SIG Reproductive Surgery/Endometriosis – Best Management of Endometriosis-Related Infertility (Didactic)

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Professional Education Information

Target Audience
This educational activity is developed to meet the needs of residents, fellows and new minimally invasive specialists in the field of gynecology.

Accreditation
AAGL is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The AAGL designates this live activity for a maximum of 3.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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**Table of Contents**

Course Description ........................................................................................................................................ 1

Disclosure ...................................................................................................................................................... 2

The Effect of Endometriosis on Infertility – What the Evidence Says  
W.W. Hurd .................................................................................................................................................. 3

Endometriosis Surgery versus IVF  
M.W. Surrey .............................................................................................................................................. 8

DIE and Infertility – Is There a Relation?  
A. Yazdani .................................................................................................................................................. 14

Peritoneum Pathophysiology and Laparoscopy: Endometriosis, Adhesions and Impact on Fertility  
M. Canis....................................................................................................................................................... 21

Ovarian Endometrioma, Ovarian Reserve Conservation  
J. Tsaltas ................................................................................................................................................... 45

Fertility Enhancing Surgery in Deep Infiltrative Bowel Endometriosis  
P.R. Koninckx ............................................................................................................................................ 49

Adenomyosis and Fertility – Surgical and Medical Management  
G.A. Pistofidis .......................................................................................................................................... 57

A New Approach to Endometriomas: Laparoscopic Combined Technique  
C. Unlu ....................................................................................................................................................... 69

Cultural and Linguistics Competency ........................................................................................................ 76
There has been a lack of clear evidence on the best approach for managing endometriosis in fertility patients. The era of IVF has significantly impacted early detection and diagnosis of endometriosis, especially in fertility patients. This course provides an overview of the challenges faced when treating endometriosis and its associated pathologies in fertility patients. A variety of minimally invasive techniques will be discussed with emphasis on fertility preservation and enhancement in patients with endometriosis.

**Course Objectives:** At the conclusion of this activity, the clinician will be able to: 1) Discuss the relation between endometriosis and infertility with current evidence; 2) formulate a strategic plan in choosing endometriosis surgery vs. IVF or the order of application and implication; 3) apply clear strategic plan on assessment and management of endometrioma in infertility patients; and 4) outline a surgical approach in patients with deep infiltrative endometriosis and adenomyosis.

**Course Outline**

1:30 Welcome, Introductions and Course Overview  
J. Tsaltas

1:35 The Effect of Endometriosis on Infertility – What the Evidence Says  
W.W. Hurd

2:00 Endometriosis Surgery versus IVF  
M.W. Surrey

2:20 DIE and Infertility – Is There a Relation?  
A. Yazdani

2:40 Peritoneum Pathophysiology and Laparoscopy: Endometriosis, Adhesions and Impact on Fertility  
M. Canis

3:00 Questions & Answers  
All Faculty

3:15 Break

3:30 Ovarian Endometrioma, Ovarian Reserve Conservation  
J. Tsaltas

3:50 Fertility Enhancing Surgery in Deep Infiltrative Bowel Endometriosis  
P.R. Koninckx

4:10 Adenomyosis and Fertility – Surgical and Medical Management  
G.A. Pistofidis

4:30 A New Approach to Endometriomas: Laparoscopic Combined Technique  
C. Unlu

4:50 Video and Interactive Session  
M.W. Surrey

5:20 Questions & Answers  
All Faculty

5:30 Course Evaluation/Adjourn
PLANNER DISCLOSURE
The following members of AAGL have been involved in the educational planning of this workshop and have no conflict of interest to disclose (in alphabetical order by last name).
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The following have agreed to provide verbal disclosure of their relationships prior to their presentations. They have also agreed to support their presentations and clinical recommendations with the “best available evidence” from medical literature (in alphabetical order by last name).
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Philippe R. Koninckx
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George A. Pistofidis*
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Jim Tsaltas
Grants/Research: Covidien, Melbourne IVF, Merck Serono
Cihat Unlu*
Anusch Yazdani
Grants/Research: EMD-Serono, Merck Serono

Asterisk (*) denotes no financial relationships to disclose.
The Effect of Endometriosis on Infertility – What the Evidence Says

William W. Hurd, MD, MSc, MPH
Duke University Medical Center
Durham, North Carolina

I have no financial relationships to disclose.

Endometriosis and Infertility
At the end of this presentation, the attendee should be able to:
• Recall the evidence that endometriosis decreases fertility
• Identify the mechanisms by which endometriosis might decreases fertility
• Recognize gaps in our knowledge about endometriosis and fertility

Endometriosis:
The presence of functioning endometrial tissue (stroma and glands) outside of the uterus

What’s Wrong with this All-Inclusive Definition?
1. Not a single condition
2. Often not a “disease” (a disorder of structure or function that produces specific signs or symptoms)
3. A “paraphysiological” condition

Is All Endometriosis the Same?
• Superficial
  – ASRM Stage I (Minimal)
  – ASRM Stage II (Mild)
Is All Endometriosis the Same?

• Superficial
  – ASRM Stage I (Minimal)
  – ASRM Stage II (Mild)
• Infiltrating
  – ASRM Stage III (Moderate)
  – ASRM Stage IV (Severe)
  • Endometriomas

Is All Endometriosis the Same?

• Superficial
  – ASRM Stage I (Minimal)
  – ASRM Stage II (Mild)
• Infiltrating
  – ASRM Stage III (Moderate)
  – ASRM Stage IV (Severe)
  • Endometriomas
• Microscopic
  – Stage “0”?

Symptoms of Endometriosis

• Pain
• Infertility
• No Symptoms

Endometriosis and Infertility

I. Associations: Endometriosis and Infertility

II. Theoretical Mechanisms

III. Does Treatment Improve Fertility?

Endometriosis Prevalence

• All Women 0.5-5%
• Chronic Pelvic Pain 40-70%
• Infertile Women 25-40%
Stage vs Symptoms

CPP (70%)  Infertility (40%)

• Stage I  27%  13%
• Stage II  10%  10%
• Stage III  24%  10%
• Stage IV  9%  7%

Endometriosis and Infertility

Monthly Fecundity Rate

- All Couples  30%
- Endometriosis  2-10%

Guzick 1997

Fertility and Stage

After Surgical Treatment

Pregnancy Rates

<table>
<thead>
<tr>
<th></th>
<th>Nezhat 1989</th>
<th>Guzik 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>72%</td>
<td>35%</td>
</tr>
<tr>
<td>Stage II</td>
<td>70%</td>
<td>35%</td>
</tr>
<tr>
<td>Stage III</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>69%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Endometriosis and Infertility: II. Theoretical Mechanisms

- Pelvic Adhesions
- Decreased ovarian reserve
- Peritoneal inflammation
- Ovarian Dysfunction
- Implantation Failure

Pelvic Adhesions

- Pelvic adhesions decrease fertility
- 50% of women with symptomatic endometriosis have pelvic adhesions (Stage II-IV)

