PRE-CONGRESS COURSE 7

Fertility-Sparing Surgery in malignant and benign conditions

Special Interest Group Reproductive Surgery
Munich - Germany, 29 June 2014
Fertility-sparing surgery in malignant and benign conditions

Munich, Germany
29 June 2014

Organised by
The ESHRE Special Interest Group Reproductive Surgery
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Course coordinators

Vasilios Tanos (Cyprus), Tin Chiu Li (United Kingdom) and Grigoris Grimbizis (Greece)

Course description

The number of cancer survivors at young reproductive age is increasing. This is due to rising incidence of gynecologic cancer in young patients and the increasing age of first pregnancy. In addition benign diseases such as severe forms of endometriosis and pelvic adhesions also endanger the reproductive integrity during surgery. The management of young patients with early diagnosed gynaecological cancer or severe pelvic pathology who desire further family presents a great challenge since future oncological and obstetrical risks vary. The conflict between fertility preserving treatments and any radical surgery in likelihood of cure most of the times involves big medical and ethical dilemmas. This advanced course aims to educate and give the most recent evidence based update on fertility-sparing surgery (FSS) in benign and malignant cases.

Target audience

Gynaecologists, Gyna-Oncologists, General Surgeons

Course type

Advanced
Scientific programme

Chairmen: Gregoris Grimbizis – Greece and Marco Gergolet - Italy

09:00 - 09:30  Fertility-sparing surgery (FSS) in severe endometriosis and recurrent endometrioma: What is the gold standard approach?
  **Stephan Gordts - Belgium**
09:30 - 09:45  Discussion
09:45 - 10:15  Severe adenomyosis: fertility preserving options
  **Gregoris Grimbizis - Greece**
10:15 - 10:30  Discussion
10:30 - 11:00  Coffee break
11:00 - 11:30  Giant ovarian and other pelvic tumors and fertility sparing surgery - laparoscopy vs laparotomy
  **Vasilios Tanos - Cyprus**
11:30 - 11:45  Discussion
11:45 - 12:15  Preservation of the uterus and endometrium in cases with huge and multiple intramural and/or submucous fibroids
  **Tin-Chiu Li - United Kingdom**
12:15 - 12:30  Discussion
12:30 - 13:30  Lunch

Chairmen: Vasilios Tanos – Cyprus and Stephan Gordts - Belgium

13:30 - 14:00  Early, low grade endometrial cancer and fertility sparing surgery
  **Kazem Nouri - Austria**
14:00 - 14:15  Discussion
14:15 - 14:45  Early cervical cancer: neoadjuvant chemotherapy and fertility- sparing radical trachelectomy. Pregnancy risks and perinatal outcome
  **Andrea Maneo - Italy**
14:45 - 15:00  Discussion
15:00 - 15:30  Coffee break
15:30 - 16:00  Low malignant potential and early stage ovarian cancer: is there a place for FSS?
  **Thomas Ind - United Kingdom**
16:00 - 16:15  Discussion
16:15 - 16:45  Ovarian chemio prophylaxis, fertility preservation against the sterilizing effects of chemotherapy and ovarian tissue cryopreservation
  **Dror Meirow - Israel**
16:45 - 17:00  Discussion
17:00 - 18:00  SIG Reproductive Surgery business meeting
Fertility-sparing surgery (FSS) in severe endometriosis and recurrent endometrioma: What is the gold standard approach?

Stephan Gordts MD

ESHRE, Munich 2014

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Fertility-sparing surgery (FSS)

How to evaluate?

Decreased ovarian reserve (DOR): may refer to three distinctly, although related, different outcomes

- Oocyte quality
- Oocyte quantity
- Reproductive potential

Testing and interpreting measures of ovarian reserve: a committee opinion

The Practice Committee of the ASRM, Fertil Steril, 2012

---

There is mounting evidence to support the use of AMH as a screening test for poor ovarian response, but more data are needed. There is emerging evidence to suggest that a low AMH level (e.g., undetectable AMH) has high specificity as a screen for poor ovarian response but insufficient evidence to suggest its use to screen for failure to conceive.

There is fair evidence to support that a low antral follicle count has moderate to high specificity as a screening test for poor ovarian response and insufficient evidence to support the use of AFC as a screening test for failure to conceive.
What is normal ovarian reserve?
Dillon KE, Gracia CR.

“Currently, these biomarkers (AFC, AMH, Inhibine B) are insufficient as predictors of fertility potential or advancement to menopause and no definitive determinations can be made about what constitutes “normal” levels of each measure.”

Endometriosis and ovarian reserve

Evaluation of serum anti-Mullerian hormone levels to assess the ovarian reserve in women with severe endometriosis

<table>
<thead>
<tr>
<th>Number</th>
<th>AMH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertile patients</td>
<td>130</td>
</tr>
<tr>
<td>Endometriosis II-IV</td>
<td>65</td>
</tr>
</tbody>
</table>

Endometriosis: damage ovarian reserve
Early sign in young women of advanced ovarian depletion
Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis


Endometriotic cyst formation and associated structural tissue alterations (fibrosis) in apparently normal ovarian cortex may be a cause of reduced ovarian reserve

Early diagnosis and intervention may be beneficial in women with endometriomas to protect their ovarian function

Histological assessment of impact of ovarian endometriomas and laparoscopic cystectomy on ovarian reserve.


<table>
<thead>
<tr>
<th>Density of follicles in ovarian tissue retrieved at moment of cystectomy</th>
<th>20 year</th>
<th>30 year</th>
<th>35 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction with</td>
<td>35.4 %</td>
<td>46.8 %</td>
<td>62.7 %</td>
</tr>
</tbody>
</table>

- Ovarian endometriomas have a detrimental impact on follicle reserve in younger patients.
- The resection rate of normal ovarian tissue in cystectomy specimen of the endometriosis group was significantly higher than in the non-endometriotic cyst group (P < 0.001).

Benign cyst and ovarian tissue

Schubert B et al. Hum Reprod 2005; 20

density of follicles in ovarian tissue surrounding cysts?

<table>
<thead>
<tr>
<th>Type</th>
<th>no/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>dermoid (n=7)</td>
<td>13.04</td>
</tr>
<tr>
<td>endometriosis (n=13)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Endometriosis invaded the surrounding cortex + fibrotic reaction
Benign cyst and ovarian tissue

Schübert B et al. Hum Reprod 2005; 20
heterogenic distribution of follicles in clusters
median of 8 – 11.4 foll/mm³
no direct correlation between density and age
after freeze-thawing: normal morphology of follicles
preserved in 79 %.

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

Benign cyst and ovarian tissue

patterns similar to normal ovarian cortex; nl vascular.
dermoid 92 % 84 %
cystadenoma 77% 78 %
endometriosis 19 % 22%

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

Surgery and impact on ovaries
Pathogenesis of ovarian endometrioma

• Superficial endometriotic implants, bleeding and invagination of ovarian cortex.
• Metaplasia of coelomic epithelium
• Involvement of functional ovarian cysts

Implantation of regurgitated endometrial cells on ovarian surface.
Adhesion formation
Bleeding at implantation site and invagination cortex

Hughesdon, 1957 / Obst. Gynec. 44:481

OVARIAN ENDOMETRIOMA

Pseudocyst
Extra-ovarian localisation
Residual ovarian volume after surgery

<table>
<thead>
<tr>
<th></th>
<th>Endometriosis</th>
<th>Dermoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>5.1 ± 3.2*</td>
<td>6.7 ± 3.3*</td>
</tr>
<tr>
<td>Control</td>
<td>4.3 ± 2.3**</td>
<td>7.1 ± 3.5*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermoid</td>
<td>4.3 ± 2.3**</td>
<td>7.1 ± 3.5*</td>
</tr>
</tbody>
</table>

*p < 0.001
**p < 0.05


Lack of correlation between residual ovarian volume and cyst diameter....
Resection of even small endometrioma significant loss of ovarian volume
Decline of AMH after cystectomy for ovarian endometrioma

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (n=38)</th>
<th>Unilateral (n=20)</th>
<th>Bilateral (n=18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.8 ±4.7</td>
<td>34.0 ±3.9</td>
<td>33.6 ±5.4</td>
<td>0.830</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.1±2.3</td>
<td>20.4±2.7</td>
<td>19.7±1.7</td>
<td>0.781</td>
</tr>
<tr>
<td>Pre-operative</td>
<td>3.9±2.5</td>
<td>4.1±2.3</td>
<td>3.6±2.7</td>
<td>0.299</td>
</tr>
<tr>
<td>Post-operative</td>
<td>2.1±1.6</td>
<td>2.9±1.6</td>
<td>1.2±1.0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Hirokawa W et al. Hum Reprod 2011; 26:904-910

The rate of decline in serum AMH is defined as 100 × (preoperative AMH level – post-operative AMH level)/preoperative AMH level.

Alborzi et al. Fertil Steril; 2014

The impact of laparoscopic cystectomy on ovarian reserve in patients with unilateral and bilateral endometriomas.

Alborzi et al. Fertil Steril; 2014

AMH level decreased and FSH levels increased after laparoscopic cystectomy for endometriomas, especially in older patients and those with bilateral cysts.
**OVARIAN ENDOMETRIOMA**

Histologic analysis of endometriomas: what the surgeon needs to know. 

Inadvertently excised ovarian tissue: 81%
Endometriotic tissue may cover from 10% - 98%

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**OVARIAN ENDOemetrioma**

Hachsiguga et al. Hum Reprod 2002

Easy removable endometral cyst: 
prim. follicles 68.9% (1-25)


Endometrioma: ovarian tissue 54%* (1-2 mm thick) 
other ovarian cyst: ovarian tissue 6%* 
(p<0.005)

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A characterization of the relationship of ovarian reserve markers with age. 

<table>
<thead>
<tr>
<th>Age trial conception</th>
<th>N</th>
<th>Med. AFC &gt;15f</th>
<th>Med. AFC &lt;15f</th>
<th>Med. Afc fertl</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>35</td>
<td>56</td>
<td>56</td>
<td>.37</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>171</td>
<td>25</td>
<td>50</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>31-40</td>
<td>141</td>
<td>25</td>
<td>44.5</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>&gt; 40</td>
<td>5</td>
<td>33.5</td>
<td>50</td>
<td>.37</td>
<td></td>
</tr>
</tbody>
</table>
Quid fertility preservation?

Growing concern:

the serious risk of diminished ovarian reserve up to 
POF:

cystectomy: aggressive stripping
extensive and aggressive hemostasis

Surgery of ovarian endometrioma:
When and how?

HOW?

FERTILITY PRESERVATION
Ovarian endometrioma
Ovarian endometrioma

TO COMPLEX
AS DISEASE
AS SURGERY
TO REDUCE TREATMENT TO
ABALATION
EXCISION

Types of endometriomas

Ovarian endometrioma:

- type 1: free or loosely fixed, usually small
- type 2: densely adherent to pelvic structures in fossa ovarica
- type 3: with adenomyosis in adherent tissue

Unilateral/ bilateral

Techniques for reconstructive ovarian surgery in endometriosis

1. EVERSION

Three steps:

1. Adhesiolysis
2. Wide opening at site of inversion
3. Superficial coagulation endometriotic implants
2. EXCISION

Three steps:
1. Adhesiolysis
2. Wide opening at site of inversion
3. Resection of fibrotic pseudo-capsule

Eversion/ablation ≠ fenestration

Opening is at site of inversion with resection of fibrotic edges

OVARIAN ENDOMETRIOMA

Ablation
Lasers: CO2 lasers, KTP, NdYag ...
Current: Bipolar forceps and probe
Plasmajet
BIPOLAR COAGULATION PROBE

Three in one

Easy handling
Good haemostasis
Helpful dissection
No carbonisation
Minimal cost

\[
V = \frac{4}{3}\pi r^3
\]

<table>
<thead>
<tr>
<th>diameter (cm)</th>
<th>radius (cm)</th>
<th>volume (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0,5</td>
<td>0,52</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>4,18</td>
</tr>
<tr>
<td>3</td>
<td>1,5</td>
<td>14,13</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>33,49</td>
</tr>
</tbody>
</table>
RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

Ablation versus Excision

<table>
<thead>
<tr>
<th>Year</th>
<th>Ablation Recurrence Rate</th>
<th>Excision Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>12% (20)</td>
<td>12% (23)</td>
</tr>
<tr>
<td>1999</td>
<td>21.9% (70)</td>
<td>6.1% (161)</td>
</tr>
<tr>
<td>1998</td>
<td>18.8% (32)</td>
<td>6.2% (32)</td>
</tr>
<tr>
<td>1991</td>
<td>33% (20)</td>
<td>6% (16)</td>
</tr>
</tbody>
</table>

TECHNIQUES FOR RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

Ablation versus Excision

**Excision:** higher incidence adhesion formation lower recurrence rate?
- Reduced ovarian volume and ovarian reserve
  - (El-Shawi, 1998; Al-Azemi, 2000; Nargund, 1995; Loh, 1999)

**Ablation:** higher recurrence rates?

HART RJ, HICKEY M, MAOURIS P, BUCKETT W: EXCISIONAL SURGERY VERSUS ABLATIVE SURGERY FOR OVARIAN ENDOMETRIOMATA
Cochrane review (2005, 2008)

- "Excisional laparoscopic surgery provides significantly better results than draining and destruction of the cyst wall with regard to the recurrence rate, both of the endometriotic cyst itself as of its symptoms, but also with regard to the subsequent chance of a spontaneous pregnancy."

SUMMARY: Some previously published reviews have probably too hastily concluded that excision is a better option than ablation. They failed to analyze the ovarian reserve, which is often significantly decreased after excisional surgery. This manuscript clearly explains the crucial importance of preserving the ovarian blood supply, as well as the ovarian cortex containing all primordial follicles, during surgery.
Type of surgery and impact on ovaries

Every kind of ovarian surgery performed for ovarian endometriotic cysts will have a negative impact upon the ovarian reserve.

