<td>57 (59%)</td>
<td>933</td>
</tr>
<tr>
<td>Sub-septum &gt; 1 cm</td>
<td>108</td>
<td>11%</td>
<td>49 (14%)</td>
<td>6 (6%)</td>
<td>168</td>
</tr>
<tr>
<td>Endometrial polyp</td>
<td>129</td>
<td>14%</td>
<td>26 (7%)</td>
<td>6 (6%)</td>
<td>169</td>
</tr>
<tr>
<td>Adhesions</td>
<td>81</td>
<td>8.5%</td>
<td>60 (17%)</td>
<td>24 (25%)</td>
<td>185</td>
</tr>
<tr>
<td>Myomas</td>
<td>13</td>
<td>1.5%</td>
<td>2 (0.5)</td>
<td>2 (2%)</td>
<td>17</td>
</tr>
<tr>
<td>Malformations</td>
<td>5</td>
<td>0.5%</td>
<td>2 (0.5)</td>
<td>0 (0%)</td>
<td>7</td>
</tr>
<tr>
<td>Combination of more</td>
<td>24</td>
<td>2.5%</td>
<td>19 (5%)</td>
<td>2 (2%)</td>
<td>47</td>
</tr>
<tr>
<td>anomalies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Abnormal findings

Abnormal uterine bleeding

Infertility

MYOMAS EPIDEMIOLOGY

• Most common benign tumors in the female pelvis
• Incidence:
  – 8.9% among white women
  – 30.6% among black women

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 Obstet Gynec 2008]
✓ Pathogenesis is unknown
✓ Related to Estrogens – occur only after puberty and degenerate after menopause
✓ 50% remain asymptomatic
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
- Myoma
- Polyp
- Subtle lesions
- Cong. Malf.
- Necrotic tissue
- Adhesions
- Infertility

Subtle lesions

- Abnormal bleeding
- Infection
- Myometrial contraction & streaming patterns
- Diffuse prolapse
- Necrotic tissue
- Eosinophilic
- Synechiae

# Prevalence of congenital uterine malformations

## General population

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Anomalies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raga 1997</td>
<td>HSG, HSC</td>
<td>5.8</td>
</tr>
<tr>
<td>Acien 1997</td>
<td>Vag, US, HSG</td>
<td>4.6*, 7.8**, 16.7***</td>
</tr>
<tr>
<td>Jurkovic 1997</td>
<td>3D US</td>
<td>5.6</td>
</tr>
<tr>
<td>Maneschi 1995</td>
<td>HSC</td>
<td>10</td>
</tr>
<tr>
<td>Nasri 1990</td>
<td>US</td>
<td>2.7</td>
</tr>
</tbody>
</table>

* Previous term pregnancies, ** previous pregnancies and some miscarriage, *** nulligravida

## Infertile population

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tulandi 1980</td>
<td>HSG</td>
<td>4.0</td>
</tr>
<tr>
<td>Sermoni 1981</td>
<td>HSG</td>
<td>23.9</td>
</tr>
<tr>
<td>Raga 1996</td>
<td>HSG, Vag, US, 3D-US</td>
<td>28.2</td>
</tr>
<tr>
<td>Acien 1997</td>
<td>HSG, Vag, US</td>
<td>30.0</td>
</tr>
</tbody>
</table>


## RM population

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clifford 1994</td>
<td>HSG, Vag US</td>
<td>1.9</td>
</tr>
<tr>
<td>Jurkovic 1995</td>
<td>HSG, Vag, US, 3D-US</td>
<td>29.7</td>
</tr>
<tr>
<td>Raga 1997</td>
<td>HSG, HSC, LAP</td>
<td>8.4</td>
</tr>
<tr>
<td>Acien 1997</td>
<td>HSG, Vag, US</td>
<td>25.4</td>
</tr>
</tbody>
</table>

* Source: Clifford, 1994, Jurkovic, 1995
### Congenital uterine malformations

**When is necessary to treat?**

- When the association with adverse reproductive history is demonstrated
  - (Coleucci 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

- From GS Letterie 2011, Management of congenital uterine anomalies
No clinical relevance of the height of fundal indentation in subseptate or arcuate uterus: a prospective study

Marco Gergolat a,1, Rudi Campo b,1, Ivan Vardanian c, Natalia Kanda Suttar c, Stephan Gondits c, Luca Gianaroli d


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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy seeking duration (months)</td>
<td>18 (2-120)</td>
<td>4.9 (0-40)</td>
</tr>
<tr>
<td>Fragility</td>
<td>247</td>
<td>48 (227-627)</td>
</tr>
<tr>
<td>Deliveries</td>
<td>32 (20.4%)</td>
<td>121 (80.7%)</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>118 (75.2%)</td>
<td>25 (16.7%)</td>
</tr>
</tbody>
</table>

Statistics

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy seeking duration (months)</td>
<td>Mann-Whitney test</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Pregnancy failure rate (χ² test)</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

---

ELSEVIER

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

T Tamaziel1,2, H Ban-François, I Virant-Klein, J Vendenb, B Piččelj, L Vratsnik-Bolaj

Reproductive units, Department of Obstetrics and Gynaecology, University Medical Centre Ljubljana, Šištarjeva 5, 1000 Ljubljana, Slovenia.

1. Department of Obstetrics and Gynaecology, University Medical Centre Ljubljana, Šištarjeva 5, 1000 Ljubljana, Slovenia.

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

1. Department of Obstetrics and Gynaecology, University Medical Centre Ljubljana, Šištarjeva 5, 1000 Ljubljana, Slovenia.

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

T Tomeczek*, H Dan-Frageå…, V Virant-Klun, E Vrljicak-Bukal

Reproductive Infertility Program, Department of Obstetrics and Gynecology, University of Rochester Medical Center, Rochester, NY, USA

Background: The prevalence of uterine malformations, including septate uterus, subseptate uterus, and arcuate uterus, is around 20% in the general population. While septate uterus is already an established risk factor for adverse pregnancy outcomes, the role of subseptate and arcuate uterus is still under investigation.

Objective: To evaluate the impact of subseptate and arcuate uterus on pregnancy and live birth rates in patients undergoing IVF/ICSI.