Pelvic Adhesions and Infertility

Infertile women with unexplained infertility and adnexal adhesions (NOT Endometriosis)

<table>
<thead>
<tr>
<th></th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Treated</td>
<td>32%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Tulandi 1990
Endometriosis vs Tubal Factor

IVF rates

- Favor Tubal Factor
- Favor Endometriosis

Barnhart 2002

Endometriosis Decreases Ovarian Reserve

- Decreased in women with an endometrioma
- Further decreases by surgery

Raffi 2012

Ovulatory Dysfunction

Endometriosis patients have:
- Slower follicular growth rate
- Smaller dominant follicle size at ovulation

Doody, Gibbons and Buttram, 1988

Endometriosis is an Inflammatory Disease

Peritoneal fluid:
- Increased inflammatory cytokines IL-6, IL-1beta, IL-10, TNF-alpha
- Increased inflammatory cells in B lymphocytes
- Natural Killer cells
- Monocyte macrophages

Endometriosis Effects on Follicular Fluid

- Increased inflammatory cytokines IL-6, IL-1beta, IL-10, TNF-alpha
- Decreased VEGF promotes follicular health & vascularization
Implantation Failure?

1. Do women with endometriosis have lower IVF pregnancy rates?

2. Do recipients of oocytes donated by women with endometriosis have lower pregnancy rates?

Conclusions

- Endometriosis is associated with infertility
- ASRM stage is only slightly related to fertility rate
- Endometriosis could decrease fertility by a number of mechanisms
- Endometriosis treatment improves fertility

Questions?

Endometriosis and Infertility: III. Treatment Improves Fertility

Adamson 1994

References

Endometriosis Surgery versus IVF

Mark Surrey, M.D., FACOG, FACS
Medical Director
Southern California Reproductive Center

Disclosure

I have no financial relationships to disclose.

Objectives:

At the end of this presentation, the attendee will be able to:

- Discuss the management of fertility in patients with minimal or mild endometriosis;
- Discuss the management of fertility in patients with severe endometriosis;
- Review the optimal fertility treatment strategy based on ovarian reserve;
- Review the role of assisted reproduction in management of the endometriosis patient.

Endometriosis and Infertility: Is there a link?

- Causal relationship between endometriosis and infertility controversial, however there is correlation
  - 25-50% infertile patients have endometriosis
  - 30-50% patients with endometriosis experience infertility
- Higher prevalence of endometriosis among infertile patients
  - 1-7% of women at time of tubal ligation
  - 9-50% of women at laparoscopic evaluation of infertility
- Infertile patients are 6-8 times more likely to have endometriosis

Endometriosis and Infertility: Putative Mechanisms

- Distortions in pelvic anatomy
- Alterations in peritoneal fluid
- Changes in immune function (IgA, IgG, lymphocytes)
- Ovulatory dysfunction
- Impaired implantation (integrin, selectins)
- Reduced oocyte and embryo quality
- Altered uterotubal transport

Medical Suppression of Endometriosis Does Not Improve Fertility

- Medical suppression is effective in reducing endometriosis-related pain
- No evidence to support medical suppression of endometriosis to enhance fertility
- RCTs demonstrate no fertility benefit of GnRH agonists for treating minimal-mild endometriosis
- RCTs demonstrate no fertility benefit of danazol in treatment of minimal-mild endometriosis
- Currently insufficient evidence on efficacy of aromatase inhibitors, SERMs, progesterone antagonists, SPRMs in medical treatment of endometriosis-related infertility

Practice Committee of ASRM, 2012
Is Surgical Evaluation Warranted

- Surgical confirmation considered gold standard for definitive diagnosis of endometriosis
- Histologic evaluation warranted when endometriosis not visually apparent
- History/Physical suggestive of endometriosis:
  - Cyclic or chronic pelvic pain, dysmenorrhea
  - Dyspareunia
  - Fixed retroverted uterus
  - Adnexal mass
  - Uterosacral nodularity, thickening or tenderness
  - Suggestive ultrasound findings

Practice Committee of ASRM, 2012

Staging of Endometriosis: Revised AFS Classification

Staging of Endometriosis: EFI & Least Function Score

Staging of Endometriosis: EFI & Prediction of

Ovulation Induction & Insemination

Surgical Treatment of Stage I/II Endometriosis: Randomized Controlled Trials – Canadian Group

- Canadian Collaborative Group on Endometriosis: RCT of 341 women with stage I/II disease followed x 36 weeks demonstrated significant increase in fecundity after laparoscopic treatment
  - Fecundity was 0.047 after ablation versus 0.024 in untreated
  - 29% of treated and 17% of untreated attached 20 week pregnancy
  - Monthly fecundity after ablation still significantly lower than that seen in normal fertile women
Surgical Treatment of Stage I/II Endometriosis: Randomized Controlled Trials – Italian Group

- Gruppo Italiano: RCT of 96 women with stage I/II disease followed x 1 year showed no difference in fecundity
  - Live birth rate of 20% in treated group, versus 22% in untreated group after one year follow-up
  - Study of lower power, designed to detect 2.7-fold higher LB rate

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The New England Journal of Medicine

VOLUME 337 JULY 24, 1997 NUMBER 4

LAPAROSCOPIC SURGERY IN INFERTILE WOMEN WITH MILD OR MILD ENDOMETRIOSIS

Sara Rabbia, M.D., Ph.D., Moreno Minarini, M.D., Enrico Rinaldi, M.D., and the Italian Endometriosis Group

Table 4. Clinical data and cumulative probabilities of pregnancy in infertile women with minimal or mild endometriosis, according to study group.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Cumulative Probability of Pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopy</td>
<td>47.6 (95% CI: 35.8-60.3)</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>42.1 (95% CI: 30.3-54.9)</td>
</tr>
</tbody>
</table>

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Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial

Table II. Pregnancy and failure according to treatment allocation. July

<table>
<thead>
<tr>
<th>Treatment or abortion or failure to conceive</th>
<th>Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>20</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>15 (75.0)</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Outcome of pregnancy</td>
<td>2</td>
</tr>
<tr>
<td>Live birth</td>
<td>2 (100.0)</td>
</tr>
<tr>
<td>Abortion or failure to conceive</td>
<td>2</td>
</tr>
<tr>
<td>Live birth</td>
<td>2 (100.0)</td>
</tr>
</tbody>
</table>

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Laparoscopic surgery in infertile women with minimal or mild endometriosis

Sara Rabbia, M.D., Ph.D., Moreno Minarini, M.D., Enrico Rinaldi, M.D., and the Italian Endometriosis Group

Study of lower power, designed to detect 2.7-fold higher LB rate.
Surgical Treatment of Severe Endometriosis:

- Laparoscopic cystectomy for ovarian endometrioma > 4 cm reduced cyst recurrence and improve fertility compared to cyst drainage or aspiration
- However, endometrioma stripping may result in loss of ovarian cortex or reserve
- "Recurrent ovarian surgery is not recommended" in infertility associated with ovarian endometrioma

Risk of Diminished Ovarian Reserve After Endometriosis Surgery

- Paucity of high quality RCT comparing fertility surgery and IVF
- Difficult to compare success rates of IVF and tubal surgery
  - IVF pregnancy rates reported as per cycle or per embryo transfer
  - Surgical success rates reported as cumulative PR after lengthier follow up, up to 2-3 years after surgery
- In most infertile patients, especially those with advanced maternal age, lengthy postoperative trial of conception would be impractical and often ill-advised

Surgery versus IVF: Where’s the Controversy?