Decline of AMH after cystectomy for ovarian endometrioma

<table>
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<tr>
<th>Characteristics</th>
<th>Overall (n=38)</th>
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<tr>
<td>Serum AMH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-operative</td>
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<td>1.2±1.0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Hirokawa et al. Hum Reprod 2011; 26, 4

Unilateral Endometrioma and frequency of ovulation after laparoscopic cystectomy

<table>
<thead>
<tr>
<th></th>
<th>Ovulation before</th>
<th>Ovulation after</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4cm (n=15)</td>
<td>41.0% (±8.0)</td>
<td>19.8% (±6.7)</td>
</tr>
<tr>
<td>&gt;4cm (n=13)</td>
<td>26.8% (±10.9)</td>
<td>13.5% (±5.8)</td>
</tr>
<tr>
<td>Total</td>
<td>34.4% (±6.6)</td>
<td>16.9% (±4.5)</td>
</tr>
</tbody>
</table>

I assisted reproduc genet 2008 25; 239-44
Endometriosis and frequency of ovulation after laparoscopic cystectomy for Horikawa T, 2008

<table>
<thead>
<tr>
<th>Pregnancy cycles/ Ovulation cycles</th>
<th>Operated site</th>
<th>Intact site</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/34</td>
<td>12/156</td>
<td></td>
</tr>
<tr>
<td>8.8%</td>
<td>5.8%</td>
<td></td>
</tr>
</tbody>
</table>

Laparoscopic cystectomy reduces the frequency of ovulations, but maintains the pregnancy rate per ovulation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cystectomy</th>
<th>Cauterization</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal follicles nr.</td>
<td>3,671±126</td>
<td>4,75±0.60</td>
<td>.001</td>
</tr>
<tr>
<td>Ov. volume</td>
<td>6,27±1.95</td>
<td>9,87±2.01</td>
<td>.005</td>
</tr>
<tr>
<td>Domin. foll</td>
<td>4,38±0.95</td>
<td>5,05±0.91</td>
<td>.03</td>
</tr>
<tr>
<td>Retrieved ooc</td>
<td>3,08±0.79</td>
<td>3,86±0.88</td>
<td>.01</td>
</tr>
</tbody>
</table>
OVARIAN RESERVE

<table>
<thead>
<tr>
<th>Ablation plasmajet</th>
<th>Cystectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non operated</td>
<td>operated</td>
</tr>
<tr>
<td>volume</td>
<td></td>
</tr>
<tr>
<td>7 (±2.7)</td>
<td>5.2 (±2.5)</td>
</tr>
<tr>
<td>AFC</td>
<td></td>
</tr>
<tr>
<td>6.8 (±3.5)</td>
<td>5.5 (±3.3)</td>
</tr>
</tbody>
</table>

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

Roman H Fertil Steril, 2011

Why surgery?

When surgery?

Surgery of ovarian endometrioma

WHY SURGERY?

POSITIVE ASPECTS:
1. creates possibility of spontaneous pregnancy !!
2. relief of pain
Surgery of ovarian endometrioma

WHY SURGERY?

NEGATIVE ASPECTS:
- Complexity of endometriosis is not resolved by surgery alone
- Impact on ovarian reserve

Surgery endometrioma and pregnancy rates

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Procedure</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniell</td>
<td>1991</td>
<td>ablation</td>
<td>38%</td>
</tr>
<tr>
<td>Mars</td>
<td>1991</td>
<td>laser ablation</td>
<td>30.4%</td>
</tr>
<tr>
<td>Domnez</td>
<td>1996</td>
<td>ablation</td>
<td>51%</td>
</tr>
<tr>
<td>Sutton</td>
<td>1997</td>
<td>ablation</td>
<td>45%</td>
</tr>
<tr>
<td>Bateman</td>
<td>1984</td>
<td>stripping</td>
<td>42.8%</td>
</tr>
<tr>
<td>Montanino</td>
<td>1996</td>
<td>stripping</td>
<td>45%</td>
</tr>
<tr>
<td>Busacca</td>
<td>1999</td>
<td>stripping</td>
<td>57.5%</td>
</tr>
<tr>
<td>Milingo</td>
<td>1999</td>
<td>stripping</td>
<td>53%</td>
</tr>
<tr>
<td>Hemmings</td>
<td>1998</td>
<td>stripping/coagul</td>
<td>50/60%</td>
</tr>
<tr>
<td>Beretta</td>
<td>1998</td>
<td>stripping/coagul</td>
<td>66/23%</td>
</tr>
</tbody>
</table>

Endometriosis

Probability of spontaneous conception?

<table>
<thead>
<tr>
<th>Type of endometriosis</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>18%</td>
</tr>
<tr>
<td>Moderate and severe (III-IV)</td>
<td>3.1%</td>
</tr>
<tr>
<td>Adamson et al.</td>
<td>37.4%</td>
</tr>
<tr>
<td>P. Barri et al.</td>
<td>11%</td>
</tr>
</tbody>
</table>
Laparoscopic surgery for subfertility associated with endometriosis - live birth

<table>
<thead>
<tr>
<th>Study</th>
<th>Control (95% CI) Fixed</th>
<th>Treatment (95% CI) Fixed</th>
<th>Weight %</th>
<th>Peto OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guttm. 99</td>
<td>10/51 10/45</td>
<td>15.1 0.86 [0.32 2.28]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marcos 97</td>
<td>50/172 29/169</td>
<td>57.6 1.96 [1.18 3.22]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nowroozi 87</td>
<td>39/69 10/54</td>
<td>27.3 4.37 [2.11 9.07]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>97/292 49/268</td>
<td>100.0 2.15 [1.47 3.14]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours control  Favours treatment

Cochrane Review - Jacobson, Barlow & Koninckx

ENDOMETRIOSIS- Associated CPP

Prospective, randomized, double-blind trial of laser laparoscopy (Sutton, Fertil Steril 1994)

<table>
<thead>
<tr>
<th>Relief</th>
<th>rAFS 1</th>
<th>rAFS 2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Laser</td>
<td>46%</td>
<td>74%</td>
</tr>
</tbody>
</table>

TECHNIQUES FOR RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

Ovarian response

- Canis et al. 2001: not reduced
- Donnez et al. 2001: no difference
- Geber 2002: reduced
- Somigliana 2003: reduced
- Barnhart 2002: reduced (meta analysis)
- Garcia-Velasco 2004: no difference
ENDOMETRIOSIS-Associated INFERTILITY

Comparison of Pregnancy Rates
(Adamson, Sem Reprod Endocrin 1997)

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>Mini/Mild</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectant</td>
<td>37.4%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Surgical</td>
<td>51.7%</td>
<td>41.3%</td>
</tr>
</tbody>
</table>

Pregnancy rates after surgery and/or IVF
(P. N. Barri RBMonline 2010)

<table>
<thead>
<tr>
<th></th>
<th>&lt; 35 y (n= 483)</th>
<th>35 y (n= 144)</th>
<th>Total (n=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I= surgery</td>
<td>61 %</td>
<td>29.7%</td>
<td>54.2%</td>
</tr>
<tr>
<td>II= surg + IVF</td>
<td>34.3%</td>
<td>25.9%</td>
<td>30.4%</td>
</tr>
<tr>
<td>III = IVF first</td>
<td>35.7%</td>
<td>25%</td>
<td>32.2%</td>
</tr>
</tbody>
</table>

Pregnancy rates after surgery and/or IVF
(P. N. Barri RBMonline 2010)

<table>
<thead>
<tr>
<th></th>
<th>262</th>
<th>262</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregn after surgery</td>
<td>56</td>
<td>68</td>
</tr>
<tr>
<td>Pregn IVF after surg</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>262</td>
<td>318</td>
</tr>
<tr>
<td>Total pregn.</td>
<td>262</td>
<td>318</td>
</tr>
<tr>
<td>Final % pregn</td>
<td>54.2%</td>
<td>65.8%</td>
</tr>
</tbody>
</table>

L.I.F.E.
Leuven Institute for Fertility & Embryology
The effect of endometriosis on in vitro fertilization outcome: A systematic review and meta-analysis
Harb H, Gallos I, et al; BJOG 2013; 120: 1308-20

<table>
<thead>
<tr>
<th>Endometriosis Stage</th>
<th>Fertilization Rates</th>
<th>Implantation Rates</th>
<th>Clinical Pregnancy Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/II</td>
<td>Reduced (RR=0.93, 95% CI p=0.03)</td>
<td>Reduced (RR=0.79, 95% CI, P=0.006)</td>
<td>Reduced (RR=0.79, 95% CI, P=0.0008)</td>
</tr>
<tr>
<td>III/IV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The presence of endometriosis (III/IV) is associated with poor implantation and clinical pregnancy rates in women undergoing IVF treatment.


Cumulative live birth rates (%) with and without frozen embryo transfer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Live Birth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>33%</td>
</tr>
<tr>
<td>II</td>
<td>22%</td>
</tr>
<tr>
<td>III</td>
<td>15%</td>
</tr>
<tr>
<td>IV</td>
<td>13%</td>
</tr>
</tbody>
</table>

Cumulative life birth rate
Tummon et al. 1991
Stage of endometriosis and IVF outcome
Meta-analysis

<table>
<thead>
<tr>
<th>rAFS I-II</th>
<th>rAFS III-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Nb ooc</td>
<td>8.19</td>
</tr>
<tr>
<td>Peak E₂</td>
<td>5813.38</td>
</tr>
<tr>
<td>Fertil.%</td>
<td>58.38%</td>
</tr>
<tr>
<td>Pregn %</td>
<td>21.12%</td>
</tr>
<tr>
<td>Implant%</td>
<td>11.31%</td>
</tr>
</tbody>
</table>

Barnhart et al. Fertil Steril 2002, 77

Results of pregnancy rates in donation programs

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

Endometriosis Association Survey

- 10,000 questionnaires mailed
- 4,000 questionnaires entered in analysis
- Average time between first symptoms and diagnosis is 9.3 years!
- 4.7 years before first medical consult
- 4.6 years before final diagnosis

www.endometriosisaswn.org
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Type</th>
<th>Age</th>
<th>Type</th>
<th>Endometriosis Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galatani</td>
<td>1980</td>
<td>66</td>
<td>66</td>
<td>50%</td>
<td>10% 38% 0% 4%  US</td>
</tr>
<tr>
<td>Vercellini</td>
<td>1989</td>
<td>18</td>
<td>18</td>
<td>67%</td>
<td>33% 0% 0%  It</td>
</tr>
<tr>
<td>Davis</td>
<td>1993</td>
<td>19</td>
<td>19</td>
<td>20%</td>
<td>22% 19% 31%  US</td>
</tr>
<tr>
<td>Reese</td>
<td>1997</td>
<td>49</td>
<td>49</td>
<td>80%</td>
<td>12% 6% 2%  US</td>
</tr>
<tr>
<td>Laufer</td>
<td>1997</td>
<td>42</td>
<td>42</td>
<td>7%</td>
<td>7% 0% 0%  US</td>
</tr>
<tr>
<td>Emmert</td>
<td>1998</td>
<td>37</td>
<td>37</td>
<td>92%</td>
<td>8% 0% 0%  Germ</td>
</tr>
<tr>
<td>Bai</td>
<td>2002</td>
<td>20</td>
<td>20</td>
<td>18%</td>
<td>64% 20% 10%  Korean</td>
</tr>
<tr>
<td>Ventolini</td>
<td>2005</td>
<td>52</td>
<td>52</td>
<td>14%</td>
<td>39% 43% 4%  It</td>
</tr>
<tr>
<td>Emmert</td>
<td>2006</td>
<td>31</td>
<td>31</td>
<td>4%</td>
<td>6% 5% 19%  It</td>
</tr>
<tr>
<td>Vicino</td>
<td>2010</td>
<td>30</td>
<td>30</td>
<td>15%</td>
<td>13% 24% 34%  It</td>
</tr>
<tr>
<td>Roman</td>
<td>2010</td>
<td>20</td>
<td>20</td>
<td>18%</td>
<td>45% 5% 10%  N. Zealand</td>
</tr>
<tr>
<td>Yang</td>
<td>2012</td>
<td>63</td>
<td>63</td>
<td>8%</td>
<td>3% 52% 37%  China</td>
</tr>
</tbody>
</table>

Prevalence of endometriosis in adolescents

rAFS I: 8% - 92%
rAFS II: 3% - 45%
rAFS III: 0% - 52%
rAFS IV: 0% - 37%
Prevalence of endometriosis in adults

<table>
<thead>
<tr>
<th></th>
<th>Parazzini 2006</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endo</td>
<td>195</td>
<td>51%</td>
<td>22%</td>
<td>20%</td>
<td>7%</td>
</tr>
<tr>
<td>Pain</td>
<td>185</td>
<td>37%</td>
<td>24%</td>
<td>30%</td>
<td>16%</td>
</tr>
<tr>
<td>Roman</td>
<td>2010</td>
<td>29%</td>
<td>40%</td>
<td>15%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Ovarian endometrioma

**Accuracy of US**

<table>
<thead>
<tr>
<th>Nr</th>
<th>Size (mm)</th>
<th>Sens.</th>
<th>Spec.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurjak</td>
<td>113</td>
<td>18-160</td>
<td>84</td>
</tr>
<tr>
<td>Guerriero</td>
<td>29</td>
<td>40 (50:10)</td>
<td>84</td>
</tr>
<tr>
<td>Alcazar</td>
<td>27</td>
<td>?</td>
<td>89</td>
</tr>
<tr>
<td>Guerriero</td>
<td>58</td>
<td>40 (50:16)</td>
<td>81</td>
</tr>
</tbody>
</table>

**QUID ENDOMETRIOMA < 2CM ?**

564 consecutive infertile women, 169 of whom show endometriosis at TVE

Detection of small endometriomas at TVS & TVE in 169 patients with endometriosis (15-16% of all TVE)

<table>
<thead>
<tr>
<th>size</th>
<th>TVS +</th>
<th>TVE +</th>
<th>TVS sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 15 mm</td>
<td>5</td>
<td>11</td>
<td>45 %</td>
</tr>
<tr>
<td>&gt; 15 mm</td>
<td>11</td>
<td>11</td>
<td>100 %</td>
</tr>
<tr>
<td>total</td>
<td>16</td>
<td>22</td>
<td>16/22 (73%)</td>
</tr>
</tbody>
</table>
Ovarian endometrioma
Transvaginal sonography

TVS is useful, if diameter of cyst is 15 mm or more

TVS is the preferred method of diagnosing an asymptomatic endometrioma, but cannot exclude the presence of endometriosis.