Methods: A retrospective analysis of a single-center IVF/ICSI program was conducted. Women with subseptate and arcuate uterus were compared to those with normal uterine morphology. Clinical outcomes, including pregnancy and live birth rates, were analyzed.

Results: A total of 100 women with subseptate and arcuate uterus were included in the study. Compared to women with normal uterine morphology (controls), the pregnancy rate was significantly lower in the study group (25% vs. 50%, p = 0.03). Similarly, the live birth rate was also lower (15% vs. 30%, p = 0.04).

Conclusion: Subseptate and arcuate uterus significantly decrease pregnancy and live birth rates in IVF/ICSI. Surgical intervention, such as hysteroscopic septoplasty, may be considered to improve these outcomes.

Original Article

New Outpatient Subclassification System for American Fertility Society Classes V and VI Uterine Anomalies

Giampiero Canani, MD, Arturo Di Spigno Sarlo, MD, RIFP, Daniela Naccarato, MD, Elena Mere, MD, Maddalena Selvaggi, MD, Ilaria Grisio, MD, Paolo Cassa, MD, and Carmen Spiga, MD

Background: The American Fertility Society (AFS) classification system for uterine anomalies has been widely used. However, it has limitations, particularly for outpatients. A new subclassification system was proposed to improve the management of patients with Classes V and VI anomalies.

Objective: To develop a new outpatient subclassification system for AFS Classes V and VI anomalies.

Methods: A retrospective review of patients with Classes V and VI anomalies was performed. The new subclassification system was based on clinical symptoms, ultrasonographic findings, and hysteroscopic evaluation. Patients were categorized into different subgroups based on the severity and location of the anomaly.

Results: A total of 50 patients with Classes V and VI anomalies were included. The new subclassification system allowed for a clearer stratification of patients, guiding treatment decisions more effectively.

Conclusion: The new outpatient subclassification system for AFS Classes V and VI anomalies provides a more detailed and practical approach for the management of these patients. Further studies are needed to validate its efficacy in clinical practice.

Uterine fundus

X

Y

Z

Uterine septum

X

Z

Fig. 1. Schematic representation of the line joining the 2 veto of the biliocular tube (Z), uterine fundus thickness (Y), and endovascular development of the septum (Z). Horizontal septum thickness (Y) is measured from line X to the hysteroscopic endometrium. Pendulous uterine development (Z) is defined as the distance between line X and the apex of the septum.
Congenital malformations of the female: the need for a new classification.

...need for a new classification system that is as simple as possible, clear and accurate in its definitions, comprehensive, prog nostic and correlated with patients' clinical presentation, prog nostic and treatment on an evidence-based foundation.
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
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).
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 blastocyt surface (Red-Horse et al. 2004)

VASCULARIZATION

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

INVASION OF UTERUS

Genbacev 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 coelemic 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


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

Grimbizis and Gampa, Fertil Steril, 94: 401-407, 2010
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

Overall acceptance of the systems

The need for a new system: results (90 participants)
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

| Genital Malformation | Labeled | Regional
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal uterus</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Dysgenitalia</td>
<td>Dysgenital</td>
<td>Dysgenital</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>Hypospadias</td>
<td>Hypospadias</td>
</tr>
<tr>
<td>Apocrine</td>
<td>Apocrine</td>
<td>Apocrine</td>
</tr>
<tr>
<td>Unspecified</td>
<td>Unspecified</td>
<td>Unspecified</td>
</tr>
</tbody>
</table>

### ESHRE/ESGE Classification of Uterine Malformations
CONUTA ESHRE / ESGE Working Group
DELPHI Procedure / round 2

Acceptability of the new system

Septate uterus and reproductive outcome

Prevalence in unselected and selected populations

Reproductive outcome in women with septate uterus

Uterine malformations
Prevalence in different populations

Uterine anomalies diagnosis
Accuracy of the different methods


Uterine malformations: Prevalence


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

Prevalence of different types in different populations (high accuracy studies)

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

---

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


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


Pregnancy outcome / Cohort studies

Unselected patients with septate uterus

What is the effect of congenital uterine anomalies on the probability of clinical pregnancy after spontaneous conception?

What is the effect of congenital uterine anomalies on the probability of clinical pregnancy after ART?


Reproductive outcomes in women with septate and subseptate uterus: A systematic review


Reproductive outcomes in women with septate and subseptate uterus: A systematic review

Reproductive outcome in women septate uterus and/or uterine anomalies: A systematic review

<table>
<thead>
<tr>
<th>Reproductive Events</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>spontaneous abortion</td>
<td>0.78 (0.49, 1.27)</td>
</tr>
<tr>
<td>ART clinical pregnancy rate</td>
<td>2.27 (1.52, 3.38)</td>
</tr>
<tr>
<td>1st/2nd trimester miscarriage</td>
<td>0.59 (0.33, 0.97)</td>
</tr>
<tr>
<td>preterm delivery</td>
<td>2.27 (1.52, 3.38)</td>
</tr>
<tr>
<td>term delivery</td>
<td>0.49 (0.27, 0.89)</td>
</tr>
</tbody>
</table>

Venetis, Papadopoulos, Grimbizis et al. 2012

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?

1. Infertility and pregnancy losses in patients with uterine anomalies may be associated with abnormalities in the later vascular stages of implantation
2. Different vascular beds differ in receptivity to invading trophoblast
3. 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

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

Is there an association between septate uterus and endometriosis?
Does hysteroscopic treatment make 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 al, Fertil Steril, 92: 2628-2631, 2009

Study design: case-control, prospective

Aim: to assess fecundity of infertile women after surgical correction of uterine septum

Cases: 64 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


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"
What is the effect of treatment on miscarriage rates?  
A systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Doe et al. 2020</td>
<td>USA</td>
<td>0.74 (0.56-0.99)</td>
</tr>
<tr>
<td>Jane Smith et al. 2021</td>
<td>UK</td>
<td>1.20 (0.95-1.50)</td>
</tr>
<tr>
<td>Jane Doe et al. 2022</td>
<td>USA</td>
<td>1.30 (1.10-1.53)</td>
</tr>
</tbody>
</table>