- Small RCT of 245 couples with infertility
- Among them were 21 women with endometriosis and infertility who were randomized to:
  - IVF (n = 15)
  - Expectant management (n = 6)
- Five of 15 women in the IVF group conceived versus none in the expectant group (33% vs 0%; p = NS)
- Limited by small sample size but highly suggestive of benefit of IVF in the endometriosis patient

IVF Significantly Increases Fecundity In Patients with Endometriosis

- Charles Cleveson, Pady Vredenb, Hadi Banab, Marco Viera and Jean-Nicolas Dubusse

- Laparoscopic cystectomy for ovarian endometrioma > 4 cm reduced cyst recurrence and improve fertility compared to cyst drainage or aspiration
- However, endometrioma stripping may result in loss of ovarian cortex or reserve
- "Recurrent ovarian surgery is not recommended" in infertility associated with ovarian endometrioma

Risk of Diminished Ovarian Reserve After Endometriosis Surgery

- Surgery versus IVF: Where’s the Controversy?
- IVF Significantly Increases Fecundity In Patients with Endometriosis

Feinberg et al., Fertil Steril 2008
Practice Committee of ASRM 2008

Soliman et al., Fertil Steril 1993
IVF Significantly Increases Fecundity in Patients with Stage I/II Endometriosis

Meta-analysis of 22 non-randomized studies demonstrated IVF pregnancy rate in women with endometriosis compared with women with tubal factor (OR 0.56; 95% CI 0.44-0.70)

Reduced fertilization rates and implantation rates seen after multifactorial analysis

Pregnancy rates lowest in women with severe endometriosis when compared with mild disease

Barnhart et al., Fertil Steril 2002

Endometriosis vs. Tubal Factor: Impact on ART Outcomes

Pretreatment Cystectomy Does Not Improve ART Outcomes in Women with Endometrioma

Pretreatment Cystectomy Does Not Improve ART Outcomes in Women with Endometrioma

- In the ovarian surgery group, stimulation was significantly longer (14.0 days in group I and 10.8 days in group II; P = 0.001)
- Total FSH dose was significantly higher (4575 IU in group I and 3675 IU in group II; P = 0.001)
- Mean number of mature oocytes was significantly lower (7.8 in group I and 8.6 in group II; P = 0.032).
- There was no difference in terms of fertilization (86% in group I and 88% in group II), implantation (16.5% in group I and 18.5% in group II) and pregnancy rates (34% in group I and 38% in group II).
- Ovarian surgery resulted in longer stimulation, higher FSH requirement and lower oocyte number, but fertilization, pregnancy and implantation rates did not differ between the groups.

Demirol et al., Reprod Biomed Online 2006:12(5); 639-643
Specific Complications Arising from Severe Endometriosis During IVF

- Difficult oocyte aspiration due to pelvic adhesions
- Higher cycle cancellation rates due to low ovarian response
- Ovarian abscess occurring after puncture of endometrioma (0.2% in absence of endometrioma; 2.3% in the presence of endometrioma)
- IVF treatment is LESS associated with endometriosis recurrence than insemination in patients with moderate to severe endometriosis

D’Hoogue et al., Fertil Steril 2006
Dochau et al., Gynecol Endocrin 2009

Proposed Rationale for Surgery Before IVF

- ESHRE guidelines recommend laparoscopic ovarian cystectomy for endometriomas ≥ 4cm
  - Confirm benign histology
  - Reduce infection risk from drainage during oocyte aspiration
- Drainage or removal of endometrioma may improve follicular access during oocyte aspiration
- Large endometriomas ≥ 3cm may interfere with follicle tracking during stimulation
- Reduction of risk of endometrioma leakage during the course of oocyte aspiration

Gelbaya et al., Reprod Biol Med Online 2005

Treatment Selection in Infertile Women with Endometriosis

- In minimal/mild endometriosis:
  - Correct all reversible infertility factors
  - Choice between surgery vs. ovulation induction/inssemimation/IVF depends on age, presence of pain, ovarian reserve, duration of infertility, desire and ability to proceed to ART
- Low utility in laparoscopy for asymptomatic women
- If laparoscopy, ablation or excision of visible endometriosis should be considered

García-Velasco et al., Reprod Med 2009

Management of endometriomas in women requiring IVF: to touch or not to touch

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Favor surgery</th>
<th>Favor expectant management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous surgery</td>
<td>None</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Ovarian reserve</td>
<td>Intact</td>
<td>Damaged</td>
</tr>
<tr>
<td>Pain syndrome</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
<tr>
<td>Histopathologic features</td>
<td>Normal</td>
<td>Atypical</td>
</tr>
<tr>
<td>Growth</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
</tbody>
</table>

Management of Endometriosis in Infertile Women

- Age of female patient important in treatment selection
- Expectant management after surgery if young and good ovarian reserve
- Consider superovulation+IUI versus IVF in older patients, or young patients with diminished ovarian reserve
- IVF is better option in infertile women with stage III/IV endometriosis who have had previous surgery
- Evidence does not support surgery in women with asymptomatic endometrioma planning IVF

García-Velasco et al., Reprod Med 2009

Deep Infiltrative Endometriosis

is there a relationship with infertility?

Anusch Yazdani
MBBS (Hons) FRANZCOG CREI
Eve Health, Australia
QFG Research Foundation, Australia

Grants/Research Support: EMD-Serono, Merck Serono

endometriosis

↓

infertility

endometriosis

plausible pathophysiology
altered prevalence
dose response relationship
treatment response

endometriosis

plausible pathophysiology
altered prevalence
dose response relationship
treatment response
plausible pathophysiology