The Transvaginal endoscopy

- Hydrolaparoscopy offers the ideal inclination angle to explore the ovarian fossa
- TVE allows for the detection of endometriomas that may be invisible at TVS (<10-12 mm)
Advantages of the transvaginal laparoscopic approach

- Minimal invasive
- Early detection of endometriosis
- When indicated early treatment
TVE and small endometrioma

- We need to focus on the early detection of the small endometrioma in the young female patient (TVS, MRI, CA-125, TVS).
- We can’t make a difference between the small endometrioma with a good prognosis and the one that will continue to grow towards the more destructive stages of the disease.
- Treat when surgery is feasible & efficient, with distinct cleavage planes, minimal fibrosis.
- Maximal preservation of healthy ovarian tissue, i.e. functional prognosis (+ postop adhesion formation) and reproductive potential of the affected ovary.

Recurrence of endometriotic cyst

Recurrence of endometriosis

Reoperation and CPR

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheewadhanaraks, 2004</td>
<td>32</td>
<td>20.5% (12m)</td>
</tr>
<tr>
<td>Wheeler, 1983</td>
<td>62</td>
<td>47% (36m)</td>
</tr>
<tr>
<td>Pagidas, 1996</td>
<td>18</td>
<td>24.4% (9m)</td>
</tr>
<tr>
<td>Bussaca, 1998</td>
<td>81</td>
<td>45-54% (24m)</td>
</tr>
<tr>
<td>Candiani, 1991</td>
<td>42</td>
<td>30.7% (27m)</td>
</tr>
</tbody>
</table>
Endometriosis rAFS III – IV
Re-operation versus ART

<table>
<thead>
<tr>
<th>IVF</th>
<th>Re-operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>23</td>
</tr>
<tr>
<td>Age</td>
<td>32.5</td>
</tr>
<tr>
<td>CPR</td>
<td>33.3%*</td>
</tr>
</tbody>
</table>

* 1 cycle
Pagidas et al. 1996 Fertil Steril, 65

Endometriosis III - IV
CPR: Re-operation versus ART

Recommendations in case of recurrence ovarian endometrioma

IVF: first choice
< 5 cm, unilateral?
patients at age,
combined male pathology
GnRha down regulation
Recommendations in case of recurrence ovarian endometrioma

Re operation
- in case of cysts larger 5 cm, bilateral pain
- experienced surgeons
- GnRHa for 2 – 3 months as preparation for IVF

Informed consent

FERTILITY PRESERVATION AND ENDOMETRIOSIS

ABLASION OR EXCISION TECHNIQUE: IN WOMEN AT REPRODUCTIVE AGE

Surgery should be carried out by experienced surgeons

FERTILITY PRESERVATION AND ENDOMETRIOSIS

Patients with endometriosis: surgery first treatment option
- if not pregnant after 6m (>35 y) - 12m (<35 y): IVF
- Individualized treatment: severity (uni- / bilateral)
  - pain
  - intestinal involvement
  - other fertility impairing factors

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Leuven Institute for Fertility & Embryology

Page 37 of 150
Do not destroy the ovary
- By missing the plane of cleavage
- By excessive coagulation especially at the hilus
- By operating in one time large cysts
- Decreased ovarian reserve
- Blame the surgeon

FERTILITY PRESERVATION AND ENDOMETRIOSIS

Growing concerns on ovarian reserve:
- Ablative surgery less impact on follicular reserve; higher recurrence rate?
- Cysts > 5 cm: 2 step operative procedure protect the hilus (Donnez et al. FS 2008)

Conclusions:
- No indication for ovariectomy in case of benign or endometriotic ovarian cyst.
- Endometrioma (extra-ovarian) is different from other cyst with potential danger of reduced follicular reserve after cystectomy.
Endometriomas in spontaneous pregnancies are rare, but a fourfold increase has been reported in recent years making it today the most common adnexal mass detected during pregnancy.


The endometrioma may not be large and although benign, may cause significant complications at any stage during gestation (Gregora and Higgs, 1998). Recently, Reif et al. (2011) presented a case of acute haemoperitoneum caused by a ruptured endometrioma in a late twin pregnancy.

Severe Adenomyosis: Fertility-Sparing Surgical Options

Grigoris F. Grimbizis
Associate Professor

1st Department of Obstetrics & Gynecology
Medical School
Aristotle University of Thessaloniki

Declaration of Interests

• None (commercial)
  - Member of the Executive Committee of ESHRE
  - Member of the advisory board of ESGE
  - Member of the Executive Committee of the Hellenic Society of Obstetrics & Gynecology
  - Member of the Executive Committee of the Hellenic Society of Gynecological Endoscopy

Adenomyosis

- Definitions and Classification
- Diagnosis and mapping
- Symptoms and aims of treatment
- Uterus sparing surgical treatment
- Safety options
Adenomyosis: Definitions

- As adenomyosis is defined the presence of heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia.
- Adenomyosis can be either diffuse or focal, taking the form of adenomyoma or adenomyotic cyst.
  - Adenomyomas are grossly circumscribed nodules of hypertrophic and distorted endometrium and myometrium usually embedded within the myometrium.
- Histologically, it could range from mostly solid to mostly cystic.
### Surgical/histological classification of adenomyosis

**Diffuse adenomyosis**
1. Smooth muscle hyperplasia with ectopic endometrium (junctional zone)
2. Micro-dilated ectopic endometrial glands throughout hyperplastic myometrium

**Focal adenomyosis**
1. Adenomyomas
2. Cystic adult adenomyosis
   2a. Juvenile cystic adenomyosis

**Polypoid adenomyosis**
1. Typical polypoid adenomyomas
2. Atypical polypoid adenomyomas

**Special categories**
1. Adenomyomas of endocervical type
2. Retroperitoneal adenomyosis
   or rectovaginal endometriosis

---

**Atypical polypoid adenomyosis**

**Histological characteristics**

- Multiple endometrial glands are found between smooth muscle bundles. Most glands are tubular, while some of them are haphazardly shaped. They somehow give an impression of an infiltrative growth pattern. (hematoxylin & eosin, X 50)
- No nuclear atypia or significant mitoses are observed in higher magnification. (hematoxylin & eosin, X 100)

---

**Adenomyosis**

- Definitions and Classification
- Diagnosis and mapping
- Symptoms and aims of treatment
- Uterus sparing surgical treatment
- Safety options
Adenomyosis: Spectrum of MRI findings

- Diffuse or focal thickening of the junctional zone (max >12mm) with low T2 signal intensity
- Ill defined myometrial nodule of low T2 signal intensity within myometrium (adenomyomas)
- Punctuate foci of high intensity within the myometrium or within the low intensity lesions
- High T2 signal intensity linear striations radiating out of the endometrium (pseudo-widening of the endometrium)


Diffuse adenomyosis

Focal adenomyosis
### Diagnostic accuracy of MRI for adenomyosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design / Patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stamatopoulos et al</td>
<td>Prospective (N=135)</td>
<td>46.15</td>
<td>92.31</td>
<td>88.52</td>
<td></td>
<td>0.726</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.643 – 0.799)</td>
</tr>
<tr>
<td>Moghadam et al</td>
<td>Retrospective (N=153)</td>
<td>38.71</td>
<td>90.98</td>
<td>52.17</td>
<td>85.38</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.567 – 0.724)</td>
</tr>
<tr>
<td>Dueholm et al</td>
<td>Prospective (N=106)</td>
<td>63.64</td>
<td>88.10</td>
<td>58.33</td>
<td>98.24</td>
<td>0.759</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.666 – 0.836)</td>
</tr>
<tr>
<td>Bazote et al</td>
<td>Prospective (N=120)</td>
<td>77.50</td>
<td>92.50</td>
<td>83.78</td>
<td>89.16</td>
<td>0.850</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.773 – 0.908)</td>
</tr>
<tr>
<td>Reinhold et al</td>
<td>Prospective (N=119)</td>
<td>85.71</td>
<td>92.50</td>
<td>64.86</td>
<td>95.12</td>
<td>(0.703 – 0.914)</td>
</tr>
<tr>
<td>Ascher et al</td>
<td>Prospective (N=20)</td>
<td>88.24</td>
<td>92.50</td>
<td>83.78</td>
<td>98.24</td>
<td>0.775</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.633 – 0.927)</td>
</tr>
</tbody>
</table>

- High Overall Diagnostic performance of MRI: Area Under the Curve (AUC) >0.75
- High specificity & high PPV: the possibility of adenomyosis found in MRI to be correctly diagnosed is very high (>90%)

Stamatopoulos et al, JMIG, 19:620-626, 2012

### Correlation of MRI findings with histology

| Low T2 intensity lesions (functional zone) | Smooth muscle hyperplasia associated with ectopic endometrium  
(Differential diagnosis: hyperplasia of myometrium / normal variant) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High T2 intensity foci within low intensity lesions</td>
<td>Ectopic endometrial glands cystically dilated</td>
</tr>
<tr>
<td>High T2 intensity linear striations into myometrium</td>
<td>Benign invasion of basal endometrium within adjacent myometrium</td>
</tr>
<tr>
<td>High T2 intensity cystic lesion within myometrium</td>
<td>Adenomyotic cyst</td>
</tr>
</tbody>
</table>

### Adenomyosis

- Definitions and variants
- Diagnosis and mapping
- Symptoms and aims of treatment
- Uterus sparing surgical treatment
- Safety options
Reduction of Bleeding
Abnormal Uterine Bleeding

Reduction of pain
Pelvic pain
Dysmenorrhea, dyspareunia, chronic pelvic pain

Achievement and evolution of pregnancy
Poor reproductive outcome
Infertility & poor pregnancy outcome

Treatment options in patients with adenomyosis

Non-surgical medical and/or interventional options
- Hormonal treatment: GnRH-a / LNG-IUS
- Uterine artery embolization
- Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS)

Uterus sparing surgical options
- Complete adenomyomectomy
- Partial adenomyomectomy
- Non-excisional techniques

Total hysterectomy

Adenomyosis

Definitions and variants
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Uterus sparing surgical treatment
Safety options
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1. Adenomyomas
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   2a. Juvenile cystic adenomyosis

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1. Typical polyoid adenomyomas
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   or rectovaginal endometriosis

Uterus sparing surgical treatment of adenomyosis
Rationale and basis for classification of the techniques

Excision or destruction of the diseased tissue with concomitant maintenance of the healthy myometrium is the goal of any surgical conservative treatment

Adenomyosis/adenomyomas infiltrate myometrium and, thus, adenomyomectomy is always associated with concomitant removal of some amount of myometrial tissue

Classification of surgical techniques should be based on:
1. Extent of removal of adjacent healthy myometrium and,
2. Preservation of the integrity (and subsequently the functionality) of the uterine wall

Classification of Surgical Techniques

1. Complete excision of adenomyosis
   Complete removal of all the clinically recognizable, non-microscopic lesions with maintenance of uterine wall integrity

2. Partial excision of adenomyosis / cytoreductive surgery
   Partial removal of the clinically recognizable non-microscopic lesions. Complete removal would lead to "functional" hysterectomy due to the concomitant excision of a critical amount of healthy myometrium

3. Non-excisional techniques
   Interventions where removal of adenomyotic tissue is not included

Grimbizis et al, Fertil Steril, advance access online, 2013
### Classification of uterus sparing techniques and their variants

#### Excisional techniques

<table>
<thead>
<tr>
<th>Surgical category</th>
<th>Techniques</th>
<th>Described variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete excision</td>
<td>Adenomyomectomy</td>
<td>1. Classical technique (Ruehm, 1952; Grimbezis et al., 2006; Hung et al., 2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Modifications:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ U-shaped resection (Sun et al., 2011)</td>
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<td>▪ Overlapping flap (Tsuchida et al., 2006)</td>
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<td>2. Triple flap method (Suzuki et al., 2011)</td>
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<td>3. Classical technique</td>
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<td>Partial excision</td>
<td>Adenomyomectomy</td>
<td>1. Classical technique (Tsuchida et al., 2004)</td>
</tr>
<tr>
<td>(cytoreductive surgery)</td>
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<td>2. Transverse resection (Tsuchida et al., 2004)</td>
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<td>3. Wedge resection of the uterus (Sun et al., 2011)</td>
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<td>4. Asymmetric dissection of the uterus (Tsuchida et al., 2003)</td>
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<td>Cysterectomy</td>
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</table>

Grimbezis et al, Fertil Steril, advance access online, 2011

### The beginning of the story ...........

**Laparoscopic Excision of Myometrial Adenomyomas in Patients with Adenomyosis Uteri and Main Symptoms of Severe Dysmenorrhea and Hypermenorrhea**

Morita et al, J Am Assoc Gynecol Laparosc, 11: 86–89, 2004

### “Classical” Technique

**REPRODUCTIVE SURGERY**

Laparoscopic excision of uterine adenomyomas

Laparoscopic adenomyomectomy has the same operative steps as myomectomy

Differences

(i) not clearly defined surgical borders
(ii) excision into the neighboring healthy myometrium
(iii) grasping and traction very difficult
(iv) rich vascularization

Adenomyoma
Careful inspection for recognition of the ill defined borders

Longitudinal incision of the uterine serosa along the lesion

Dissection of the adenomyoma with the use of scissors / Attention to secure hemostasis

Difficulties in grasping and traction with tearing of the adenomyotic tissue

Dissection of the adenomyotic lesion with excision into the neighboring healthy myometrium

Uterine wall after the removal of the adenomyotic tissue: normal myometrium with rich vascularization
Adenomyotic tissue

Closure of the uterine wall

**Operative steps**

(i) Local injection by diluted vasopressin solution
(ii) Transverse incision in the adenomyotic tissue up to the endometrium
(iii) Surgical removal of the adenomyotic tissue with a monopolar needle
(iv) The normal muscle layer on the serosal membrane side was left as an upper and lower serosal flap
(v) Overlapping of the flaps were overlapped and sutured to counteract the lost muscle layer to reconstruct the uterus.