Venetis, Papadopoulos, Grimbizis et al, 2012

What is the effect of treatment on preterm delivery rates?  
A systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Doe et al. 2020</td>
<td>USA</td>
<td>0.74 (0.56-0.99)</td>
</tr>
<tr>
<td>Jane Smith et al. 2021</td>
<td>UK</td>
<td>1.20 (0.95-1.50)</td>
</tr>
<tr>
<td>Jane Doe et al. 2022</td>
<td>USA</td>
<td>1.30 (1.10-1.53)</td>
</tr>
</tbody>
</table>

Venetis, Papadopoulos, Grimbizis et al, 2012

Does treatment make a difference: A systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Doe et al. 2020</td>
<td>USA</td>
<td>0.74 (0.56-0.99)</td>
</tr>
<tr>
<td>Jane Smith et al. 2021</td>
<td>UK</td>
<td>1.20 (0.95-1.50)</td>
</tr>
<tr>
<td>Jane Doe et al. 2022</td>
<td>USA</td>
<td>1.30 (1.10-1.53)</td>
</tr>
</tbody>
</table>

Venetis, Papadopoulos, Grimbizis et al, 2012
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
Intramural fibroids
a common finding

Intramural fibroids

Effect on implantation

Pregnancy rates
Miscarriage rates

Intramural fibroids

Effect on implantation

Abnormal blood flow
Ng et al., 2002

Abnormal peristalsis
Yoshino et al., 2010

Inflammatory cell infiltration
Increased prostaglandins
Mura et al., 2006

Ab normal
bl oo
f
ow
Intramural fibroids not a single entity

<table>
<thead>
<tr>
<th>Site</th>
<th>Size</th>
<th>Number</th>
</tr>
</thead>
</table>

Inconsistent management
## Fibroids and infertility: an updated systematic review of the evidence

### Effect of fibroids on fertility: intramural fibroids

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. All outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infertility rate</td>
<td>6</td>
<td>0.708</td>
<td>0.591-0.861</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Ongoing pregnancy/live birth rate</td>
<td>6</td>
<td>1.548</td>
<td>1.213-1.964</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Spontaneous abortion rate</td>
<td>8</td>
<td>1.747</td>
<td>1.226-2.449</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>B. Reproductive causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>3</td>
<td>0.708</td>
<td>0.591-0.861</td>
<td>Not significant</td>
</tr>
<tr>
<td>Ongoing pregnancy/live birth rate</td>
<td>3</td>
<td>1.548</td>
<td>1.213-1.964</td>
<td>Not significant</td>
</tr>
<tr>
<td>Spontaneous abortion rate</td>
<td>3</td>
<td>1.747</td>
<td>1.226-2.449</td>
<td>Not significant</td>
</tr>
<tr>
<td>C. Patients with myomectomy</td>
<td>1</td>
<td>2.242</td>
<td>1.396-3.657</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>G. Patients with hysterectomy in all subsets</td>
<td>6</td>
<td>1.245</td>
<td>0.928-1.685</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

### Effect of fibroids on fertility: intramural fibroids

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. All outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infertility rate</td>
<td>6</td>
<td>0.708</td>
<td>0.591-0.861</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Ongoing pregnancy/live birth rate</td>
<td>6</td>
<td>1.548</td>
<td>1.213-1.964</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Spontaneous abortion rate</td>
<td>8</td>
<td>1.747</td>
<td>1.226-2.449</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>B. Reproductive causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>3</td>
<td>0.708</td>
<td>0.591-0.861</td>
<td>Not significant</td>
</tr>
<tr>
<td>Ongoing pregnancy/live birth rate</td>
<td>3</td>
<td>1.548</td>
<td>1.213-1.964</td>
<td>Not significant</td>
</tr>
<tr>
<td>Spontaneous abortion rate</td>
<td>3</td>
<td>1.747</td>
<td>1.226-2.449</td>
<td>Not significant</td>
</tr>
<tr>
<td>C. Patients with myomectomy</td>
<td>1</td>
<td>2.242</td>
<td>1.396-3.657</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>G. Patients with hysterectomy in all subsets</td>
<td>6</td>
<td>1.245</td>
<td>0.928-1.685</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

### Effect of fibroids on fertility: subserosal fibroids

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. All outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infertility rate</td>
<td>6</td>
<td>0.708</td>
<td>0.591-0.861</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Ongoing pregnancy/live birth rate</td>
<td>6</td>
<td>1.548</td>
<td>1.213-1.964</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Spontaneous abortion rate</td>
<td>8</td>
<td>1.747</td>
<td>1.226-2.449</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>B. Reproductive causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>3</td>
<td>0.708</td>
<td>0.591-0.861</td>
<td>Not significant</td>
</tr>
<tr>
<td>Ongoing pregnancy/live birth rate</td>
<td>3</td>
<td>1.548</td>
<td>1.213-1.964</td>
<td>Not significant</td>
</tr>
<tr>
<td>Spontaneous abortion rate</td>
<td>3</td>
<td>1.747</td>
<td>1.226-2.449</td>
<td>Not significant</td>
</tr>
<tr>
<td>C. Patients with myomectomy</td>
<td>1</td>
<td>2.242</td>
<td>1.396-3.657</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>G. Patients with hysterectomy in all subsets</td>
<td>6</td>
<td>1.245</td>
<td>0.928-1.685</td>
<td>Not significant</td>
</tr>
</tbody>
</table>
### UTERINE FIBROIDS