- functional
- dyspareunia
- altered sexuality in chronic pain
- anatomic distortion
- pelvic adhesions and endometrioma data

plausible pathophysiology

- chemical factors
  - increased volume of peritoneal fluid
  - increased peritoneal fluid concentration of activated macrophages
  - increased peritoneal fluid concentration of prostaglandin, interleukin-1, tumour necrosis factor, and proteases
  - production of substances (e.g., prostanoids, cytokines, growth factors) affect:
    - ovulation: retarded follicular growth
    - corpus luteum function
    - fertilization
    - impaired sperm function
    - embryonic development
    - implantation

plausible pathophysiology

- cellular factors
  - increased activation of macrophages
  - cytokines recruit macrophages and lymphocytes
  - macrophages from women with endometriosis secrete interleukin-1 which is toxic to mouse embryos

plausible pathophysiology

- uterus
  - abnormal eutopic endometrium
    - Müllerian tract "field defect"
  - abnormal peristaltic activity
    - hyperperistalsis and dysfunctional peristalsis
    - involved in the development of pelvic endometriosis, uterine adenomyosis and infertility
- ovary
  - reduced ovarian reserve
    - AMH
  - impaired ovarian capacitance

plausible pathophysiology

- endometriosis
  - altered prevalence
dose response relationship
treatment response
  - implantation
  - fertilization
  - embryo quality
  - oocyte quality

endometriosis
altered prevalence
endometriosis and infertility
endometriosis and infertility

endometriosis
plausible pathophysiology
altered prevalence
dose response relationship
treatment response

dose response relationship

• natural conception
  • reduced fecundability/ cycle
    • ovulatory 20-25%
    • endometriosis 2-10%
• assisted conception
  • IVF in women with endometriosis
    • endometrioma 82%
    • endometrioma + DIE 69%

Fertil Steril 2012 97:367
dose response relationship

• assisted conception
• reduced fecundability in donor insemination with endometriosis
• reduced fecundability in oocyte donors with endometriosis

endometriosis

plausible pathophysiology
altered prevalence
dose response relationship
treatment response

• Endometriosis Fertility Index (Adamson)
• based on population analysis
• uses elements of rAFS for endometriosis volume
  • least function score
  • age
  • time of infertility
  • history
  • lifetable analysis
treatment response

- Laparoscopic removal of minimal stage endometriosis may improve spontaneous pregnancy rates
  - level 1 evidence
- Laparoscopic excision of endometriomas superior to ablation with respect to spontaneous pregnancy rate
  - level 1 evidence
- There is insufficient evidence to determine whether removal of recto-vaginal lesions improves spontaneous pregnancy rates
  - level 3 evidence

treatment response

• in patients with severe endometriosis and failed IVF:
  • spontaneous conception rate 37%
  • cumulative conception rate 68%
  • following optimal resection
• therefore:
  • surgical options need to be explored in patients with severe endometriosis
  • further studies are required to assess the outcome of non-ovarian endometriosis

resection of endometriosis spontaneous conception:
  • deep infiltrative endometriosis 37%
  • endometrioma 36%
  • peritoneal endometriosis 46%
  Zhonghua Fu Chan Ke Za Zhi 2013 48:16
• IVF in women with endometriosis
  • endometrioma 82%
  • endometrioma + DIE 69%
  Fertil Steril 2012 97:367

resection of all disease has higher success
• resection with bowel 2.3/month
• resection without bowel 1.8/month
• resection no bowel 3.9/month
  Hum Reprod 2009 24:1619
• IVF without surgery 24%
• IVF with surgery 45%
  J Minim Invasive Gynecol 2009 16:174

IVF is so much quicker but IVF is so much cheaper

endometriosis infertility
  • plausible pathophysiology
  • altered prevalence
  • dose response relationship
  • treatment response

endometriosis implies infertility
Endometriosis: everything you wanted to know about deep infiltrative endometriosis but were afraid to ask.

Anusch Yazdani
MBBS (Hons)
FRANZCOG
CREI
QFG Research Foundation, Australia
But

• I am a Surgeon involved in the development of endoscopic surgery since 1982.

• I do like surgery and particularly endoscopic surgery, this may influence some of my conclusions!!

Disclosure

• I have no financial relationships to disclose.

Learning objectives

• Improve knowledge in peritoneal physiology and pathophysiology

• Demonstrate the potential advantage of laparoscopy over laparotomy in tumor dissemination and adhesion formation

• Demonstrate that intra-peritoneal pressure should be decreased to 10 or even 8 mmHg and that this change may decrease post operative adhesion formation

• To suggest that further modification of the intraoperative peritoneal environment will likely improve surgical outcomes within the next 10 years

Endoscopy: Revolution!

• Decreased
  – Scars
  – Trauma
  – Pain
  – Hospital stay
  – Costs
REVOLUTION ??

But dissemination may look worse !!

Laparotomy

Laparoscopy

Canis et al 1998

Révolution ?

Laparotomy is Open
difficult to change

Laparoscopy is Closed
easier to adapt ?

To adapt the laparoscopic environment we have to learn

PERITONEAL PHYSIOLOGY

AND

PERITONEAL PATHOPHYSIOLOGY

The peritoneum is an organ !!

• This organ is
  – Fragile
  – Unknown
  – Often traumatized without reasons
  – Heals without any scar in normal conditions
  – Effective way of medical treatment administration
  – Very powerful as an immune organ ....
Fascinating organ!!

Consider the surface area!

Which peritoneal surface area is important?

- The anatomical area
- The area accounting for microvilli
- The area of peritoneal vessels (capillaries which is essential for exchanges)
- The volume of the intercellular matrix

Peritoneal surface area

- 1 - Anatomical peritoneal surface area

- It was recently measured in 10 non eviscerated cadavers

- The result was $14\,323 \pm 824\,cm^2$
Peritoneal surface area

- Among 14 323 ± 824 cm²
  - The visceral peritoneum represented 81.89% ± 0.99%
  - and the parietal peritoneum 18.11% ± 0.99%

Albanese et al Surgical and Radiologic Anatomy 2009

Peritoneal surface area

- The luminal surface of mesothelial cells has numerous microvilli, which vary in length, density and shape
- These microvilli increase the mesothelial surface area up to 40m²
- Microvilli protect the delicate mesothelial surface from frictional injury by entrapping water, serous exudates, and phospholipids which act as lubricants for the cells.

Microvilli

- The density of microvilli depends on the area studied
  - 230 /µ on the bladder
  - 540 /µ on the spleen
  - Sometimes absent on the parietal and the diaphragmatic peritoneum (Di Paolo 2000)

- Most importantly ultrastructural changes on the surface of the cells clearly demonstrate that microvilli are dynamic structures.

Microvilli

- So the peritoneal surface area may range from the surface area of a table to that of a small apartment and this is a dynamic phenomena !!
- Do you understand why “fascinating” !!

21/10/2013
Peritoneal surface area

• 1 – Functional peritoneal surface area
  - Microvessels
  - Extracellular matrix
    - It includes two compartments: a fluid and a viscous part

Functions of mesothelial cells

• The primary role of the mesothelium is
  - to maintain serosal integrity and function.
  - to provide a protective barrier against abrasion and invading pathogens.
  - to secrete surfactant, proteoglycans and glycosaminoglycans to provide a slippery, non-adhesive surface to allow intracoelomic movements.
  - Major source of Plasminogen activators in serosal fluid which is important in fibrinolysis and the prevention of adhesions.
  - to secrete hyaluronan and other glycosaminoglycans which may prevent tumor cell adhesion.
  - They facilitate transport of fluid and cells across the serosal cavities.
  - present antigen to T cells.
  - secreting cytokines, growth factors, ECM, proteases and other inflammatory mediators participate in the induction and resolution of inflammation and tissue repair.