**“Classical” Technique: Overlapping flaps**

Laparoscopic adenomyomectomy and hysteroplasty: A novel method

Mireyuki Takeuchi, MD, Miki Kikado, MD, Saho Kikuchi, MD, Mineo Shimazu, MD, Ken Kumaiziri, MD, Takanori Kikama, MD, and Katsuyuki Kinoshita, MD

Operative steps

(i) Local injection by diluted vasopressin solution
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(iii) Surgical removal of the adenomyotic tissue with a monopolar needle
(iv) The normal muscle layer on the serosal membrane side was left as an upper and lower serosal flap
(v) Overlapping of the flaps were overlapped and sutured to counteract the lost muscle layer to reconstruct the uterus.

Triple flap technique

(A) Bisection of the uterus & Opening of the cavity
(B & C) Excision of adenomyotic tissue leaving myometrial flaps from the serosa and endometrium

(D) Closure of the endometrium
(E & C) Closure of the uterine wall with the characteristic triple flap technique (overlapping of the two sutured flaps with the third one)
Patient's age: 46 years
Abnormal uterine bleeding / Severe anemia
Myomas & adenomyoma
Wishing pregnancy with oocyte donation

Partial adenomyomectomy & myomectomy

Myoma ⇒
Adenomyoma ⇨

Laparoscopic myomectomy

Incision of uterine wall and removal of intramural myoma of the posterior wall
Recognition of adenomyoma’s borders & partial resection of adenomyotic lesion (cytoreductive operation)

Partial adenomyomectomy (“cytoreductive” resection)
Suturing of the uterine wall

Adenomyomectomy under US trans-trocar control

Successful Total Laparoscopic Cystic Adenomyomectomy After Unsuccessful Open Surgery Using Transsteroac Ultrasoundographic Guiding

(a) MRI: a cystic adenomyoma was present, (b) Small-diameter (10 mm) ultrasonographic (USG) probe used for laparoscopy. Uterine shape is roughly normal and cystic lesion is not identifiable, (c) USG view obtained intraoperatively showing location of cystic adenomyoma (yellow arrow)

Classification of uterus sparing techniques and their variants

Non-excisional techniques

Non-excisional

Combined with excisional

1. Uterine artery ligation (Wang et al., 2009)

Non excision only

1. Endometrial ablation (Woo, 1998, Park et al., 2000, Kurian et al., 2007, Mino et al., 2007)
2. Endometrial ablation (Paris-Schlienger et al., 2000)
3. Hysteroscopic cryosurgery

Hysteroscopic

Others

1. High frequency ultrasound (Stein et al., 2000)
2. Alcohol instillation for cystic adenomyosis (Perin et al., 1997)
3. Endometrial non-hysteroscopic ablation
4. Radiofrequency (Park et al., 2003)
5. Microwave (Kaspar et al., 2006)
6. Balloon (Chao et al., 2001)

.... electrocaugulation of the myometrium

Laparoscopic Bipolar Coagulation for the Conservative Treatment of Adenomyomata

Douglas R. Phillips, M.D., FACOG; Howard G. Ondracek, M.D., FACOG; Steven C. Reiner, M.D., FACOG; and John S. Diamond, M.D., FACOG

Operative steps

(i) Use of a 32-cm-long myoma bipolar coagulation instrument with two distal, parallel, 5cm-long needles
(ii) Systematic perforation and slow coagulation of the adenomyomas at 5- to 10-mm intervals through the serosal surface to its base, forming parallel cylinders of desiccated and denatured tissue
(iii) The end point of the procedure was pallor and blanching of the entire over-lying serosal surface.


Laparoscopic Uterine Artery Ligation for Treatment of Symptomatic Adenomyosis

Chin-Li Wang, M.D., Chih-Yang Yen, M.D., Chyi-Lung Lin, M.D., and Yung-Huai Shiau, M.D.

Study population: 20 patients
Parameters: uterine volume, bleeding control, pain control

Overall satisfaction: 3/20
Hysterectomy: 3/20, Consider hysterectomy: 5/20,
Stationary: 9/20
Overall estimation: poor results

Uterus sparing operative treatment for adenomyosis. A systematic review

Grimbizis et al, Fertil Steril, advance access online, 2013

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Quality Score</th>
<th>Evidence for Study Evaluation</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Type of Study Design</td>
<td>10</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2. Number of Patients</td>
<td>8</td>
<td></td>
<td>1</td>
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<tr>
<td>3. In the definition of the extent of the adenomyosis disease</td>
<td>8</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>4. MR or US and Clinical</td>
<td>8</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5. Clinical/Pathological</td>
<td>8</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

High Quality: Score >5

Complete Adenomyomectomy
Partial Adenomyomectomy

Reduction of Pain 82, 81, 8
Reduction of Bleeding 68, 80

Adenomyomectomy: post-operative results
Reduction of pain and bleeding

Grimbizis et al, Fertil Steril, advance access online, 2013

Page 54 of 150
Is the surgical approach beneficial to subfertile women with symptomatic extensive adenomyosis?

Peng-Hui Wang, Jong-Ling Fuh, Hsiang-Tai Chao, Wei-Min Liu, Ming-Huei Cheng and Kuan-Chong Chao

Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (n=28)</th>
<th>Pregnancy rates</th>
<th>Delivery rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Conservative surgery ± GnRH a</td>
<td>13/28 – 46.4%</td>
<td>9/28 – 32.1%</td>
</tr>
<tr>
<td>B</td>
<td>GnRH a only (6 months)</td>
<td>4/37 – 10.8%</td>
<td>3/37 – 8.1%</td>
</tr>
</tbody>
</table>

Adenomyomectomy: post-operative results

Grimbizis et al, Fertil Steril, advance access online, 2013
Adenomyosis

- Definitions and variants
- Diagnosis and mapping
- Symptoms and aims of treatment
- Uterus sparing surgical treatment
- Safety options

Safety aspects

Spontaneous uterine rupture of a twin pregnancy after a laparoscopic adenomyomectomy: A case report
Shin-Ichiro Wada, MD, Masataka Kado, MD, and Hisamori Hirasumi, MD

- Spontaneous rupture at 30th week of gestation
- Laparoscopically assisted vaginal excision
  Incision of the vaginal posterior wall after laparoscopic removal of the uterosacral ligaments and separation of the vagina from the rectum. Uterus extraction and turning over to a vaginal approach


Angioleiomyoma resembling adenomyosis

Important: histology of the lesion!!!
safety aspects

Endometrial stromal sarcoma resembling adenomyosis

Important: histology of the lesion!!!

Conclusions

- Adenomyosis represents a clinical challenge due to its various histological forms and to the fact that it infiltrates myometrium
- MRI is an extremely useful tool with high diagnostic accuracy and excellent correlation of MRI findings with histology
- Uterus sparing surgical treatment is feasible and it is associated with a significant reduction of symptoms and an improved reproductive outcome
Giant ovarian and other pelvic tumors
and fertility sparing surgery
Laparoscopy versus Laparotomy

Pre Congress Course - Reproductive Surgery

Vasilios Tanos MD, PhD
Prof Obstetrics & Gynaecology

Ovarian masses

- corpus luteum cysts
- functional / simple cysts and complex masses
- endometriomas and implants
- dermoid cysts
- Ovarian tumors: LMP and EOC
- Pelvic masses due to PID / Abscess
- Adhesion conglomerates

Functional ovarian cysts and Oral Contraceptives treatment

- common gynecological problem of reproductive age worldwide
- when large, persistent, or painful, may require operations
- treatment with oral contraceptives since 70s
- 7 RCTs from 4 countries - 500 women.
- with cysts that occurred spontaneously and/or after ovulation induction
- Results: most cysts resolved without treatment within a few cycles
- persistent cysts tended to be endometrioma or para-ovarian cyst
- Conclusion: Combined oral contraceptives have no benefit in ovarian cyst resolution

Cochrane Database of Systematic Reviews 2006
DA Grimes et al. 2009
Benign ovarian cysts in US
Prospective Observational longitudinal study
- 323 women, 19-50 y old, with ovarian cysts
- 120 study group, 6-12 months follow up
- Endometriomas 3.3 cm (SD 1.5)
- Simple cyst 4.1 cm (SD 1.6)
- Dermoid cyst 3.2 cm (SD 1.4)
- Haemorrhagic cyst 3.5 cm (SD 1.2)
- Follow up median 42 months (18-94 months)
- 8.3% disappear during follow up
- Non developed to ovarian Ca
- Conclusion: Conservative management is recommended for Bg ovarian cysts / masses until final possible diagnosis
J L Alcazar et al. 2005 Hum Reprod

Ovarian reserve is damaged after excision of ovarian masses
- gonadal damage is at least partly caused by the presence of an ovarian mass per se preceding surgery
- laparoscopic / laparotomy by
- stripping or excision or
- electrosurgical coagulation / bipolar /monopolar causes
- local inflammation
- vascular compromise following
- lack of local fibrinolytic response and
- creation of adhesions and
- destruction of microvascularization

Reduced ovarian reserves after Surgery
- 20 w Bg ovarian cysts – lappic cystectomy
- AMH & ovarian volume by US
- AMH level recovered to 65% of the preop level 3 months pop
- AMH level was higher 1 week pop in endometriosis as compared to non endometriotic cysts
H J Chang et al 2010 - Fertil Steril
Ovarian cyst in Adolescence

- Incidence ovarian cysts 2-5 / 100,000 girls / year
- Major symptom is abdominal pain
- 0.2% of all pediatric surgery
- Tumor Markers – Ca 125, alfa-fetoprotein, beta hCG,
- TAU - all, TVU - 40%, CTS - 21%, MRI – 20%
- Malignant - 1% of all cancers in children and adolescents
  Benign functional cysts 30% and cystic teratomas 26%
- Fertility sparing surgery – preserve ovarian hilus and avoid
destruction of mesosalpingos, ie microvascularization

Templeman C et al Obst Gyneco 2000,
Bristow RE J Adolesc Health 2006

Ovarian cysts pathological findings and incidence

<table>
<thead>
<tr>
<th>Pathology</th>
<th>%</th>
<th>Pathology</th>
<th>%</th>
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<tbody>
<tr>
<td>I. Benign</td>
<td>46</td>
<td>II. Neoplastic Benign</td>
<td></td>
</tr>
<tr>
<td>Follicular cysts</td>
<td>83</td>
<td>Mature cystic teratoma</td>
<td></td>
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<tr>
<td>Corpus Luteum cyst</td>
<td>Serous Cystadenoma</td>
<td></td>
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<tr>
<td>Paraovarian cysts</td>
<td>Mucinus Cystadenoma</td>
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<tr>
<td>Endometriosis</td>
<td>Fibroma</td>
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<tr>
<td>Salpingo- oophoritis</td>
<td>Serous Cystadenofibroma</td>
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<tr>
<td>III. Malignant</td>
<td>1</td>
<td>Yolk Sac Tumor</td>
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<tr>
<td>Sex Cord stromal Tumors</td>
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Giant Ovarian cysts and pelvic tumors

Any relations to the large size ??

- Related to pathological classification
- Time of existence
- Age
- Any other factors
- Inherited
- Relation to infertility
- Management options
Persistent Corpus Luteum Cysts

- Clinical manifestations
- Discomfort and pain due to compression
- Ovarian / adnexal Torsion
- Ruptured CL cyst

Laparoscopic cystectomy

Ovarian cyst in torsion during adolescence carries high risk for a torsion to the contralateral side

Detorsion and Expectant management
Avoid oophorectomy or salpingoophorectomy
Giant ovarian cysts can be treated laparoscopically. Aspiration of the cysts can be performed under US guidance to reduce the size and then to perform laparoscopy.

Germ cell tumours
- Derived from primitive germ cells of embryonic gonad
- Account for 2-10% of all ovarian tumours
- Most common in young women < 35
- Often curable with high survival rates
- Usually present as a rapidly enlarging abdominal mass, which causes considerable pain.
- They often rupture or undergo torsion.
- Dysgerminoma is the most common type and has an excellent prognosis for Stage I tumours.
- Types of germ cell tumours are:
  - Dysgerminoma, Endodermal sinus tumours, Teratoma.
  - Embryonal carcinoma, Choriocarcinoma, Sarcomas

Sex cord-stromal tumors
Derive from connective tissue cells
Less than 5% of all ovarian tumours
- Fibroma.
- Fibrosarcoma.
- Sertoli-Leydig tumours.
- Granulosa cell tumours.
**Dermoid cysts**

Patients’ Age & US findings

- dermoid cysts registered in 20 tertiary and secondary hospitals
  multicentric review 2000 and 2005  RS 306 cases
- Results: - patients’ mean age 32 and median age 30
- Average size 7cm (2-30cm)
- Mostly Cystic (solid in 1/3)
- Bilateral 8.5%

M Arab et al J Gyn Surgery 2010

---

24y with abdominal pain
 Abd US longitudinal pelvic US bladder (asterisk)
 uterus (U)
 multilisepated, cystic mass (arrow)
 Dig: hemorrhagic ovarian cyst
 US follow-up showed complete resolution

17y, Lt ovarian dermoid of 2cm heterogenous, echogenic mass
 (cursors and arrow)
 Stable for 1 year and later growth
 A hemorrhagic cyst would have been resolved after this period of time

---

**Dermoid spill facts**

- Spillage in laparoscopy 15-100% and Spillage in laparotomy 4-13%
- 26 laparoscopic dermoid cysts excision 1999 - 2005
- 31 cysts with mean diameter 7.5cm,
  28 dermoid cysts – treated with conservative cystectomy
  Encountered 14 spillages. The chemical peritonitis risk was (1/14) 0.2%
- Review of 14 studies
  470 laparoscopic dermoid cystectomies and Spillage in 310 cases (66%)
  The incidence of chemical peritonitis was 0.2%
- Only 1 case, 9 months post op developed granulomatous peritonitis
- NS differences in complications noted between the spillage and non spillage groups.