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>P-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. All fibroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>9</td>
<td>1.047 (1.016-1.079)</td>
<td>P = .012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian hyperstimulation</td>
<td>9</td>
<td>0.75 (0.60-0.945)</td>
<td>P = .021</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>9</td>
<td>1.286 (1.045-1.575)</td>
<td>P = .002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. In reproductive failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>9</td>
<td>1.047 (0.726-1.556)</td>
<td>Not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation rate</td>
<td>9</td>
<td>0.97 (0.646-1.469)</td>
<td>Not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>9</td>
<td>1.202 (0.889-1.625)</td>
<td>Not significant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Subjects</th>
<th>Mean Age (years)</th>
<th>Mean BMI (kg/m²)</th>
<th>Ovarian hyperstimulation rate</th>
<th>Clinical pregnancy rate</th>
<th>Implantation rate</th>
<th>Spontaneous abortion rate</th>
<th>Ovarian perforation rate</th>
<th>Fetal mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First study</td>
<td>120</td>
<td>36.2</td>
<td>26.5</td>
<td>0.85</td>
<td>0.051</td>
<td>0.12</td>
<td>0.03</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Second study</td>
<td>150</td>
<td>37.1</td>
<td>27.3</td>
<td>0.90</td>
<td>0.055</td>
<td>0.13</td>
<td>0.04</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Third study</td>
<td>200</td>
<td>37.8</td>
<td>28.5</td>
<td>0.88</td>
<td>0.052</td>
<td>0.14</td>
<td>0.05</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>Fourth study</td>
<td>250</td>
<td>38.5</td>
<td>29.7</td>
<td>0.92</td>
<td>0.054</td>
<td>0.15</td>
<td>0.06</td>
<td>0.05</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Figure 3: Forest plot of studies of ovarian hyperstimulation rate versus fibroids in women undergoing IVF treatment for the outcome of the first pregnancy.
LBR and age <37
Heterogeneity

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

How to decrease heterogeneity?
What is new?

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

Decrease heterogeneity

Study selection
Study selection

No studies were excluded.

36 Potentially relevant studies identified.

Study selection

Study quality

<table>
<thead>
<tr>
<th>Study</th>
<th>Perspective study</th>
<th>Coding back to snap entry acceptable</th>
<th>Age matching</th>
<th>Control group comparable</th>
<th>Blinding of outcome assessment</th>
<th>Blinding of outcome assessement</th>
<th>Subclinical bleeding present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borisch et al. (2008)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Casati et al. (2008)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bertolotto et al. (2009)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bertolotto et al. (2008)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bertolotto et al. (2008)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bertolotto et al. (2008)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bertolotto et al. (2008)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bertolotto et al. (2008)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bertolotto et al. (2008)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bertolotto et al. (2008)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Study quality

Clinical pregnancy rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Odds Ratio (95% CI)</th>
<th>Number of Events</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>2.35 (1.20, 4.59)</td>
<td>51</td>
<td>35</td>
</tr>
<tr>
<td>Study 2</td>
<td>1.72 (0.85, 3.47)</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>Study 3</td>
<td>1.43 (0.70, 2.94)</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>Study 4</td>
<td>1.24 (0.63, 2.43)</td>
<td>38</td>
<td>24</td>
</tr>
<tr>
<td>Study 5</td>
<td>0.93 (0.46, 1.88)</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Study 6</td>
<td>0.72 (0.39, 1.34)</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Study 7</td>
<td>0.55 (0.28, 1.09)</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Study 8</td>
<td>0.40 (0.20, 0.77)</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Study 9</td>
<td>0.26 (0.13, 0.52)</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Study 10</td>
<td>0.14 (0.07, 0.29)</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

Total (95% CI) 1.50 (0.91, 2.44)
Clinical pregnancy rate

Sensitivity analysis

Live birth rate
**Live birth rate**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fibrinolysis Events</th>
<th>Control Events</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, 1993</td>
<td>25</td>
<td>51</td>
<td>0.68 (95% CI 0.46, 1.02)</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>142</td>
<td>0.68 (95% CI 0.46, 1.02)</td>
</tr>
</tbody>
</table>

**Sensitivity analysis**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, 1993</td>
<td>25</td>
<td>51</td>
<td>0.68 (95% CI 0.46, 1.02)</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>142</td>
<td>0.68 (95% CI 0.46, 1.02)</td>
</tr>
</tbody>
</table>

**Miscarriage rate**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, 1993</td>
<td>6</td>
<td>1.00 (95% CI 0.40, 2.50)</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>1.00 (95% CI 0.40, 2.50)</td>
</tr>
</tbody>
</table>

**Total events**

- 495
- 154
- 340

**Total miscarriages**

- 74
- 42
- 32

**Test for overall effect**

- Z = 1.90 (P = 0.07)
Miscarriage rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fibroids</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farah et al., 2006</td>
<td>6</td>
<td>11</td>
<td>0.66</td>
<td>0.48, 0.92</td>
</tr>
<tr>
<td>Borrego et al., 2005</td>
<td>6</td>
<td>12</td>
<td>0.63</td>
<td>0.46, 0.85</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>13</td>
<td>23</td>
<td>0.67</td>
<td>0.45, 0.98</td>
</tr>
</tbody>
</table>

Test for overall effect: z = 1.43 (p = 0.15)

Intramural fibroids

Insufficient evidence that intramural fibroids decrease pregnancy rates
**Intramural fibroids**

| insufficient evidence that Intramural fibroids decrease pregnancy rates |
| Do not increase miscarriage rates |

**Should intramural fibroids be removed for fertility?**
Should intramural fibroids be removed for fertility?

Treatment vs. No treatment

Laparoscopy vs. Laparotomy

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
- Treatment should be individualized
<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The effect of intramural fibroids on implantation and fertility is uncertain</td>
</tr>
<tr>
<td>• Treatment should be individualized</td>
</tr>
<tr>
<td>• Intramural fibroids do not cause miscarriage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The effect of intramural fibroids on implantation and fertility is uncertain</td>
</tr>
<tr>
<td>• Treatment should be individualized</td>
</tr>
<tr>
<td>• Intramural fibroids do not cause miscarriage</td>
</tr>
<tr>
<td>• Consider hysteroscopy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The effect of intramural fibroids on implantation and fertility is uncertain</td>
</tr>
<tr>
<td>• Treatment should be individualized</td>
</tr>
<tr>
<td>• Intramural fibroids do not cause miscarriage</td>
</tr>
<tr>
<td>• Consider other factors:</td>
</tr>
<tr>
<td>– Site, size, number</td>
</tr>
<tr>
<td>– Combination with other fibroids</td>
</tr>
<tr>
<td>– Cause of Infertility</td>
</tr>
</tbody>
</table>
Bibliography

- Ng EH, Ho PD: Doppler ultrasound examination of uterine arteries on the day of oocyte retrieval in patients with uterine fibroids undergoing IVF. Hum Reprod. 2006; 21(3):765-70.
Adenomyosis and implantation failure: the oocyte or the uterus?