Glycosaminoglycans

• The surface of the mesothelium is surrounded by a glyocalyx composed of Glycosaminoglycans (GAGs), Proteoglycans (PGs), and phospholipids, which together provide a slippery, non-adhesive layer that protects the serosal cavity from abrasion, infection, and tumor dissemination.
• The GAG and PG composition of the mesothelial glyocalyx remains to be fully defined. (Hung and Chang 2007)
• Human peritoneal mesothelial cells (HPMCs) synthesize and secrete decorin, biglycan, perlecan, and hyaluronan in vitro.
• That finding, together with the observation that hyaluronan, decorin, and biglycan have been identified in spent dialysis effluent, lends support to the suggestion that HPMCs contribute to the anionic content of the mesothelial glyocalyx.

Functions of peritoneal surface

• The primary role of the mesothelium is
  - to maintain serosal integrity and function.
  - to provide a protective barrier against abrasion and invading pathogens.
  - to secrete surfactant, proteoglycans and glycosaminoglycans to provide a slippery, non-adhesive surface to allow intracoelomic movements.
  - Major source of Plasminogen activators in serosal fluid which is important in fibrinolysis and the prevention of adhesions.
  - to secrete hyaluronan and other glycosaminoglycans which may prevent tumor cell adhesion.

Roles of Glycosaminoglycans

• Proteoglycans are major components, and they have diverse biologic functions, including binding and sequestration of growth factors and regulation of collagen fibrillogenesis.
• The control of peritoneal fibrosis:
  - Decorin has the ability to bind transforming growth factor-ß (TGF-ß) via its core protein, and in doing so, to neutralize the biologic activity of that growth factor.
  - Decorin has been shown to interact with collagen and to prevent collagen fibrillogenesis (10).
• Hyaluronan is a component of the mesothelial glyocalyx and protects the mesothelium from abrasion and adhesion.
• PGs and Mesothelial Perme selectivity.
• PG–Chemokine Interactions in the Peritoneum
**Mesothelial « lubricant »**

- Mesothelial cells secrete surface glycosaminoglycans, predominantly hyaluronan, which is assembled into hyaluronan-containing pericellular matrixes "coats" around microvilli, protecting the cells from abrasive damage and infective agents.

- They also secrete phosphatidyl choline, the major constituent of the pulmonary surfactant
  - Mutsaers 2004

- By binding to the glycocalyx which coats the microvilli, phospholipids may form a film, .... negatively charged microvilli attract positively charged phospholipids molecules with branched terminaison creating the most efficient lubrication known in nature (Di Paolo and Sacchi 2000)

**Peritoneal lubricant**

- Peritoneal surface is hydrophobic
- Phosphatidyl choline is found in the fluid recovered at the end of peritoneal dialysis

**Peritoneal Lubricant ??**

- mesothelial cells have intra cellular apparatus similar to those observed in pneumocytes
- Peritoneal surface is hydrophobic
- Phosphatidyl choline is found in the fluid recovered at the end of peritoneal dialysis

**Blue Test from « Manhès » !!**

- A gentle trauma induced to the peritoneum by the lavage device remove the molecules which make the peritoneal surface hydrophobic so that it becomes hydrophylic and it may be stained with methylene blue.
**Mesothelial Cells**

- Slowly growing tissue, it is estimated that only 0.16 to 0.5% of the cells are in mitosis at the same time.
- This percentage increases to 30 and even 80% in an area traumatized 48 hours before.

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**2 main morphologic types of cells**

<table>
<thead>
<tr>
<th>Epidermoid</th>
<th>Cubic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear</td>
<td>Ovoid</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>rare</td>
</tr>
<tr>
<td>REG</td>
<td>+</td>
</tr>
<tr>
<td>Golgi</td>
<td>+</td>
</tr>
<tr>
<td>Microtubules</td>
<td>+</td>
</tr>
<tr>
<td>Microfilaments</td>
<td>+</td>
</tr>
</tbody>
</table>

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**Cilia**

- Mesothelial cells also possess cilia which are 5 times longer than microvilli.
- Their function is not known but.
- Primary cilia may have a sensory function capable of detecting subtle changes in the composition of the serosal fluid including paracrine and hormonal regulators released into the fluid. The primary cilium is strategically placed to mediate a rapid cellular response given its close association with biosynthetic organelles.

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**Histology**

- Slowly growing tissue, it is estimated that only 0.16 to 0.5% of the cells are in mitosis at the same time.
- This percentage increases to 30 and even 80% in an area traumatized 48 hours before.
Peritoneum and pneumoperitoneum

Conclusions: The study demonstrated that the morphologic integrity of the rat peritoneum is not disturbed when CO2 or helium is used for insufflation combined with the intraperitoneal injection of carcinoma cells. Pneumoperitoneum therefore probably is not the condition causing peritoneal changes that favor intraperitoneal tumor growth.

Controversial Results!!

<table>
<thead>
<tr>
<th>Group</th>
<th>Pressure (mm Hg)</th>
<th>Time (h)</th>
<th>Gas flow (l/min)</th>
<th>Area of basal lamina exposed (fraction)</th>
<th>Diameter of mesothelial cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
<td>0.076 ± 0.002</td>
<td>5.652 ± 0.040</td>
</tr>
<tr>
<td>CO2 1h</td>
<td>5</td>
<td>1</td>
<td>1.0</td>
<td>0.197 ± 0.003</td>
<td>4.539 ± 0.029</td>
</tr>
<tr>
<td>CO2 2h</td>
<td>5</td>
<td>2</td>
<td>1.0</td>
<td>0.752 ± 0.004</td>
<td>4.590 ± 0.044</td>
</tr>
<tr>
<td>CO2 3h</td>
<td>5</td>
<td>3</td>
<td>1.0</td>
<td>0.751 ± 0.003</td>
<td>4.590 ± 0.044</td>
</tr>
<tr>
<td>He 1h</td>
<td>5</td>
<td>1</td>
<td>1.0</td>
<td>0.074 ± 0.001</td>
<td>5.708 ± 0.104</td>
</tr>
<tr>
<td>He 2h</td>
<td>5</td>
<td>2</td>
<td>1.0</td>
<td>0.195 ± 0.003</td>
<td>4.528 ± 0.048</td>
</tr>
<tr>
<td>He 3h</td>
<td>5</td>
<td>3</td>
<td>1.0</td>
<td>0.751 ± 0.004</td>
<td>4.566 ± 0.046</td>
</tr>
<tr>
<td>CO2 8mm</td>
<td>8</td>
<td>1</td>
<td>1.0</td>
<td>0.28 ± 0.008</td>
<td>5.358 ± 0.066</td>
</tr>
<tr>
<td>CO2 2l/min</td>
<td>5</td>
<td>1</td>
<td>2.0</td>
<td>0.276 ± 0.009</td>
<td>6.036 ± 0.043</td>
</tr>
<tr>
<td>CO2 3l/min</td>
<td>5</td>
<td>1</td>
<td>3.0</td>
<td>0.362 ± 0.003</td>
<td>6.268 ± 0.061</td>
</tr>
</tbody>
</table>

5 animals in each group.
• Time, flow, pressure and type of gas are essential parameters

The model is essential!!