© Shawki et al 2007
Mg transformation in ovarian dermoid cyst

- 10 centers in Australia, Canada, Germany, and Austria
- 33 patients mean age 49, followed between 1979 – 2007
- Frequency of Mg transformation was 1% to 2%

Results:
- 15 pts at S I and most of S II and S III were optimally debulked.
- Platinum-based regimens most commonly used
- Chemotherapy after surgery was not effective
- 4 S I had fertility-sparing surgery (FSS) with good outcomes
- 2 pts had a sustained remission after second surgery for relapsed disease
- 5 pts had a good outcome 2 alive and well at 12 months of follow-up

Conclusions:
- FSS may be an option in Stage I young patients willing to have a child
- Patients with advanced disease do poorly, regardless of treatment


Pregnancy outcome with dermoid and other benign ovarian cysts (1)

- 93 occurred in patients with benign ovarian cysts
- Benign cystadenoma 41.9%, adenofibroma 1.8%, dermoid cyst 36.7%
- 12.9% were diagnosed during pregnancy by US
- 10.8% were diagnosed before pregnancy
- The mean diameter at diagnosis was
  - 9.05 ± 7.6 cm for cystadenoma
  - 6.09 ± 3.0 cm for dermoid cyst
  - 4.55 ± 4.1 cm for adenofibroma.

L Katz et al. Archives of Gynecology, 2010

Pregnancy outcome with dermoid and other benign ovarian cysts (2)

Results:
- Only 3 cases of ovarian torsion were noted (3.2%), and 15 cases hospitalized due to abdominal pain (16.2%).
- Pregnancy and perinatal outcome with dermoid and other benign ovarian cysts is favorable.
- The cysts should be managed conservatively with routine US follow up during the pregnancy since complications are extremely rare

L Katz et al. Archives of Gynecology, 2010
Classification of Mg Ovarian Germ Cell Tumors

I. Primitive germ cell tumors
   A. Dysgerminoma
   B. B. Yolk sac tu
   C. Embryonal carcinoma
   D. Polyembryoma
   E. Nongestational choriocarcinoma
   F. Mixed germ cell tumor, specify components

II. Biphasic or triphasic teratoma
   A. Immature teratoma
   B. Mature teratoma
      1. Solid
      2. Cystic, dermoid cyst
      3. Fetiform teratoma, homunculus

III. Monodermal teratoma and somatic-type tumors associated with biphasic or triphasic teratoma
   A. Thyroid tumor group
   B. Carcinoid group
   C. Neuroectodermal tumor group
   D. Carcinoma group
   E. Melanocytic group
   F. Sarcoma group
   G. Sebaceous tumor group
   H. Pituitary-type tumor group
   I. Retinal anlage tumor group
   Others

Borderline tumours
(tumors of low malignant potential)
10-15% of ovarian tumours managed primarily by surgery and do not respond well to chemotherapy

- Borderline serous - the most common.
- Borderline mucinous.
- Borderline endometrioid

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2013)

Epithelial ovarian tumours

- Arise from the ovarian epithelium
- Most common type, 85-90% of all ovarian cancers
- Most commonly in women >50
- Serous - most common subtype, > 50% of epithelial Tu
- Occur in women between 40-60 years of age
- Clear cell tumours, 5-6% of epithelial tumours
- Affect ages 40-80, often associated with endometriosis
- Mucinous tumours, 10% of epithelial tumours
- Most commonly affect ages 30-50
Metastatic tumours

Ovarian secondary tumours may arise from

- Breast
- GIT
- haemopoietic system
- uterus
- cervix

OC - Epidemiology

- Ovarian cancer is 5th most common Ca in women
- lifetime risk of around 2% for women in EU
- it is the leading cause of death from gyn cancer
  NICE Clinical Guideline, April 2011
- Incidence rate 17.1 per 100,000 women
  (NCIN)/Trent Cancer Registry report, Nov 2012
- 61% mortality rate (OC Statistics) Cancer Research UK

Risk factors (1)

- Increasing age,
- lifestyle (21%) Parkin DM et al. Br J Cancer. 2011
- Smoking (2%) Parkin DM BJ C 6;105 Suppl 2 2011
- Lack of exercise
- Obesity during menopause
- Infertility and fertility drugs (cc)
- Nulliparity
- Early menarche
- Late menopause
Risk factors

- FBOC Syndrome 3-4 times risk of developing OC
- only 10% of cases arise in women with a positive family history (Gavther SA, Pharoah PD Curr Opin Genet Dev. 2010)
- BRCA1 and 2 genes mutations (Melin A, Sparen P, Bergqvist A. Hum Reprod. 2007)
- Endometriosis and link - ov endometriosis and clear-cell oc - mutation of the ARID1A gene (Wiegand KC et al NEJM 2010)

Symptoms of Ovarian Tumors

- women of 50 with recent IBS history (rarely 1st time at this age)
- unexplained fatigue, weight loss or change in bowel habit
- abdominal distension (often described as 'bloating')
- early feeling of fullness whilst eating (satiety) and/or loss of appetite
- pelvic or abdominal pain
- Urinary frequency or urgency

Clinical evaluation and Lab workup

- **Clin Exam:** ascites and/or a pelvic/abdo mass
- **Laboratory:** Raised Ca 125, CEA, LFTs
- **Imaging:** TVU, Abd US, CTS, MRI
- **Treatment:**
  - Neoadjuvant therapy
  - Surgery
  - Chemotherapy
Ovarian cancer types most appropriate for fertility sparing surgery

- Borderline ovarian tumors
- Invasive Epithelial OC (Stage 1A)
- Malignant Ovarian Germ Cell Tumors
- Ovarian Sex Cord-Stromal Tumors
  Granulosa -Cell Tumors and
  Sertoli - Leydig Cell Tumors

FSS for epithelial ovarian cancer Safety and Reproductive outcomes (1)

- EOC young patients frequently want to preserve their fertility
- 62 patients underwent FSS,
- [preservation of ovarian tissue in one or both adnexa and the uterus]
- 1990 – 2006, retrospective review
- 36 - S IA, 2 - S IB, 21 S - IC, and 1 - S IIB, 1 - S IIIA, 1 - S IIIC;
- 48 - G I, 5 - G II, and 9 - G III
- 48 - platinum-based chemo (mean 4.6 cycles, range 1–9 cycles)

JY Park, et al. 2008

FSS for epithelial ovarian cancer Safety and Reproductive outcomes (2)

Results:
- median follow-up of 56 months (range, 6–205 months),
- 11 -with tumor recurrence, 6 died of disease, 2 were alive with disease
- 54 alive without disease
- Patients with stage > IIC (p = 0.0014) or grade III (p = 0.0002) tumors had significantly poorer survival.
- 19 attempted to conceive, 22 - term pregnancies, with no congenital anomalies in any of the offspring.

Conclusion:
Fertility-sparing surgery in young patients with EOCs at Stage IA–C and G I–II who desire to preserve their fertility seems to be acceptable

JY Park, et al. 2008
## Conclusion

The size of pelvic cysts should not be an obstacle to laparoscopic surgery.

Oophorectomy should be avoided in young women without completed family planning.

FSS for certain types of ovarian malignancies, at early stage and low grade, is possible once an extensive and detailed workup of the disease has been performed.
Huge & Multiple Fibroids

Preservation of the uterus and endometrium in cases with huge and multiple intramural and/or submucous fibroids

Professor T C Li
Professor of Reproductive medicine & Surgery
Sheffield, England

29 June 2013

Outline

- Avoiding loss of uterus
- Protecting endometrial function

Huge fibroids

Surgical challenges

- Laparotomy often required
- Often increased vascularity, blood loss could be rapid
- Uterus often grossly distorted, risk of cavity being occluded after reconstruction
- Increase risk of hysterectomy
COMPLICATIONS OF MYOMECTOMY

1-2% risk of hysterectomy due to uncontrolled bleeding

Outline

- Avoiding loss of uterus
  1. peri-operative loss
  2. delayed loss
- Protecting endometrial function

Managing Blood loss

A. Pre-operative

- X-match
- Competent assistant
- Experienced anaesthetist
- GnRH or progesterone receptor blockade
- Consent re increased risks
- Preparation - Cell saver, Foley catheter for tourniquet
Managing Blood loss

B. Immediate Pre-operative

- Team brief
- Vasopressin
- Tourniquet
- Cell saver
Managing Blood loss

C. Intra-operative

- Vasopression
- One incision at a time
- Slick but effective haemostatic sutures
- Drain?

Vasopressin Injection

![Image of Vasopressin Injection]
CASE HISTORY

- Two cases of cardiac arrest immediately following vasopressin injection prior to myomectomy in Sheffield over a 20 year period

USE OF VASOPRESSIN

safety guidelines

- Correct dose - 6 units (minimum effective dose)
- Correct dilution – 20 units in 20 ml normal saline
- Correct location – midline, not close to cornua or broad ligament (vessel there)
- Correct technique – before injection, apply suction to ensure tip of needle not in a vessel
- Correct protocol – ensure anaesthetist is alert (wake up the anaesthetist)

Bleeding after Hysteroscopic resection of submucus fibroid
Bleeding after Hysteroscopic resection of submucous fibroid

Foley tamponade

Does it work?

A prospective randomised controlled trial on the effectiveness of routine Foley Balloon Tamponade on the reduction of bleeding after hysteroscopic resection of myoma.
Gynae Surgery 3: 93-96
Volume of balloon?

The same volume as the fibroid

\[ \text{Volume} = \frac{4}{3} \pi r^3 \]
Volume of balloon?

- The same volume as the fibroid diameter
  - Diameter: 2cm  Volume: 4.2ml
  - Diameter: 3cm  Volume: 14ml
  - Diameter: 4cm  Volume: 34ml
  - Diameter: 5cm  Volume: 65ml

How long for?

6 hours or so

Managing Blood loss

D. Post-operative

- Close monitoring
- Quick response to any sign of bleed
CASE HISTORY

- 28 year old women underwent myomectomy
- Operation performed by trainee supervised by a consultant
- 3 hours post-op urine output low
- 5 hour post-op drop in BP, given colloid
- 7 hour post-op haemoglobin 3.7
- Immediate laparotomy, haematoma in uterus, hysterectomy

Outline

- Avoiding loss of uterus
  1. peri-operative loss
  2. delayed loss
- Protecting endometrial function

Laparoscopic Myomectomy
Scar rupture leading to delayed loss of uterus

Risk factors for uterine rupture after laparoscopic myomectomy

Parker et al, 2010
Journal Minim Invasive Gynecol 17:551

1. Excessive use of electro-cautery
2. Poor suturing technique (16/19 cases had single layered suture)

Report of 7 uterine rupture cases after laparoscopic myomectomy: update of the literature

Pistofidis et al 2012
J Minim Invasive Gynecol 19:762

1. Excessive use of electro-cautery (6/7 cases)
2. Poor suturing technique (6/7 cases had single layered suture)
Delayed Mortality
Rupture Gravid Uterus

How to prevent?

1. Use minimal amount of diathermy
2. Proper suturing, in layers
3. Avoid full thickness cut
Avoid full thickness cut in the management of intramural fibroid

Outline

- Avoiding loss of uterus
  1. peri-operative loss
  2. delayed loss
- Protecting endometrial function
Preserving the endometrium

Avoid intra-cavity adhesions
Incise, not excise endometrium
Prophylaxis against infection

CASE HISTORY

32 year women
Became amenorrhoea after myomectomy
FSH normal, oestradiol normal
Progestogen challenge test negative

HSG 'not possible' because there was no uterine cavity
Fibroids

- Fundus
- Uterine wall
- Cervix

Anatomical Reconstruction

- Foley in uterine cavity
- Check carefully if cavity entered
- First layer – interrupted sutures

Intra-operative
Risk of intra-uterine adhesion

Higher in multiple submucosal fibroids

Removal of multiple submucosal fibroids

- High risk of intra-cavity adhesions formation
- Consider removing fibroids in stages
- Intra-uterine balloon

Does cold loop hysteroscopic myomectomy reduce intrauterine adhesions? A retrospective study
Ivan et al 2013
Fertility & Sterility
Does the shaver help to preserve the endometrium?

Resection of Submucus fibroid

Incision of the endometrium

Pre-op treatment to shrink fibroid

UAE impairs wound healing and increases risk of intra-cavity adhesion
Pre-op treatment to shrink fibroid

GnRH or P receptor blockade better

Cervical dilatation more difficulty

Cervical priming to reduce trauma to cervix during dilatation (Yu et al 2006)
cervical pretreatment

- Misoprostol – 1000 microgram 12 hours pre-op
- laminara

THANK YOU
Early, low grade endometrial cancer and fertility sparing surgery

K. Nouri
Medical school of Vienna
Department for gynecological Endocrinology and reproductive medicine

I certify that there is no conflict of interest with any financial organization regarding the material discussed in presentation.

Learning objectives

1- To review the basic about the endometrial cancer and its epidemiology with focus on the young age patients

2- To discuss the feasibility and efficacy of conservative therapy options of endometrial cancer in women who desire fertility preservation.

3- To analyze the different ART options in Endometrium cancer patients after conservative therapy.
Epidemiology

Endometrial cancer is the most common gynecologic malignancy in the United States, with over 40,000 cases diagnosed each year, typically in the postmenopausal women.

25% of cases affect premenopausal women.

14% of endometrial cancers are diagnosed in women younger than 45 years old.

5% of these tumors are diagnosed in women younger than 40 years old.

Risk factors!

- Infertility and nulliparity
- Hyperestrogenic state
- Hypertension and diabetes

hyperestrogenic state

1. Obesity
2. PCO
3. Anovulation
4. Irregular menses
5. Functional ovarian tumors

References:
hyperestrogenic state

Subset of young women with endometrial cancer are slim with regular menses

Endometrial sampling !!