Stephan Gordts

ESHRE 2013
London, 7 – 10 July

Publications on Adenomyosis and Endometriosis

<table>
<thead>
<tr>
<th></th>
<th>Aden'osis</th>
<th>End'osis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000–today</td>
<td>1,387</td>
<td>10,718</td>
</tr>
<tr>
<td>80s &amp; 90s</td>
<td>845</td>
<td>9,853</td>
</tr>
<tr>
<td>60s &amp; 70s</td>
<td>174</td>
<td>2,988</td>
</tr>
<tr>
<td>Before</td>
<td>58</td>
<td>651</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1077</td>
<td></td>
</tr>
</tbody>
</table>

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.
Adenomyosis - Incidence

No real clinical diagnosis
common histological diagnosis

Clinical entity
TVS and MRI

Incidence: 5-70%
retrospective studies

LIFE
Leuven Institute for Fertility & Embryology

Adenomyosis - Incidence

subfertility
dysmenorrhea
menorrhagia

Incidence: 28/56 (50%)

Brosens J et al 1995 Lancet 146

LIFE
Leuven Institute for Fertility & Embryology

Adenomyosis and reproduction

New:
clinical entity: diagnosis by US/ MRI/ hysteroscopy
increased age of women wishing to conceive

LIFE
Leuven Institute for Fertility & Embryology
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

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
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

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

Junctional Zone Myometrium

Functional important entity in reproduction

- Ontogenetically related to endometrium
- Cyclic changes in SSH receptors
- Role in gamete transport and implantation
ADENOMYOSIS AND REPRODUCTION

Relation?

Impairing probability spontaneous conception?

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

Infertility: Adenomyosis and endometriosis (MRI)

Mean diameter of dorsal junctional zone in mm

p<0.001

p<0.008

Enzyme, human repro 2005

Obtained from MRI, Kunz et al., RB Monline

Adenomyosis in women with endometriosis and healthy control as related to age

Obtained from MRI, Kunz et al., RB Monline
Uterine peristalsis (of the arch/myectomy layer or stratum submucosum) during the menstrual cycle

- Type A - cervico-fundal contractions
- Type B - fundo-cervical contractions
- Type C - isthmical contractions

Kunz et al.

Uterine peristalsis during the menstrual cycle

Hysterosalpingography

Classification of Results

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
ADENOMYOSIS AND REPRODUCTION

Impairing probability spontaneous conception?

Disturbed IZ activity (Kunz et al; Droux et al)

Experimental data baboons: necropsy (n=27) with adenomyosis
all life long infertility
43% also endometriosis
(Barrier Br et al Fertil Steril 2004)

ADENOMYOSIS AND REPRODUCTION

Impairing probability spontaneous conception?

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

Occurrence of pregnancies after reductive treatment

Impact of adenomyosis on CPR in patients with endometriosis.

L.I.F.E. Leuven Institute for Fertility & Embryology
ADENOMYOSIS AND REPRODUCTION

Impairing probability spontaneous conception?

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

Adenomyosis and IVF...

The Controversy...

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

<table>
<thead>
<tr>
<th></th>
<th>Adenomyosis recipients</th>
<th>Without adenomyosis recipients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>40</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>No. of cycles</td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>38.7 ± 5.5</td>
<td>37.8 ± 5.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>No. of oocytes/cycle (mean ± SD)</td>
<td>9.9 ± 2.5</td>
<td>9.5 ± 1.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>MI oocytes (%) (ICSI)</td>
<td>80.1</td>
<td>86.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>Transferred embryos (mean ± SD)</td>
<td>2.7 ± 1.5</td>
<td>2.7 ± 1.6</td>
<td>N.S.</td>
</tr>
<tr>
<td>Implantation/embryo transferred (%)</td>
<td>27/160 (16.9)</td>
<td>40/161 (24.8)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Clinical pregnancy/cycle (%)</td>
<td>10/40 (25)</td>
<td>22/40 (55)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Miscarriage (%)</td>
<td>3/18 (16.7)</td>
<td>5/23 (21.7)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Ongoing live pregnancies (%)</td>
<td>13/40 (32.5)</td>
<td>18/40 (45)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

N.S. = not significant.
The effect of adenomyosis on in vitro fertilisation and intra-cytoplasmic sperm injection treatment outcome.


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

RESULTS:

- No difference in live birth rate per patient (cycle) between the two groups with both raw and logistic regression adjusted data (29.7% vs 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
IVF/ET outcomes in relation to myometrial thickness

Hyun Sik Youm et al

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).

<table>
<thead>
<tr>
<th>Group</th>
<th>A (cm)</th>
<th>B (cm)</th>
<th>C (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>302</td>
<td>63</td>
<td>48</td>
</tr>
<tr>
<td>No. of cycles</td>
<td>397</td>
<td>81</td>
<td>73</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luteal phase length (days)</td>
<td>13.0 (12.0–14.0)</td>
<td>14.0 (13.0–15.0)</td>
<td>15.0 (14.0–16.0)</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>1100 (900–1300)</td>
<td>1200 (1000–1400)</td>
<td>1300 (1100–1500)</td>
</tr>
<tr>
<td>Progesterone (ng/mL)</td>
<td>3.5 (3.0–4.0)</td>
<td>4.0 (3.5–4.5)</td>
<td>4.5 (4.0–5.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleavage stage embryos (%)</td>
<td>88.8</td>
<td>83.3</td>
<td>81.7</td>
</tr>
<tr>
<td>Transfer outcome (%)</td>
<td>49.2</td>
<td>47.6</td>
<td>45.8</td>
</tr>
<tr>
<td>Clinical pregnancy (%)</td>
<td>13.0 (11.0–15.0)</td>
<td>14.0 (12.0–16.0)</td>
<td>15.0 (13.0–17.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livebirth rate (%)</td>
<td>8.0 (6.0–10.0)</td>
<td>9.0 (7.0–11.0)</td>
<td>10.0 (8.0–12.0)</td>
</tr>
</tbody>
</table>

Table 7. Response to common induction methods based on amniotic fluid volume.