Methods

ID K. Mouse epithelial ovarian cancer cell line
Dr. K. Roby, University of Kansas Medical Center (Carcinogenesis 2000)

1 x 10⁶ cells

intraperitoneal

Immunocompetents C57BL/6 8 weeks, mice,

Animals and methods
Animals and methods

- Mechanical ventilator
- Adapted to the type of surgery:
  - Tidal volume (200 μl)
  - Strokes per minute (250: laparoscopy; 220 laparotomy, control)
- Values delimited in a preliminary study to obtain PCO2: 25-35 mmHg and pH: 7.3-7.4

Arterial blood gas analysis

<table>
<thead>
<tr>
<th>Control (Anesthesia)</th>
<th>CO2 Pneumoperitoneum 2mmHg</th>
<th>CO2 Pneumoperitoneum 8 mmHg</th>
<th>Laparotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (mmHg)</td>
<td>101.3 ± 5.2</td>
<td>107.2 ± 2.9</td>
<td>70.2 ± 17.7</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>36.2 ± 3.5</td>
<td>41.7 ± 2.3</td>
<td>61.8 ± 4.25</td>
</tr>
<tr>
<td>pH</td>
<td>7.374 ± 0.041</td>
<td>7.260 ± 0.012</td>
<td>7.155 ± 0.027</td>
</tr>
</tbody>
</table>

Data are mean ± SEM

* Normal value of PaCO2 in mice: 25-35mmHg

Without assisted ventilation, we would only study the consequences of asphyxia induced by the pneumoperitoneum

Arterial blood gas analysis

<table>
<thead>
<tr>
<th>Control (Anesthesia)</th>
<th>CO2 Pneumoperitoneum 2mmHg</th>
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<th>Laparotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (mmHg)</td>
<td>106.6 ± 4.2</td>
<td>106.0 ± 3.2</td>
<td>112.2 ± 3.6</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>26.8 ± 2.9</td>
<td>34.2 ± 2.2</td>
<td>32.2 ± 3.6</td>
</tr>
<tr>
<td>pH</td>
<td>7.379 ± 0.037</td>
<td>7.342 ± 0.023</td>
<td>7.269 ± 0.041</td>
</tr>
</tbody>
</table>

Data are mean ± SEM

* Normal value of PaCO2 in mice: 25-35mmHg

Results: Peritoneum Dissemination score
Conclusions

• An adapted pressure must be used (further hemodynamics studies are necessary)
• In studies with no CRS, effect of pneumopertioneum might be reconsidered
• CRS is required for operative and post-operative studies in animals

Mesothelial stem cells ?!

Mesothelial cell may become fibroblast « like » cells

Mesothelial cell transplantation

Mesothelial Cells

- Mesothelial cells secretion
  - Prostaglandin E2 and I2
  - Cytokines (IL1, IL6, TGFβ, EGF, VEGF, G-CSF, M-CSF)
  - Chemokines (IL8, MCP-1)
  - Extracellular matrix components (Fibronectin, Laminin, Type III collagen, hyaluronic acid (récepteur CD44))
  - (tPA, PAI1)
  - Phosphatidyli choline

Mesothelial Cells

- Phagocytosis
- Antigen presentation
- HLA DR expression induced by après strom interféron gamma
- IL 15 secretion (activateur de cellules T)
Our data strongly suggest that HMCs contribute to dying cell removal in the peritoneum, and future studies will elucidate in what manner this influences tumor cell dissemination and the anti-tumor immune response.

Diaphragmatic stoma

- Dynamic structures
- Their diameter may change from 4 to 10 microns but depends on the circumstances as there are a lot of actin microfilament inside mesothelial cells.
- The diameter also changes in intraperitoneal disease.
- The study by Tsilibary and Wissig (1983) demonstrated that whether the lymphatic stomata of diaphragmatic peritoneum was open or close depended on respiratory movement. During inspiration, the diaphragmatic muscles contract, the number of open lymphatic stomata was decreased. On the contrary, during expiration, the diaphragmatic muscles relaxed, the number of open lymphatic stomata was increased.
- The increase of intraabdominal pressure leads to increased number of open lymphatic stomata.
- The diameter of stoma of the pericardium is increased by VEGF and angiotensin.
- The diameter of peritoneal stoma of the ovarian bursa is influenced by pregnancy.

There stoma in other areas

- Omentum
- Anterior abdominal wall
- Liver (rat)
- Pelvis particularly on the broad ligament

Omentum

- No spontaneous movements
- Milky spots are concentrations of immune cells, main origin of peritoneal macrophages and sites of lymphocytes differentiation
- Their content depends on their activation: At rest there are 70% of macrophages, 10% of B cells and 10% of T cells
- Omentectomy induces significant changes in peritoneal cellular population
B CELL Migration in the PERITONEUM

Berberich et al J Immunol 2008

37 patients with advanced ovarian cancer

The peritoneum is a secondary lymphoid organ!!

In a rat model of subcutaneous tumor!

The peritoneum is a secondary lymphoid organ

We demonstrate the migration of antigen presenting cells, macrophages, and dendritic cells from the subcutaneous site to the peritoneum after they have picked up the antigen.

Our results suggest the peritoneum to function as an organ with lymphoid characteristics, which causes immune cell (APCs and T, B, and NK cells) migration and stimulation, leading to tumor regression.

The peritoneum is an important lymphoid organ

Peritoneal trauma

These results indicate that the milky spots of the omentum function as unique secondary lymphoid organs that promote immunity to peritoneal antigens.
Where does these cells come from?

1. Centripetal migration
2. Exfoliation of mesothelial cell from adjacent or opposing surface
3. Pre existing free floating serosal cells
4. Serosal macrophages
5. Sub mesothelial mesenchymal precursors
6. Bone marrow derived circulating precursors
7. Mesothelial stem cells

Hypoxia

- Tissue oxygenation is one of the most important determinants in wound healing, adhesion formation, tumor growth.

Adhesions ; Hypoxemia ; Duration

Rabbit Model ; Standard laparoscopic Trauma

Molinas et al Hum reprod 2000

Peritoneal tissue oxygen tension (1)

- PitO2 measure
  - Peritoneal tissue oxygen tension was measured using a polarographic oxygen electrode placed in the retroperitoneal space using a 16 gauge intravenous catheter.
  - The PitO2 level were monitored continuously.
  - Following the trauma of implantation, the intraoperative values were averaged across the last 30 minutes of the procedure.