Key Symptoms

1. Abnormal bleeding !
2. Prolonged anovulation

other malignancy

Ovarian malignancy
Young women with endometrial cancer are at significant risk for concomitant adnexal disease:

1. Synchronous primary ovarian tumors (10-29.4%)
2. Endometrial metastases to the ovary (5%)

Lynch/HNPCC
Good prognosis

5-year disease-specific survival rate of 93% in younger patients, in contrast to older patients (86%)

Fertility Preservation

Staging FIGO 2010

Carcinoma of the Endometrium
IA  Tumor confined to the uterus, no or < ½ myometrial invasion
IB  Tumor confined to the uterus, > ½ myometrial invasion
II  Cervical stromal invasion, but not beyond uterus
IIA  Tumor invades serosa or omentum
IIB  Vaginal and/or parametrial involvement
IIC1  Pelvic node involvement
IIC2  Para-aortic involvement
IIBA  Tumor invasion bladder and/or bowel mucosa
IVB  Distant metastases including abdominal metastases and/or inguinal lymph nodes

Grade

Grade 1 tumors have 95% or more of the cancerous tissue forming glands.

Grade 2 tumors have between 50% and 94% of the cancerous tissue forming glands.

Grade 3 tumors have less than half of the cancerous tissue forming glands.
### Staging of endometrial carcinoma

1. Pelvic exam  
2. Pap smear  
3. D&C  
4. Hysteroscopy  
5. Transvaginal ultrasound  
6. CT/MRI  
7. CA125  
8. LSK


### Hysteroscopy with D&C

1. Hysteroscopy with directed biopsies and D&C  
2. Following the lesion during the course of therapy


### Hysteroscopy with D&C

Fluid based hysteroscopy could cause retrograde seeding of the peritoneal cavity with malignant cells, the prognostic significance of positive peritoneal cytology in clinical stage I endometrial adenocarcinoma remains controversial.


The Role of Laparoscopy

- Extraterine disease
- Peritoneal cytology
- Pelvic lymphadenectomy

Hysteroscopy and direct resection

- Advantages
  - Tumor grade
  - Extent of myometrial invasion
- Disadvantages
  - Tumor grade
  - Extent of myometrial invasion
### Grade 1 Endometrial carcinoma

- Pelvic lymph-node involvement (3%)
- Para-aortic lymph node involvement (1.7%)
- Deep myometrial invasion (9%)
- Spread of tumor to the adnexa (6%) coexisting ovarian neoplasms (19%)

### Risk of Disease Progression

The risk of disease progression during conservative management of grade 1 endometrial carcinoma is 6%.

- Deferral of definitive surgery to achieve childbearing, but no replacement!!

---

**Reproductive Endocrinology**
**Gynecologic Oncology**
**Maternal–Fetal Medicine**

---

Multidisciplinary management team
Conclusiones

1- Detailed informed consent

2- Both physician and patient should be aware of the potential risks of deviation from standard therapy

3- Careful oncologic, psychotherapeutic, genetic and reproductive counseling is essential before starting conservative management

Thank you for your attention!

Andrea Maneo, MD, Ph.D
Gynecologic Oncology Unit
Azienda Ospedaliera Bolognini
Seriate (Italy)

No commercial relationships or conflicts of interest are present

Learning objectives

• main fertility-sparing strategies in cervical cancer
• oncologic and obstetrics outcomes of each policy
• current trends towards conservative therapies with less morbidity

No commercial relationships or conflicts of interest are present

Radical trachelectomy
Selection criteria

• Fertility - preservation desire
• No apparent reason of sterility
• Stage IA2 - IB1
• T size < 2 cm.
• Limited endocervical extension (colposcopy)
• Negative nodes

Roy and Plante 1998; Dargent 2000
### Radical trachelectomy

**Oncologic results**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. pts.</th>
<th>Residual mean tumor</th>
<th>FUP</th>
<th>Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steed</td>
<td>2003</td>
<td>93</td>
<td>0</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Mathevet</td>
<td>2003</td>
<td>95</td>
<td>0</td>
<td>76</td>
<td>4</td>
</tr>
<tr>
<td>Plante</td>
<td>2004</td>
<td>72</td>
<td>60 %</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>Ungar</td>
<td>2005</td>
<td>30</td>
<td>NA</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Hertel</td>
<td>2006</td>
<td>100</td>
<td>NA</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>Shepherd</td>
<td>2006</td>
<td>112</td>
<td>63 %</td>
<td>45</td>
<td>3</td>
</tr>
</tbody>
</table>

**Obstetric results**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. pts.</th>
<th>% Desiring offspring</th>
<th>Miscarriages</th>
<th>% Pregnant (pregnancies)</th>
<th>1st trim</th>
<th>2nd trim</th>
<th>Births ≤ 32 w.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steed</td>
<td>2003</td>
<td>42 %</td>
<td>46 % ( )</td>
<td>2</td>
<td>2</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathevet</td>
<td>2003</td>
<td>44 %</td>
<td>81 % (56)</td>
<td>14</td>
<td>8</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plante</td>
<td>2004</td>
<td>47 %</td>
<td>43 % (50)</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ungar</td>
<td>2005</td>
<td>17 %</td>
<td>60 % (3)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hertel</td>
<td>2006</td>
<td>NA</td>
<td>18 % (18)</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shepherd</td>
<td>2006</td>
<td>63 %</td>
<td>41 % (55)</td>
<td>14</td>
<td>7</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patients' selection**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. pts.</th>
<th>% IB1</th>
<th>% N+</th>
<th>% Adenoca.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steed</td>
<td>2003</td>
<td>93</td>
<td>34 %</td>
<td>1 %</td>
<td>52 %</td>
</tr>
<tr>
<td>Mathevet</td>
<td>2003</td>
<td>108</td>
<td>74 %</td>
<td>3 %</td>
<td>20 %</td>
</tr>
<tr>
<td>Plante</td>
<td>2004</td>
<td>82</td>
<td>63 %</td>
<td>5 %</td>
<td>42 %</td>
</tr>
<tr>
<td>Ungar</td>
<td>2005</td>
<td>33</td>
<td>70 %</td>
<td>6 %</td>
<td>13 %</td>
</tr>
<tr>
<td>Hertel</td>
<td>2006</td>
<td>108</td>
<td>64 %</td>
<td>4 %</td>
<td>31 %</td>
</tr>
<tr>
<td>Shepherd</td>
<td>2006</td>
<td>123</td>
<td>98 %</td>
<td>6 %</td>
<td>29 %</td>
</tr>
</tbody>
</table>
## Vaginal radical trachelectomy
### Oncologic results

<table>
<thead>
<tr>
<th>Author</th>
<th>pts.</th>
<th>fertility</th>
<th>relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanowska 2011</td>
<td>225</td>
<td>6%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Shepherd 2012</td>
<td>208</td>
<td>11%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Covens 2013</td>
<td>180</td>
<td>9%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Plante 2011</td>
<td>140</td>
<td>11%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Marchiolè 2007</td>
<td>135</td>
<td>13%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Kim 2012</td>
<td>51</td>
<td>18%</td>
<td>3.9%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>924</strong></td>
<td><strong>10%</strong></td>
<td><strong>4.4%</strong></td>
</tr>
</tbody>
</table>

## Vaginal radical trachelectomy
### Obstetrical outcome

<table>
<thead>
<tr>
<th>Author</th>
<th>pts.</th>
<th>1 trimester miscarriage</th>
<th>2 trim. delivery</th>
<th>3 trim. delivery</th>
<th>delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shepherd 2012</td>
<td>125</td>
<td>22%</td>
<td>14%</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Plante 2011</td>
<td>106</td>
<td>20%</td>
<td>3%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Covens 2013</td>
<td>86</td>
<td>16%</td>
<td>8%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>Speiser 2011</td>
<td>60</td>
<td>8%</td>
<td>5%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Mathevet 2003</td>
<td>56</td>
<td>16%</td>
<td>14%</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>Kim 2012</td>
<td>19</td>
<td>5%</td>
<td>0%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>452</strong></td>
<td><strong>17%</strong></td>
<td><strong>8.6%</strong></td>
<td><strong>64%</strong></td>
<td></td>
</tr>
</tbody>
</table>

## Radical trachelectomy
### Different approaches

<table>
<thead>
<tr>
<th>Author</th>
<th>pts.</th>
<th>Recurrence</th>
<th>Pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRT 2003-13</td>
<td>924</td>
<td>4.4%</td>
<td>452 49%</td>
</tr>
<tr>
<td>ART 2008-12</td>
<td>337</td>
<td>3.7%</td>
<td>44 13%</td>
</tr>
<tr>
<td>LPS 2003-12</td>
<td>120</td>
<td>7%</td>
<td>8 7%</td>
</tr>
<tr>
<td>Robotic 2008-12</td>
<td>36</td>
<td>0</td>
<td>5 14%</td>
</tr>
</tbody>
</table>
Vaginal radical trachelectomy
Obstetric results
Boss et al. Gynecol. Oncol. 2005

16 studies 1998-2005 355 patients

- 43% attempted to conceive
- 70% became pregnant (161 pregnancies)
- 30% showed infertility
- 21% losses 1st trimester, 8% 2nd trimester
- 29% preterm deliveries (≤ 36 weeks)

Obstetrical outcome after conisation
for early cervical lesions
Kyrgiou et al. Lancet 2006

<table>
<thead>
<tr>
<th>Method</th>
<th>pts</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLETZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature labor</td>
<td>3141</td>
<td>1.70</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>2463</td>
<td>0.88</td>
</tr>
<tr>
<td>pPROM</td>
<td>1943</td>
<td>2.69</td>
</tr>
<tr>
<td>LASER conisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature labor</td>
<td>1488</td>
<td>1.71</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>908</td>
<td>1.16</td>
</tr>
<tr>
<td>pPROM</td>
<td>729</td>
<td>2.18</td>
</tr>
<tr>
<td>Cold-knife conisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature labor</td>
<td>28378</td>
<td>2.59</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>1020</td>
<td>3.17</td>
</tr>
<tr>
<td>pPROM</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Expanding RVT/ART with tumor > 2 cm
Wethington et al. Int J Gynecol Cancer 2012

29 patients

Adenocarcinoma 41 %
RVT 20%    ART 80%

Positive margins 24 %
Positive nodes 45 %

Fertility preservation: 31 %
One recurrence
Expanding RVT/ART with tumor > 2 cm

<table>
<thead>
<tr>
<th>Papers</th>
<th>range</th>
<th>pts &gt;2 cm</th>
<th>recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVT</td>
<td>11</td>
<td>2003-08</td>
<td>766 67</td>
</tr>
<tr>
<td>ART</td>
<td>9</td>
<td>2005-11</td>
<td>221 40</td>
</tr>
</tbody>
</table>

Ribeiro Cubal et al. IJSO 2012

Parametrial involvement by tumor diameter (stage IB1)
Primary radical surgery 1982 - 2010 at S. Gerardo Hospital - Monza

<table>
<thead>
<tr>
<th>Tumor size (cm)</th>
<th>pts.</th>
<th>Parametrial involvement</th>
<th>RR</th>
<th>Node involvement</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>190</td>
<td>9 (5%)</td>
<td>1</td>
<td>18 (9%)</td>
<td>1</td>
</tr>
<tr>
<td>1.1 – 2</td>
<td>212</td>
<td>21 (10%)</td>
<td>2</td>
<td>29 (14%)</td>
<td>1.5</td>
</tr>
<tr>
<td>2.1 – 3</td>
<td>201</td>
<td>42 (21%)</td>
<td>4.2</td>
<td>38 (20%)</td>
<td>2.2</td>
</tr>
<tr>
<td>3.1 – 4</td>
<td>122</td>
<td>33 (27%)</td>
<td>5.4</td>
<td>39 (32%)</td>
<td>3.5</td>
</tr>
<tr>
<td>Total</td>
<td>725</td>
<td>105 (14%)</td>
<td>124(17%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary radical surgery 1982 - 2010 at S. Gerardo Hospital - Monza

Initial evaluation:
- Colposcopy, hysteroscopy, PAP, biopsy (optionally LEEP)

Neoadjuvant chemotherapy:
- Paclitaxel (175 mg/sqm)
- Cisplatin (75 mg/sqm)
- Ifosfamide (5 g/sqm) or Epirubicin (80 mg/sqm)
  every 3 weeks for 3 courses

Intraoperative evaluation:
- massive cervical residue — radical surgery
- pCR or microresidue — cold knife conisation + PLND
### Neoadjuvant chemotherapy

#### Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>preserved /total</th>
<th>histotype squamous + adeno ≤ 2 cm</th>
<th>Cons. surgery &gt; 2 cm</th>
<th>Cons. surgery ≤ 2 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plante 2006</td>
<td>3 / 3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Kobayashi 2006</td>
<td>1 / 1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Landoni 2007</td>
<td>3 / 3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Maneo 2008</td>
<td>19 / 24</td>
<td>9</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Rob 2008</td>
<td>12 / 15</td>
<td>8</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Liu 2008</td>
<td>1 / 1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Marchiolè 2011</td>
<td>7 / 7</td>
<td>4</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Palia 2011</td>
<td>1 / 1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tsubamoto 2012</td>
<td>3 / 7</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Vercellino 2012</td>
<td>6 / 6</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Maneo unpubl.</td>
<td>1 / 2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**TOTAL** 57 / 70 56% 44% 64%

---

### Oncologic and obstetric results

#### Author Newborns CR or PR1 Relapses Pregnant Miscarriage /total patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Newborns /total</th>
<th>CR or PR1</th>
<th>Relapses</th>
<th>Pregnant</th>
<th>Miscarriage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plante 2006</td>
<td>3 / 3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0 + 3</td>
</tr>
<tr>
<td>Kobayashi 2006</td>
<td>1 / 1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0 + 1</td>
</tr>
<tr>
<td>Landoni 2007</td>
<td>2 / 3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0 + 3</td>
</tr>
<tr>
<td>Maneo 2008</td>
<td>18 / 24</td>
<td>0 (S CIN)</td>
<td>10</td>
<td>3</td>
<td>2 + 11</td>
</tr>
<tr>
<td>Rob 2008</td>
<td>9 / 15</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>1 + 6</td>
</tr>
<tr>
<td>Liu 2008</td>
<td>1 / 1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0 + 1</td>
</tr>
<tr>
<td>Marchiolè 2011</td>
<td>4 / 7</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0 + 1</td>
</tr>
<tr>
<td>Palia 2011</td>
<td>1 / 1</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tsubamoto 2012</td>
<td>3 / 7</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vercellino 2012</td>
<td>4 / 6</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0 + 1</td>
</tr>
<tr>
<td>Maneo unpubl.</td>
<td>1 / 2</td>
<td>1 (ovary)</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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### Pregnancy outcomes by method of conservative therapy

<table>
<thead>
<tr>
<th>Pregnant women</th>
<th>Odds ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal T 483</td>
<td>30 %</td>
<td>1</td>
</tr>
<tr>
<td>Abdom. T 194</td>
<td>15 %</td>
<td>0.4</td>
</tr>
<tr>
<td>Simple T 32</td>
<td>53 %</td>
<td>2.6</td>
</tr>
<tr>
<td>NACT 26</td>
<td>50 %</td>
<td>2.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Deliveries</th>
<th>Odds ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal T 621</td>
<td>30 %</td>
<td>1</td>
</tr>
<tr>
<td>Abdom. T 194</td>
<td>10 %</td>
<td>0.3</td>
</tr>
<tr>
<td>Simple T 32</td>
<td>37 %</td>
<td>1.4</td>
</tr>
<tr>
<td>NACT 26</td>
<td>61 %</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Modified from Rob et al. *Lancet Oncology* 2011
### Trachelectomy vs. conization

**Pros and cons**

**Trachelectomy**
- Tumor size up to 2 cm.
- Histologic evaluation of parametria
- No chemotherapy
- Permanent cerclage set up at the time of surgery
- Major obstetric risk

**Chemo – conization**
- Tumor size up to 3 cm.
- Sterilisation of micrometastases and LVSI
- Well known technique

### Final proposal

**Stage IB1 tumors**

- \( \leq 1 \text{ cm} \)
- 1 - 2 cm
- 2-3 cm (4?)