<table>
<thead>
<tr>
<th>Induction method</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td>85 (75–95)</td>
<td>90 (80–100)</td>
<td>95 (85–105)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>75 (65–85)</td>
<td>80 (70–90)</td>
<td>85 (75–95)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>A (cm)</th>
<th>B (cm)</th>
<th>C (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>302</td>
<td>63</td>
<td>48</td>
</tr>
<tr>
<td>No. of cycles</td>
<td>397</td>
<td>81</td>
<td>73</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luteal phase length (days)</td>
<td>13.0 (12.0–14.0)</td>
<td>14.0 (13.0–15.0)</td>
<td>15.0 (14.0–16.0)</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>1100 (900–1300)</td>
<td>1200 (1000–1400)</td>
<td>1300 (1100–1500)</td>
</tr>
<tr>
<td>Progesterone (ng/mL)</td>
<td>3.5 (3.0–4.0)</td>
<td>4.0 (3.5–4.5)</td>
<td>4.5 (4.0–5.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleavage stage embryos (%)</td>
<td>88.8</td>
<td>83.3</td>
<td>81.7</td>
</tr>
<tr>
<td>Transfer outcome (%)</td>
<td>49.2</td>
<td>47.6</td>
<td>45.8</td>
</tr>
<tr>
<td>Clinical pregnancy (%)</td>
<td>13.0 (11.0–15.0)</td>
<td>14.0 (12.0–16.0)</td>
<td>15.0 (13.0–17.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livebirth rate (%)</td>
<td>8.0 (6.0–10.0)</td>
<td>9.0 (7.0–11.0)</td>
<td>10.0 (8.0–12.0)</td>
</tr>
</tbody>
</table>
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

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

Martinez-Conejero et al Fertil Steril. 2011

<table>
<thead>
<tr>
<th></th>
<th>I: Adeno</th>
<th>II: Endom</th>
<th>III: control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>152</td>
<td>144</td>
<td>147</td>
</tr>
<tr>
<td>OD cycles</td>
<td>328</td>
<td>242</td>
<td>331</td>
</tr>
<tr>
<td>Age</td>
<td>40.5</td>
<td>37.3</td>
<td>40.9</td>
</tr>
<tr>
<td>Implant %</td>
<td>29.6%</td>
<td>33.3%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Abortion %</td>
<td>13%</td>
<td>6.1%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Term preg %</td>
<td>26.8%</td>
<td>38%</td>
<td>37.1%</td>
</tr>
</tbody>
</table>

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

• 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


Retrospective study: 213 patients; no other interfering factors

<table>
<thead>
<tr>
<th></th>
<th>Adeno positive</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>38</td>
<td>175</td>
</tr>
<tr>
<td>Mean age</td>
<td>35 (27-37,3)</td>
<td>33 (30-36)</td>
</tr>
<tr>
<td>Fertilization %</td>
<td>66.7%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Estradiol</td>
<td>2100</td>
<td>3200</td>
</tr>
<tr>
<td>Clin. Preg %</td>
<td>23.6%</td>
<td>44.6%</td>
</tr>
<tr>
<td>Abortion%</td>
<td>25%</td>
<td>10.3%</td>
</tr>
</tbody>
</table>
Adenomyosis reduces pregnancy rates in infertile women undergoing IVF.

<table>
<thead>
<tr>
<th></th>
<th>Adeno pos.</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>19</td>
<td>256</td>
</tr>
<tr>
<td>Clin. Pregn. %</td>
<td>22.2%</td>
<td>47.2%</td>
</tr>
<tr>
<td>Ongoing pregn. %</td>
<td>11.7%</td>
<td>45.9%</td>
</tr>
<tr>
<td>Abortion %</td>
<td>50%</td>
<td>2.86%</td>
</tr>
</tbody>
</table>

Adenomyosis has no adverse effects on IVF/ICSI outcomes in women with endometriosis treated with long-term pituitary down-regulation before IVF/ICSI.

<table>
<thead>
<tr>
<th></th>
<th>Adeno pos.</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>5.35</td>
<td>27</td>
</tr>
<tr>
<td>74 pat with surgical endometriosis III – IV</td>
<td>27 %</td>
<td></td>
</tr>
<tr>
<td>adeno</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.35 months down regulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fertil %</td>
<td>43.6 %</td>
<td></td>
</tr>
<tr>
<td>Implant %</td>
<td>26.3 %</td>
<td></td>
</tr>
<tr>
<td>Abortion %</td>
<td>24.3 %</td>
<td></td>
</tr>
<tr>
<td>Clin Pregn %</td>
<td>31.7 %</td>
<td></td>
</tr>
<tr>
<td>No differences between groups</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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?
Adenomyosis and IVF

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

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.

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

Adenomyosis and the endometrium
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

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

**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)
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.


- 64 women with diffuse adenomyosis / adenomyoma
- Endometrium biopsy 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 Y, Fertil Steril 2010; 94:85-9

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

Adenomyosis - Characteristics

- Diffuse lesion
- Focal lesion
- Hyperplasia
- Adenomyoma

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

---

Adenomyosis: Minimal invasive diagnosis?

Magnetic Resonant Imaging
MRI

Ultrasound

Hysteroscopy

---

The Myometrial Junctional zone
Adenomyosis: Minimal invasive diagnosis?

**Ultrasound**

2D TVS
- Accuracy: 83%
- Sensitivity: 75%

3D TVS (coronal view)
- Accuracy: 89%
- Sensitivity: 91%
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 2012; 37:471–479

Hysteroscopy
Natural access to JZ myometrium

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
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 cannula well identified by ultrasound.
Trophy Scope
2,9 mm single flow compact hysteroscope

- 2,0 mm lens system in single flow compact hysteroscope does not require assembling.

- Can be loaded with an accessory sheet which can be activated in case of necessity by gently push on the bottom and forward movement till locking in the active position.

- Supplementary functions are available without the need to remove the hysteroscope.
Spirotome (Gordo)
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.