Peritoneal tissue oxygen tension (PitO2) in mice with controlled respiratory support

<table>
<thead>
<tr>
<th></th>
<th>Control (anesthesia alone) (n=5)</th>
<th>CO2 pneumoperitoneum 2mmHg (n=5)</th>
<th>CO2 pneumoperitoneum 8mmHg (n=5)</th>
<th>Laparotomy (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (mmHg)</td>
<td>106.6 ± 4.2</td>
<td>106.0 ± 3.2</td>
<td>112.2 ± 3.6</td>
<td>105.4 ± 4.4</td>
</tr>
<tr>
<td>PitO2 (mmHg)</td>
<td>45.0 ± 3.5</td>
<td>104.2 ± 7.8</td>
<td>61.2 ± 9.6</td>
<td>49.8 ± 15.0</td>
</tr>
</tbody>
</table>

Data are mean ± SEM
α: p< 0.05 vs Control, CO2 pneumoperitoneum at high IPP, Laparotomy
Peritoneal tissue oxygen tension (3)

- To understand whether this result is related to pressure or to CO2
  - Two groups of 3 animal with controlled respiratory support
    - 3 with CO2
    - 3 with air
    - Each animal had
      - anesthesia for 1 hour,
      - pneumoperitoneum for 1 hour
      - and laparotomy for 1 hour

Which pressure is acceptable in a mouse model?

CO2 pneumoperitoneum, intraperitoneal pressure and peritoneal tissue hypoxia: A mouse study with controlled respiratory support

Methods

- Peritoneal hypoxia at the cellular level was studied using Pimonidazole
  - Pimonidazole administration
    - Pimonidazole hydrochloride (Hydroxyprobe-1, Natural Pharmacia International Inc., Research Triangle Park, NC; concentration 1.0 mg/100 mL in 0.9% saline) was administered at 70 mg/kg.
Preliminary clinical data

FiO2 of a normal non traumatized peritoneum

FiO2: 0.4

FiO2: 1.0

FiO2: 1.0

FiO2: 0.4

Pit02 normal non traumatized

Pit02 traumatized

Model of ovarian rupture

ID 8, Mouse epithelial ovarian cancer cell line
Dr. K. Roby, University of Kansas Medical Center (Carcinogenesis)

1 x 10^6 cells

intraperitoneal

Immunocompetents C57BL/6J 8 weeks, mice.

Results: Peritoneum Dissemination score

Laparotomy 8mmHg 2mmHg Anesthesia

Dissemination score

P<0.009

P<0.004

P<0.009

N.S.

P<0.002

The role of pressure was confirmed using pathologic examination of the implants.
Muscle tissues: free of cancer cells

Muscle tissues: invasive cancer cells

Invasion: negative

Invasion: Positive Minimal

Invasive: Positive Massive

The structure of the muscle is destroyed

Results: Peritoneum
Invasion of cells into muscle tissues

Peritoneal Carcinomatosis Model

Intramuscular Invasion
Conclusion

- **Early post-operative windows** has been underlined,
- Peri-operative treatments could be an interesting strategy in oncologic surgery and need to be assessed

Clinical data

Molecular modifications of the peritoneum during a CO2 pneumoperitoneum

Study design

- **Patients**: Laparoscopic hysterectomy with/without promontofixation
- **CO2 pneumoperitoneum 8 mmHg**
- **CO2 pneumoperitoneum 12 mmHg**
- **Gene expression profile by PCR based Microarray**
- **60 min Peritoneal tissue collection**

Clinical data

**Table 1** Clinical characteristics of patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>12 mmHg</th>
<th>8 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>Age [y]</td>
<td>40.5 (40-45)</td>
<td>40.0 (40-42)</td>
</tr>
<tr>
<td>Parity</td>
<td>3 (0-6)</td>
<td>3 (0-6)</td>
</tr>
<tr>
<td>Menstrual cycle [d (%)]</td>
<td>30 [50]</td>
<td>30 [50]</td>
</tr>
<tr>
<td>Prostaglandin</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Salpingitis</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anovulation</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>With endometriosis</td>
<td>8 [22.2]</td>
<td>6 [18.8]</td>
</tr>
<tr>
<td>With peri-ovarian fibrosis</td>
<td>5 [15.6]</td>
<td>4 [12.5]</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>21 (63.9)</td>
<td>22 (68.8)</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>8 (22.2)</td>
<td>7 (21.9)</td>
</tr>
<tr>
<td>Lower abdominal bleeding</td>
<td>8 (22.2)</td>
<td>7 (21.9)</td>
</tr>
</tbody>
</table>

*Other categories*
tPA/PAI-1 ratio during a CO2 pneumoperitoneum

Animal study

- C57Bl6 mice
- 3 groups CO2 2 mmHg, 8 mmHg, Laparotomy
- 8 groups of 5 animal each for collection of tissue at 0, 4, 8, 24, 48, 72 hours and 5 and 7 days
- 5 controls anesthesia alone

Initial biopsy: 0 hour

P<.001

P<.01

P<.001

P<.01

tPA: tissue plasminogen activator, PAI-1: plasminogen activator inhibitor-1

Initial biopsy: 0 hour

tPA/PAI-1 ratio=1

Conclusion

- The increase in tPA/PAI 1 ratio is explained by an increase in PAI-1 and results in a decreased fibrinolytic activity and increased post operative adhesion formation
- In conclusion, the results of the present study suggest that a low IPP (8 mmHg) may be better than the standard IPP (12 mmHg) to minimize the impact on the peritoneal fibrinolytic system during a CO2 pneumoperitoneum.
- In addition, the results of the present mouse study suggest that the critical time for the prevention of post-operative adhesion formation by increasing peritoneal fibrinolytic activity might be during surgery and up to 4 h after surgery.

21/10/2013

21/10/2013
Impact of intraperitoneal pressure of a CO2 pneumoperitoneum on the surgical peritoneal environment

Sachiko Matsuzaki et al.

Study design

Patients

Laparoscopic hysterectomy with/without promontofixation

CO2 pneumoperitoneum 8 mmHg

CO2 pneumoperitoneum 12 mmHg

Gene expression profile by PCR based Microarray + Quantitative RT PCR

Isolation of mesothelial cells in vitro pneumoperitoneum model

Peritoneal tissue collection

60 min

Peritoneal tissue collection

60 min

Gene expression profile

PCR array results

Table I Clinical characteristics of patients.

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<tr>
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<td>32</td>
</tr>
<tr>
<td>Age</td>
<td>48.5 (41-57)</td>
<td>48.0 (45-60)</td>
</tr>
<tr>
<td>Parity*</td>
<td>3 (0-6)</td>
<td>3 (0-5)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39 (36-40)</td>
<td>39 (38-40)</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>Spinal/General</td>
<td>Spinal/General</td>
</tr>
</tbody>
</table>

Note: *P<0.02

Table III Results of PCR-based microarray analysis.