- **Simple T or conization**
- **Radical T or NACT + conization**
- **NACT + conization**
- **NACT + radical T**

Decision also depending on:
- Obstetric outcomes
- Risk of parametrial and nodal involvement
- Patient’s acceptance of chemotherapy
Low malignant potential and early stage ovarian cancer: is there a place for FSS?

Thomas Ind
Gynaecological Surgeon
St George's & Royal Marsden Hospitals

FIGO & WHO – 1973
Imprecisely defined tumours which show intermediate behaviour between benign and malignant
- Borderline
- Low Malignant Potential

1973
"...epithelial component shows some, or all, of the characteristics of malignancy but in which there is no stromal invasion."
1983

Every unit had a published series

- Recurrence rates for stage 1 borderline tumours – Ind & Shepherd 2002 *
  - Yankelev et al 1983 (15.0%)
  - Losano et al 1988 (13.5%)
  - Itoh & Tachibana et al 1988 (15.7%)
  - Hou et al 1991 (8.0%)
  - Sawada et al 1991 (3.5%)
  - Malthaner et al 1992 (13.0%)
  - Gervy et al 1993 (22.3%)
  - Tripe et al 1994 (18.0%)
  - Chao et al 1996 (23.0%)
  - Chao et al 1995 (21.0%)
  - Hon et al 1996 (16.4%)
  - Venugopal & Hart 1996 (13.5%)
  - Tylee et al 1997 (15.0%)
  - Chamberlain et al 1998 (13.0%)
  - TOTAL 17/227 (7.5%)

Not a single entity
No such thing as a BOT

Just borderline pathologists

Flow cytometry
- Haploid
- Diploid
- Aneuploid
Bethesda Classification 2006

- Serous
  - Serous cystadenoma
  - S-BOT
  - MPS
  - S-BOT with microinvasion
  - S-BOT with extra-ovarian lesions
  - Peritoneal endosalpingiosis
    - Non-invasive peritoneal implants
    - Invasive peritoneal implants
  - S-BOT associated with serous epithelium in lymph nodes
- Mucinous
  - Mucinous cystadenoma
  - M-BOT gastro-intestinal type
  - (pseudomyxoma peritonei)
  - M-BOT endo-cervical like type (AKA Müllerian & mixed epithelial)
  - M-BOT with intra-epithelial carcinoma (CIS)
  - M-BOT with microinvasion
  - Others (Endometrioid, Clear Cell, & Brenner)

Dilemma – Ovarian cyst on ultrasound

- Radical Surgery
- Tentative Surgery
- Conservative Surgery
- Observation

PROD
Conservative surgery

Presentation
- Suspicious for borderline on USS or MRI
  - Predominantly cystic with a few papillary projections and a normal or marginally raised CA125.
- Suspicious for borderline on frozen section.
- Diagnosis of borderline on final paraffin section after surgery for suspected benign disease.

Dilemma
- Adequate treatment and staging of cancer
- Adequate treatment of other conditions
- Curing symptoms
- Maintaining fertility
- Maintaining ovarian function
Radical Surgery

- PROD
  Primary Radical Ovarian Debulking Procedure
  - Hysterectomy (Womb, tubes, & cervix)
  - Omentectomy
    - If cancer removal of cancer
  - Colectomy +/- stoma
  - Splenectomy
  - Staging laparotomy
  - Pelvic lymphadenectomy
  - Para-aortic lymphadenectomy
  - ULTRARADICAL PERITONEECTOMY
  - BOWEL RESECTIONS

PROD

TEntative Radical Ovarian Surgery

- TEROS
  - Surgery determined by frozen sections
  - Midline Operation
    - Frozen section to determine if hysterectomy and contra lateral ovary removed
    - Frozen section to determine if full staging and lymphadenectomy is performed
Conservative surgery
- Unilateral oophorectomy
- Unilateral salpingo-oophorectomy
- Ovarian cystectomy
- No place for cyst aspiration

Conservative surgery
- Pfannensteil (bikini line) incision
- Laparoscopic surgery

Observation
- Repeat scan in 3/12 +/- cyclical suppression
  - ? Discharge
  - ? Intervene
  - ? Continue observation
Bethesda Classification 2006

- **Serosal**
  - Serosal cystadenoma
  - S-BOT
  - M-PSC
  - S-BOT with microinvasion
  - S-BOT with extra-ovarian lesions
  - Peritoneal endosalpingiosis
  - Non-invasive peritoneal implants
  - Invasive peritoneal implants
  - S-BOT associated with serous epithelium in lymph nodes

- **Mucinous**
  - Mucinous cystadenoma
  - M-BOT gastro-intestinal type
  - M-BOT endo-cervical like type (AKA Müllerian & mixed epithelial)
  - M-BOT with intra-epithelial carcinoma (CIS)
  - M-BOT with microinvasion
  - Others (Endometrioid, Clear Cell, & Brenner)

1700 evening talk

1700 evening talk
1700 evening talk

No just thing as BOT
S-BOT
- THEY ARE BENIGN (not borderline)
- Cystednomas with atypical proliferative
- Survival 100% for Stage I
- Three time more likely to die from treatment than cancer
- Can have invasive implants but probably another cell line

No just thing as BOT
MPSC
- THEY ARE MALIGNANT
- Often associated with advanced disease
  - 60% ten year survival
- THE PROGNOSIS IS NOT GOOD
No just thing as BOT

S-BOT
  – Invasive implants represent MALIGNANCY
  – Non-invasive implants and endosalpingiosis can occur in conjunction with S-BOT and behave in a BENIGN manner

No just thing as BOT

M-BOT (gastro-intestinal type)
  – All advanced forms probably associated with PMP and Appendiceal tumours
  – All others are probably BENIGN

No just thing as BOT

M-BOT (PMP)
  – Probable appendiceal CANCER
  – Refer to Basingstoke
No just thing as BOT

M-BOT (Endocervical / Mullerian)
- Mixed epithelial borderline tumours
- Can have a sero-mucinous
  - Atypical proliferative sero-mucinous tumours
- Can even MPSC component in which case MALIGNANT

Having identified that no such thing as a BOT how do we manage equivocal cysts

Risk of Malignancy Indices (RMI)
- Histological diagnosis only adequate one
  - No good imaging technique
  - No good tumour marker
- RMIs help differentiate between low and high risk cysts
- Also low & high risk populations
An RMI

- $U \times M \times Ca125$
  - $U =$ Number of ultrasound features
    - $U = 0$ – None
    - $U = 1$ – One
    - $U = 3$ – More than one
  - $Ca125 =$ Ca125 concentration in IU
  - $M =$ Menopausal status
    - $M = 1$ – Premenopausal
    - $M = 3$ – Postmenopausal (or equivocal)

- HE4 & ROMA

Ultrasound features

- Includes
  - Solid elements
  - Bilaterality
  - Multiple septae
  - Ascites
  - Papillary projection

- Does not include
  - Dopplers (not universally available)
  - Size (a poor indicator)

RMI groups

- <25 Population risk
- 25 – 200 Increased risk
- >200 High risk
Other Risk Tools

- Other RMIs
- ROMA (HE4 + CA125)
- IOTA criteria

Other tests

- CT scan (not as good as USS)
  - Good for spread
- MRI
- Radio-immunoscan
- Place for PET still undetermined

RCOG guidelines

- Population risk
  - Conservative management
    - Observation & ovarian suppression
    - Discharge
- Increased risk
  - Short term observation
  - Conservative surgery
- High Risk
  - PROD or TEROS by 'sub-specialist based in a cancer centre'
Frozen sections

- Borderline tumour at Frozen section
  - 20% invasive
- 20% of Borderline tumours
  - Benign at Frozen section
- Is a second operation really all that bad

Second operations
### Post-op Diagnosis of ‘BENIGN’ Borderline
- Salpingo-oophorectomy  
  - Unless only one ovary  
- Hysteroscopy  
- Assessment of contra lateral ovary  
- Omentectomy  
- Appendicectomy  
- LAPAROSCOPIC

### Post-op Diagnosis of ‘MALIGANT’ Borderline
- Fertility sparing surgery still acceptable  
- Salpingo-oophorectomy or TAH BSO  
- Hysteroscopy  
- Assessment of contralateral ovary  
- Omentectomy  
- Appendicectomy  
- Pelvic and para-aortic lymphadenectomy  
- LAPAROSCOPIC OR ROBOTIC

### Laparoscopic para-aortic LN
Laparoscopic surgeon

Conclusion

- Medical independence is the last refuge of the medically incompetent
Title:
Ovarian chemo prophylaxis, fertility preservation against chemotherapy sterilizing effects and ovarian tissue cryopreservation.

Dror Meirow Disclosure:
Nothing to disclose.

Learning Objectives

- Effects of chemotherapy on female reproduction.
- Effects of chemotherapy on the ovary.
- Chemo-protective agents.
- Mechanism of protection.
- Ovarian tissue freezing & transplantation results.
- Comparison with other fertility preservation methods.
- Future role in benign conditions.
Chemo Drugs According to Gonadotoxicity

- **High Risk**
  - Cyclophosphamide
  - Chlorambucil
  - Melphalan
  - Norgestrel/Trimethoprim
  - Procarbazone

- **Intermediate Risk**
  - Cylosporin
  - Adriamycin

- **Low Risk**
  - Methotrexate
  - Vinorelbine

- **Unknown Risk**
  - Oxaliplatin
  - Vindesine

Pre-pubertal gonad is not protected

---

Ovarian function in patients treated for Hodgkin’s disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/ treatment</th>
<th>Reference</th>
<th>Age/ treatment</th>
<th>Reference</th>
<th>Age/ treatment</th>
<th>Reference</th>
<th>Age/ treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behringer 05</td>
<td>50-70 years</td>
<td>Beral 07</td>
<td>Normal</td>
<td>Decanter 07</td>
<td>Normal</td>
<td>AMH</td>
<td>Hormone preserved</td>
</tr>
<tr>
<td>Kiserud 07</td>
<td>22-27 years</td>
<td>30-60 years</td>
<td>Low dose parenthood</td>
<td>30-60 years</td>
<td>Survival</td>
<td>Fertility</td>
<td>Hormone preserved</td>
</tr>
</tbody>
</table>

Ovarian failure - treatment related
- 1st line chemo - very low
- Advanced chemo - significant

---

Ovarian damage after Cy. protocols for breast cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Failure</th>
<th>Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goodwin P. 1999</td>
<td>Pre menopause</td>
<td>45%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Meirow D. 1999</td>
<td>Pre menopause</td>
<td>50%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Jonat W. 2001</td>
<td>Pre menopause</td>
<td>60%</td>
<td>39-55%</td>
</tr>
<tr>
<td>Petrek 2006</td>
<td>Pre menopause</td>
<td>39-55%</td>
<td>10-25%</td>
</tr>
</tbody>
</table>

Failure

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample Size</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Partridge 2013</td>
<td>0.0004</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Damage
Ablative Chemotherapy & Bone Marrow Transplantation

<table>
<thead>
<tr>
<th>Name</th>
<th>No.</th>
<th>Age</th>
<th>% failure</th>
<th>Mean Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanders</td>
<td>96</td>
<td>73</td>
<td>mean 38</td>
<td>99</td>
</tr>
<tr>
<td>Teinturier</td>
<td>68</td>
<td>21</td>
<td>2 - 17</td>
<td>72</td>
</tr>
<tr>
<td>Thibaud</td>
<td>98</td>
<td>31</td>
<td>3.2 - 17</td>
<td>80</td>
</tr>
<tr>
<td>Meirow</td>
<td>99</td>
<td>63</td>
<td>mean 29</td>
<td>79</td>
</tr>
<tr>
<td>Grigg</td>
<td>2000</td>
<td>19</td>
<td>mean 30</td>
<td>100</td>
</tr>
</tbody>
</table>

Ovarian failure risk - very high.