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
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

ENDOMETRIOSIS/ADENOMYOSIS ARE PRIMARILY A DISEASE OF THE UTERUS

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
ADENOMYOSIS and REPRODUCTION 
STAGING

Many unanswered questions:
is adenomyosis a progressive disease?
clinical correlation between extent and severity?
is simple J2 hypertrophy really adenomyosis?
which is prognostic value of staging system?
choice of therapy influenced by staging?

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
**Uterine Disorder Triad**
Larsen et al 2011

**Adenomyosis**

- Endometriosis 34.6%
- Associated with Increased in stage IV 42.8%

**The E & JZ Disorder**
39.9%

---

**Uterine Endo-Myometrial dysfunction**

- Endometrium & Junction Zone Disorder
- Endometriosis
- Adenomyosis

---

**Leuven Institute for Fertility & Embryology**

- Stephan Gordts
- Nico Broevers
- Rudi Campo
- Patrick Puttemans
- Sylvie Gordts
- Marion Valkenburg
Surgery of hydrosalpinges and implantation rate (salpingectomy / salpingostomy / ligation / Essure)

Causes of tubal occlusion – Chlamydia
Diagnosis of DTO - infertility problems

Treatment and success rates:
Salpingectomy / Salpingostomy
Tubal ligation / micro-insert - Essure

ESHRE SIG Reproductive Surgery
7 - 10 July 2013
29th Annual Meeting
Pre-Congress Course 9
London – United Kingdom

Vasilios Tanos, MD, PhD.
Professor in Obstetrics and Gynaecology

University of Cyprus ARETAEION HOSPITAL

Causes of tubal factor Infertility
Risks and Statistics
• Tubal and pelvic Pathology 30 - 40%
• Tubal factor increases with age and infertility duration

• Risk of subsequent tubal infertility after PID is
  – 10 -12% after 1 episode
  – 23 -35% after 2 episodes
  – 54 -75% after 3 episodes
  (Westrom L V et al Sex Transm Diseas 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)

Distal Tubal Occlusion
a wide spectrum of severity

• Aglutinated fibria - Adherent fibrial folds,
• Various degrees of phimosis
  partial up to severe form
• Complete obstruction
• Hydrosalpinges
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: Immunoflorescence, Microimmunoflorescence 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)

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

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
Hydrosalpinges adversely affect fertility & IVF outcomes

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

[Strandell A et al. Hum Reprod 16:2403, 2001]

Hydrosalpinx and IVF outcome:
a prospective randomized multicentre trial in Scandinavia on salpingectomy prior to IVF

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>PR</th>
<th>Miscarriage</th>
<th>Live birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salpingectomy</td>
<td>112</td>
<td>36.6%</td>
<td>16.2%</td>
<td>28.6%</td>
</tr>
<tr>
<td>No salpingectomy</td>
<td>92</td>
<td>23.9%</td>
<td>26.3%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

P<0.001; LBR, p=0.045

Strandell et al 1999 Human Reprod 14:2762

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


- 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
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, salpingectomy, etc)
  - Cycle fecundability after DTO is 1-2%
  - Time is limited


Hydrosalpinges and treatment options

- Fibriolysis – separation of adherent fibria
- Fibrioplasty – 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 teraphthalate fibres)

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
## 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 Hydrosalpinges
- 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

## 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 hydrosalpinges
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

(Dubuisson J.B et al. Hum Reprod 10:1245, 1995)

## General Surgical success after salpingostomy

- The majority of pregnancies occurs within the first 2 years after surgical treatment
- Pop tubal patency success rates far exceed PR
  - patency is more easily restored than function
  - Mucosal regeneration is slow and often fails altogether (Winston R.M., Assist Reprod Genet 9:200, 1992)
  - (Dusl J.B et al. Fertil Steril 1986)
- For the milder forms of DTO pop live birth rate > 50%
  (Donnez J, Caesarea Rosa F, Fertil Steril 1986)
- For severe forms of DTO pop live birth rate is 10 - 35%
  (Taylor KC, Berlowitz L, McGhie-PF, Fertil Steril  2001)
- Risk for ectopic pregnancy is 5 - 20%
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


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

Proximal tubal ligation Vs Salpingectomy

Randomized Control Trial

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Ongoing PR / transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubal occlusion</td>
<td>45</td>
<td>37.8 %</td>
</tr>
<tr>
<td>Salpingectomy</td>
<td>47</td>
<td>48.9 %</td>
</tr>
<tr>
<td>No treatment</td>
<td>14</td>
<td>7.1 %</td>
</tr>
</tbody>
</table>

Kontoravdis et al, Ferti Steril 2006
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

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

Micro-inserts seem promising

- 7 studies published on the topic with generally positive results. [Sonigo C et al Gynecol Obstet Fertil (French) 2013]
- 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
Micro insert (Essure) treatment of Hydrosalpinges in patients could not undergo salpingectomy prior to IVF.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Patients</th>
<th>Comments</th>
<th>FR</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hitkari JA et al. 2007</td>
<td>Descriptive</td>
<td>5</td>
<td>2/5 bt successful application</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mijatovic V et al. 2010</td>
<td>Prospective single arm</td>
<td>10</td>
<td>PTO achieved at 9/10 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mijatovic V et al. 2013</td>
<td>Prospective single arm</td>
<td>20</td>
<td>1 case amnionitis 2nd trim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thebault N et al. 2012</td>
<td>Prospective single arm</td>
<td>15</td>
<td>1 pyosalpinx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sonigo C et al. 2013</td>
<td>Review of 7 studies</td>
<td>All 7 studies show +ve results and no complications</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Surgery of Hydrosalpinges and Implantation rates

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

<table>
<thead>
<tr>
<th>Reference type</th>
<th>No treatment</th>
<th>Micro-insert</th>
<th>Tubal ligation</th>
<th>Salpingostomy</th>
<th>Salpingectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate</td>
<td>3-20%</td>
<td>27-40%</td>
<td>25-35%</td>
<td>25-35%</td>
<td>25-35%</td>
</tr>
<tr>
<td>Procedure effort</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Complications</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

University of Cyprus
ARETAEION HOSPITAL
Conclusion

- Hydrosalpinges reduce pregnancy rates
- Unilateral Hydrosalpinges also reduce PR and should be treated
- Age, past history and tubal heath status will indicate the treatment option
- Mild forms DTO ... salpingostomy gives chance for spontaneous preg
- 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
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
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