Premature ovarian Failure in Childhood Cancer Survivors

<table>
<thead>
<tr>
<th>Disease</th>
<th>Odds ratio (patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s D.</td>
<td>3.8 (66 / 467)</td>
</tr>
<tr>
<td>Non-Hodgkin’s Ly</td>
<td>3.2 (19 / 168)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2.6 (27 / 290)</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>3.0 (35 / 329)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.0 (43 / 1088)</td>
</tr>
</tbody>
</table>

Our studies on chemotherapy effects on the ovaries enabled:

- Understand Follicle dynamics and reveal universal mechanism of follicle loss.
- Selection of effective & safe Fertility preservation procedures.
- Search for protective agents.
Effects of cytotoxic drugs on the ovary:

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Action</th>
<th>Outcome</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growing follicles</td>
<td>Apoptosis, DNA damage</td>
<td>Cell death</td>
<td>Alkylating agents</td>
</tr>
<tr>
<td></td>
<td>Cell cycle arrest</td>
<td></td>
<td>Anthracycline antibiotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Taxanes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vinca alkaloids</td>
</tr>
<tr>
<td>Bland vessels</td>
<td>Apoptosis*</td>
<td>Follicle growth suppression</td>
<td>Anthracycline antibiotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Taxanes</td>
</tr>
<tr>
<td>Stromal effect</td>
<td></td>
<td></td>
<td>Ischemia, focal fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neovascularisation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased blood flow</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Narrowing and hyalinization of small blood vessels</td>
</tr>
</tbody>
</table>


Chemotherapy effects on the ovary

Primordial follicle pool - reduced

Growing follicles – destroyed

Stromal effect Blood

Effects of chemotherapy
on resting primordial follicles

Lab Experiments
What is the mechanism
Clinical implications
Cyclophosphamide triggers follicle activation causing ovarian reserve ‘burn out’

Kalish Philsouph et al 2013

Cy causes PMF activation

- Loss of PMFs
- No apoptosis of PMFs
- Apoptosis only in growing follicles
- But no decrease in growing follicles?
- Increase in early growing follicles
- Increase in proliferation of transitional follicles

PMF activation

Ratio of growing/non growing follicles with different doses of Cy

[Graph showing the ratio of growing/non growing follicles with different doses of Cy, indicating statistical significance with asterisks for certain doses.]
What triggers the activation?

TOR is a central controller of cell growth

The mechanism for Cy-induced follicle loss is two fold:

1. Activation and growth of the primordial follicles via PI3K pathway. Once recruited, the follicles develop, die, resulting in loss of ovarian follicle reserve.
2. Direct apoptosis in growing follicles loss of suppression.
Potential preventive agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Protective effect in vivo</th>
<th>Dosage</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH-a</td>
<td>May interfere with apoptosis action of chemotherapy drugs</td>
<td>Rodent: Kaya, 2008; Rodent: Morita, 2000; Rodent: Jurisicova, 2006; Rodent: Hancke, 2007; Rodent: Kaya et al., 2008</td>
<td>Rodent: Kaya, 2008</td>
<td>May interfere with chemotherapy drugs</td>
</tr>
<tr>
<td>S1P</td>
<td>May interfere with apoptosis action of chemotherapy drugs</td>
<td>Rodent: Kerr, 2012</td>
<td>Rodent: Gonfloni, 2009</td>
<td></td>
</tr>
<tr>
<td>Imatinib (GNF-2)</td>
<td>Inhibition of c-ABL kinase apoptotic pathway</td>
<td>Rodent: Ochalski, 2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Inhibition of angiogenic factors, suppression of pituitary-gonadal axis</td>
<td>Human: Sveririsdottir, 2009; Rodent: Ting, 2010; Rodent: Mahran, 2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Antioxidant via IGF-1 axis, possibly via gonadal suppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G-CSF</td>
<td>Does not interfere with and may have additive/synergistic interaction with treatment drug.</td>
<td>Rodent: Kalich-Philosoph, 2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS101</td>
<td>Modulation of PI3K/PTEN/Akt follicle activation pathway</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tellurium based compound developed by us. Immunomodulator – decrease in IL-10 and IL-1β. Non-toxic to cancer patients, minimal side effects.

AS101 restores the balance of negative regulation

1. Activation and growth of the primordial follicles via PI3K pathway
2. Direct apoptosis in growing follicles

Loss of inhibition
AS101 improves fertility outcomes

- Increased litter size and cumulative pups
- Increased pregnancy rate
- Increased ovarian volume & number of corpus lutei.

Ovarian tissue storing and transplantation

Different approaches for fertility preservation
Currently used & experimental
Tissue harvesting "Primum Non Nocere"

- Safety of laparoscopic procedure in sick cancer patients.
- Not delay in cancer treatment.
- No mechanical infertility.
- If not sterilized post cancer treatment high spontaneous pregnancy rate (60-70%).
Transportation of ovarian tissue prior to Cryopreservation

<table>
<thead>
<tr>
<th>Author</th>
<th>Transport time</th>
<th>Temp.</th>
<th>Live birth</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosendahl M. et al.</td>
<td>4.5 h</td>
<td>On ice</td>
<td>&gt;2</td>
<td>Immunoablation</td>
</tr>
<tr>
<td>Dittrich R. et al.</td>
<td>20 h</td>
<td>5-8°C</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Isachenko et al.</td>
<td>&lt;24 h</td>
<td>4°C</td>
<td>80-90%</td>
<td>In vitro growth</td>
</tr>
</tbody>
</table>

Ovarian tissue can be safely transported from one clinic to a highly specialized center.

Factors affecting procedure success

Factors affecting transplantation success

Most follicles are lost immediately post transplantation

Location: Grafting to the ovary

Sub cortical pockets
Meinow D. Dor J. et al. NEJM 2005

Sub cortical pockets

cortical replacement
Donnez J. et al. 2008

cortical replacement
Silber S. Meinow D. 2010
**Location: Orthotopic Surgical grafting**

**Publications:** Donnez, Demeestere, Azem, Revel, Pellicer, Muller

- Additional space
- No ovary
- Fibrosis of vascular bed

**Additional approaches to improve grafting and prevent follicle loss**

- Thin micro-ovarian fragments prepared prior to transplantation (Revel A. et al 2011).

- Double procedure preparation of transplantation site (Donnez J. et al 2008).
- Double procedure-two steps transplantation (Pier P. et al 2010).

**The “Burn-Out” mechanism**

**Follicle activation and destruction**

**Universal route of follicle loss**
- post chemotherapy
- post transplantation

[Cell Cycle](http://www.cellcycle.com)
Primordial follicle activation

Depletion of growing follicles. Can it cause Reduced inhibition and activation?

Ovarian tissue transplantation model

Post transplantation follicle activation

the effect of graft thickness.

Thin prepared grafts significantly more follicle loss.

Z. Gavish et al. 2013

The “Burn-Out” mechanism

post transplantation
Most follicles are lost post transplantation.

Not only due to transplantation technique.

Important factor is the ‘Burn-Out’ effect.

To improve tissue transplantation it is important to find add factors that prevent ‘Burn-Out’.

---

### Function of frozen / thawed ovarian tissue transplantation

<table>
<thead>
<tr>
<th>Location</th>
<th>Continent</th>
<th>Case</th>
<th>Diagnosis</th>
<th>Frozen/Ovulation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>Europe</td>
<td>2/22</td>
<td>frozen</td>
<td>100%</td>
<td>+</td>
</tr>
<tr>
<td>Russia</td>
<td>Europe</td>
<td>6/17</td>
<td>peritoneum</td>
<td>70%</td>
<td>+</td>
</tr>
<tr>
<td>Belgium</td>
<td>Europe</td>
<td>8/13</td>
<td>ovaries</td>
<td>77%</td>
<td>+</td>
</tr>
<tr>
<td>Israel</td>
<td>Europe</td>
<td>8/13</td>
<td>ovaries</td>
<td>100%</td>
<td>+</td>
</tr>
</tbody>
</table>

- AMH – not predictive usually low.
- Endocrine function – most of patients – years.
- Ovulation - Not in heterotopic transplantsations.

---

### Transplantation of stored ovarian tissue works

- Live birth post OTOP & transplantation. [Donnez et al, Lancet 2004.](#)
- Dozens of babies born post OTOP & transplantation until now. [Raanani et.al, 2014.](#)

---

Live birth post OTCP & Transplantation after bilateral oophorectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Age</th>
<th>Diagnosis / Indication</th>
<th>Transplant</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Callejo J.</td>
<td>BMJ 2012, Ovarian Research 2013</td>
<td>21</td>
<td>Mature teratoma</td>
<td>10</td>
<td>1 cycle</td>
</tr>
<tr>
<td>Donnez J.</td>
<td>Fertil Steril 2012</td>
<td>19</td>
<td>Tubo ovarian abscess</td>
<td>7</td>
<td>5 cycles</td>
</tr>
</tbody>
</table>

1. Posterior leaflet broad ligament
2. Anterior leaflet broad ligament

To practice OTCP routinely
To improve technique results

we should first show procedure success rate.
However, many centers, sporadic cases!

Approach:
1. Collecting world’s data.
2. Report total results from single centers.

Transplantation results - Sheba
RESULTS

- Spontaneous menstruation returned in all patients,
- AMH, FSH & E2 not predictive.
- Long term graft survival in most patients.
- IVF cycles - modified natural protocol in all cycles.
- Empty follicles – only a few after first cycles.
- No. of embryos post transplantation HIGHER. Number of embryos stored prior to chemotherapy.

Cryopreservation/transplantation of ovarian tissue works and is effective.

Safety data - Detection of cancer cells

Transmission of donor-related malignancy by organ transplantation is recognized.

Tissue handling for cancer cells evaluation

Storing tissue, Future evaluation, Fresh cortex
Minimal residual disease detection in cryopreserved ovarian cortex using molecular markers

- Leukemia and Lymphoma patients (Meirow et al. 2008, 2013)
  - BCR-ABL (1/3 pt.)
  - T-cell receptor and immunoglobulin rearrangement genes (5/2 pt.)
- leukemia patients (Rosendahl et al. 2010)
  - BCR-ABL (6/6 pt.)
  - TEL-AML1 (1/1 pt.)
- Acute lymphoblastic leukemia (Rosendahl et al. 2010)
  - BCR-ABL (2/3 pt.)
  - T-cell receptor and immunoglobulin rearrangement genes (7/10 pt.)

- Ewing sarcoma (Ros et al. 2011)
  - EWS-FLI1 (1/5 pt.)
- Leukemia (Greve et al. 2012)
  - CML, ALL, AML (4/12 pt.)

Rec. Transp. period No. of pt. Disease Malignancy Reference

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Greve T. Blood 2012</td>
<td>Leukemia</td>
<td>AML, ALL</td>
<td>25</td>
<td>20 w</td>
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<td>Kim S.S. Hum Reprod 2001</td>
<td>Lymphoma</td>
<td>HD, NHL</td>
<td>10</td>
<td>15 w</td>
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<td>Dolmans M.M. Blood 2010</td>
<td>Leukemia</td>
<td>CML, ALL</td>
<td>18</td>
<td>6 mo</td>
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<td>Lots L., Fertil &amp; Steril 2011</td>
<td>Ovarian cancer</td>
<td>Germinal Border line</td>
<td>10</td>
<td>24 w</td>
<td>0/12</td>
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Xenotransplantation studies

The “Road map” of fertility preservation in young female patients with acute leukemia.
However, the applicability of sensitive molecular markers methods varies by the specific disease subtype:

- CML, ALL > 90%
- AML < 50%
- Solid tumors < 10%

**Personalized molecular markers discovery**

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**Comparison with IVF for Fertility preservation in cancer Patients**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Eggs</th>
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<td>cancer</td>
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<tr>
<td>Chong, 2010</td>
<td>12.1</td>
<td>5.5</td>
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<td>Abrams, 2011</td>
<td>12.6</td>
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<td>Dinares, 2012</td>
<td>12.6</td>
<td>5.5</td>
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<tr>
<td>Meier, 2012</td>
<td>12.6</td>
<td>5.5</td>
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</tbody>
</table>

The mean number of eggs 12-14, embryos 5-7.
Conclusive remarks
- Ovarian tissue cryo/transport works—natural & IVF pregnancies.
- Post-transplantation IVF results indicate effectiveness.
- Technical improvements and standardization will continue.
- Specialized fertility preservation centers are recommended.
- Small number of highly specialized centers to evaluate MRD.

Cryopreservation/transplantation of ovarian tissue should no longer considered experimental strategy for fertility preservation in severe diseases.

Future roll in benign conditions
- Endometriosis
- Genetic-mosaic Turner, Galactosemia
- Ovarian operations—large cysts?
- BRCA prophylactic procedures
- Social freezing?

Fertility preservation center and Research laboratory

Collaborations:
Bar Ilan University
Prof. Benjamin Sredni
Sheba Medical Center
Dr. Ido Wolff
Dr. Hannah Kanety
Prof. Gideon Rechavi
Dr. Sant Aviel

Dr. Roness Hadassa
Dr. Gavrida Zohar
Dr. Ramani Hla
Dr. Kalich-Philosoph Lital
Dr. Polan Gil
Dr. Horam Cohen
Sioni Noa
Elmaleh Lital
Derech Haim Sanaz
Shapira Moran
Oren Kashi
Prof. Orvieto Raoul
## UPCOMING ESHRE EVENTS

### ESHRE CAMPUS EVENTS

<table>
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<tr>
<td>ESHRE’s 30th Annual Meeting</td>
<td>Munich, Germany 29 June - 2 July 2014</td>
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<tr>
<td>Epigenetics in reproduction</td>
<td>Lisbon, Portugal 26-27 September 2014</td>
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<td>Endoscopy in reproductive medicine</td>
<td>Leuven, Belgium 15-17 October 2014</td>
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<td>Making OHSS a complication of the past: State-of-the-art use of GnRH agonist triggering</td>
<td>Thessaloniki, Greece 31 October-1 November 2014</td>
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<td>From gametes to blastocysts – a continuous dialogue</td>
<td>Dundee, United Kingdom 7-8 November 2014</td>
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<td>Controversies in endometriosis and adenomyosis</td>
<td>Liège, Belgium 4-6 December 2014</td>
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<td>Bringing evidence based early pregnancy care to your clinic</td>
<td>Copenhagen, Denmark 11-12 December 2014</td>
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<tr>
<td>An update on preimplantation genetic screening (PGS)</td>
<td>Rome, Italy 12-13 March 2014</td>
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For information and registration: [www.eshre.eu/calendar](http://www.eshre.eu/calendar) or contact us at info@eshre.eu