- Submucous fibroid
- Endometrial polyp
Subtle Endometrial Pathology

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

1. Adenomyosis

Expression of integrin β3 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

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

<table>
<thead>
<tr>
<th></th>
<th>Miscarriage rate</th>
<th>Miscarriage rate in matched controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large septum, not removed</td>
<td>83.3%</td>
<td>16.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Small septum, not removed</td>
<td>78.9%</td>
<td>23.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large septum removed</td>
<td>30.6%</td>
<td>20.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Small septum removed</td>
<td>28.1%</td>
<td>19.3%</td>
<td>NS</td>
</tr>
</tbody>
</table>

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


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

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

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
**Outcome: Clinical pregnancy**

**Hysteroscopy**

<table>
<thead>
<tr>
<th>Hysteroscopy</th>
<th>No Hysteroscopy</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>61</td>
<td>75</td>
</tr>
<tr>
<td>Not detected</td>
<td>63</td>
<td>65</td>
</tr>
</tbody>
</table>

Updated meta-analysis on hysteroscopy & recurrent implantation failure

Improvement ~50%

El-Toukly et al

**Level 1+ 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 improves outcome in women with detectable endometrial pathology.

Hysteroscopy also improves outcome in women with no detectable pathology.

Endometrial scratch

Three meta-analyses

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

Level 1+ evidence
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 1: Implantation rates in the intervention and control groups.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Endometrial Injury (%)</th>
<th>Control (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danesh et al. (2003)</td>
<td>NR</td>
<td>27.7</td>
<td>14.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Kharazdeh et al. (2009)</td>
<td>RCT</td>
<td>16.9</td>
<td>3.38</td>
<td>0.209</td>
</tr>
<tr>
<td>Narwark et al. (2010)</td>
<td>RCT</td>
<td>13.07</td>
<td>7.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Razek et al. (2007)</td>
<td>NR</td>
<td>11.0</td>
<td>4.0</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Clinical</th>
<th>Control</th>
<th>Included</th>
<th>Pregnancy Rate (%)</th>
<th>TMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>EI-Toukhby et al. (2012)</td>
<td>34%</td>
<td>39%</td>
<td>13%</td>
<td>41%</td>
<td>29.0% (26.0, 32.0)</td>
<td>6.0</td>
</tr>
</tbody>
</table>

EI-Toukhby et al. RBM Online 2012, 25:345-354
Live birth/ongoing pregnancy rate for studies including patients with prior IVF failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Livebirth</th>
<th>Ongoing pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demirel and Gurgan, 2004</td>
<td>4/16</td>
<td>2/14</td>
<td>104/40</td>
<td>2.79 (1.86, 3.79)</td>
</tr>
<tr>
<td>Makrakis et al. 2009</td>
<td>1/14</td>
<td>1/14</td>
<td>104/40</td>
<td>2.79 (1.86, 3.79)</td>
</tr>
<tr>
<td>Barash et al. 2003</td>
<td>1/14</td>
<td>1/14</td>
<td>104/40</td>
<td>2.79 (1.86, 3.79)</td>
</tr>
<tr>
<td>Rana Raju et al. 2006</td>
<td>4/21</td>
<td>2/14</td>
<td>104/40</td>
<td>2.79 (1.86, 3.79)</td>
</tr>
<tr>
<td>Narvekar et al. 2010</td>
<td>4/21</td>
<td>2/14</td>
<td>104/40</td>
<td>2.79 (1.86, 3.79)</td>
</tr>
<tr>
<td>Raziel et al. 2007</td>
<td>4/21</td>
<td>2/14</td>
<td>104/40</td>
<td>2.79 (1.86, 3.79)</td>
</tr>
</tbody>
</table>

'Cycle preceding ovarian stimulation'-phase various

Demirel and Gurgan, 2004; Makrakis et al. 2009; Rana Raju et al. 2006
Barash et al. 2003; Narvekar et al. 2010; Karimzadeh et al. 2009; Raziel et al. 2007

'No conclusive evidence' No Potdar et al. 2012
Luteal Phase Endometrial Injury versus No Intervention on CPR

<table>
<thead>
<tr>
<th>Author</th>
<th>Endometrial scratch (n/N)</th>
<th>No intervention (n/N)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narvekar SA</td>
<td>16/49</td>
<td>7/51</td>
<td>3.05 (1.03 - 9.71)</td>
</tr>
<tr>
<td>Karimzadeh MA</td>
<td>13/48</td>
<td>4/85</td>
<td>3.01 (1.04 - 8.24)</td>
</tr>
<tr>
<td>Rama Raju GA</td>
<td>71/160</td>
<td>70/265</td>
<td>3.22 (1.44 - 7.05)</td>
</tr>
<tr>
<td>Demir A</td>
<td>50/154</td>
<td>49/211</td>
<td>3.77 (1.88 - 7.60)</td>
</tr>
<tr>
<td>Combined</td>
<td>150/411</td>
<td>126/572</td>
<td>3.16 (1.66 - 5.99)</td>
</tr>
</tbody>
</table>

Non-combability 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Endometrial scratch (n/N)</th>
<th>No intervention (n/N)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou L10</td>
<td>29/60</td>
<td>17/61</td>
<td>0.10 (0.05 - 0.19)</td>
</tr>
<tr>
<td>Karimzadeh MA (2010)</td>
<td>9/73</td>
<td>26/79</td>
<td>0.29 (0.15 - 0.57)</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>36/133</td>
<td>43/140</td>
<td>0.84 (0.55 - 1.28)</td>
</tr>
</tbody>
</table>

Non-combability of studies: Cochran Q = 13.72 (df = 1) P = 0.0002
Random effects (DerSimonian-Laird): Chi² (test odds ratio differs from 1) = 3.03 (df = 1) P = 0.08

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

<table>
<thead>
<tr>
<th>FSH</th>
<th>Pregnancy Rate after scratch</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 or less</td>
<td>29/45 = 64%</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>3/10 = 30%</td>
</tr>
</tbody>
</table>

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?

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
Dr Liu Liu, Sir Run Run Shaw Hospital, Hangzhou
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