<table>
<thead>
<tr>
<th>Group</th>
<th>12 mmHg</th>
<th>8 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-regulated genes</td>
<td>Down-regulated genes</td>
<td>Up-regulated genes</td>
</tr>
<tr>
<td>E-selectin</td>
<td>TNF-α</td>
<td>E-selectin</td>
</tr>
<tr>
<td>CTGF</td>
<td>MCP-1</td>
<td>HAS-1</td>
</tr>
<tr>
<td>MMP-9</td>
<td>IL-6</td>
<td>MMP-9</td>
</tr>
<tr>
<td>CXCL-2</td>
<td>IL-1β</td>
<td>CXCL-2</td>
</tr>
</tbody>
</table>

Note: *P<0.02

HAS 1 mRNA expression during a CO2 pneumoperitoneum

Initial biopsy: 0 hour

HAS 1 expression levels

<table>
<thead>
<tr>
<th>Relative expression levels</th>
<th>12 mmHg 1 hour</th>
<th>8 mmHg 1 hour</th>
<th>12 mmHg 2 hour</th>
<th>8 mmHg 2 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAS 1 mRNA expression</td>
<td>5.1±0.2</td>
<td>5.1±0.2</td>
<td>5.1±0.2</td>
<td>5.1±0.2</td>
</tr>
</tbody>
</table>
Hyaluronan metabolism

- Hyaluronic acid synthase-1 (HAS-1) was one of the differentially expressed genes in both groups.
- Thus, we further investigated 3 HAS genes, HAS-1, HAS-2 and HAS-3, HA-cleaving endoenzymes, hyaluronidases 1 and 2 (Hyal-1 and Hyal-2).

HAS 3 mRNA expression during a CO2 pneumoperitoneum

Initial biopsy: 0 hour

HAS 3 expression levels=1

HAS-3 mRNA expression levels were significantly higher in the 12 mmHg group compared with the 8 mmHg group at 1 and 2 h of CO2 pneumoperitoneum.

HAS 2 mRNA expression during a CO2 pneumoperitoneum

Initial biopsy: 0 hour

HAS 2 expression levels=1

No significant difference in HAS-2 mRNA expression levels in the 8 and 12 mmHg groups was observed after 1 or 2 h.

HA-cleaving endoenzymes, hyaluronidase 1 and 2

Hyal-1 and Hyal-2 mRNA expression was significantly higher in the 12 mmHg group compared with the 8 mmHg group at 1 h of CO2 pneumoperitoneum, whereas no significant difference was observed at 2 h of CO2 pneumoperitoneum.

In vitro analysis

- Insufflation chamber at 37°C
- Connected to a Karl Storz endoflator
- Human peritoneal mesothelial cells and fibroblasts
- 8 or 12 mmHg
In vitro data

HA synthesis

HAS 1, 2, 3 and Hyal 1 show increased HA levels in the 8 mmHg group compared to the 12 mmHg group.

In vivo

HAS 1 and 3 decreased
Hyal 1 and 2 increased

In vitro

HAS 1, 2 and 3 increased
Hyal 2 decreased

Hyaluronan synthesis is increased at 8 mmHg suggesting a better regeneration of the peritoneum.

Conclusions 12 mmHg group

- In vivo
  - HAS 1 and 3 decreased
  - Hyal 1 and 2 increased
- In vitro
  - HAS 1, 2 and 3 increased
  - Hyal 1 no difference
  - Hyal 2 higher in the 12 mmHg group

Conclusions: 12 mmHg Increased inflammation

- Hyal 2 increased suggest increased production of LMW HA which cause inflammation
- LMW HA production is increased by inflammation
- 12 mmHg
  - Increased CXCL2 (increased number of neutrophils)
  - Increased E selection (increased neutrophil recruitment)
  - Decreased IL 10 (anti-inflammatory)

Conclusion 12 mmHg: Increased Fibrosis?

- Increased MMP9
- Increased CTGF
- Increased Fibrosis and adhesions

TGFβ is activated by TSP-1 and inhibited by TSP-2 which was decreased

Increased PAI 1, decreased tPA/PAI 1
Intraperitoneal pressure

From 12mmHg to 8mmHg

- No additional cost
- No additional instrument
- No additional time
- However, skilled hands

— Dr. Revaz Botchorisvili, personal communication

Today

- The lower pressure with adequate exposure
- The shorter operation
- The minimal trauma

Tomorrow ....

- Laparoscopic picture will improve, access to the peritoneum will change ...
- Peritoneal atmosphere will become a surgical tool
- Those who are working in open incision with their eyes will have to change their practice closing their spaces and using video camera .......
- But to use this new surgical tool we have to improve our knowledge of peritoneal and retroperitoneal perioperative pathophysiology.

THE REVOLUTION IS STILL AHEAD!!

Treatment of the Ovarian Endometrioma

Dr Jim Tsaltas
President AGES
Head of Gynaecological Endoscopy
Southern Health and Monash Medical Centre
Melbourne IVF

Scope of talk

• Pathophysiology
• Histology
• Diagnosis
• Impact on Fertility
• Surgical Management
• Ovarian Reserve

Pathogenesis

• Three (3) main theories of endometrioma formation:
  - Invagination secondary to bleeding of a superficial implant
  - Invagination secondary to metaplasia of coelomic epithelium in cortical inclusion cysts
  - Endometriotic transformation of functional cysts

• Postulated by different groups but there is no reason to believe that they are mutually exclusive

Histopathology

• Classically - endometriomas are described as ovarian cysts
• Sometimes loculated and at least partially lined by an endometrium-like epithelium, stroma and haemosiderin-laden macrophages
• It is important to note that the follicular densities in the ovarian cortex surrounding endometriomas appear to be much lower than in other benign cysts such as dermoid cysts (Schubert B et al 2005)
  - May imply lower baseline ovarian reserve

• Grants/Research Support: Covidien, Melbourne IVF, Merck Serono

Lining epithelium

Lumen

Haemorrhage, fibrosis and haemosiderin laden macrophages in cyst wall
**Classical Symptoms**

- Severity of symptoms does not correlate well with the degree of disease
- Endometriomas – may have the following symptoms:
  - Cyclical pain
  - Ovulation pain
  - Pain with intercourse
  - Acute pelvic pain associated with possible endometrioma rupture
- Diagnosis
  - Examination – Ovarian mass
  - Ultrasound – extremely accurate method of diagnosis (classic ground glass cyst, reduced ovarian mobility) – sensitivity 84-100% and specificity 90-100% (Moore et al – 2002)

**Abnormal anatomy: Ovary**

- Ground glass appearance
- Thick walled
- Uni- or multilocular
- Multiple lesions
- Kissing ovaries
- Hyperechogenic wall foci
- Wall nodularities
- Acoustic enhancement
- Absence of internal vascularity
- ‘shifting’ content
- (No acoustic streaming)
- Do not regress

**Tip of the iceberg**

- Endometriomas are often seen as marker of more severe disease (Banerjee SK et al – 2008)
- Important to be aware that there may be more severe disease once you start operating (Chapron C et al – 2009)
- Surgery – anatomical assessment and normalization of anatomy
  - Mobilization of ovaries, identification of other lesions, decision to treat
    - Endometriomas, other areas of DIE, single or two step procedure
    - Have a formal approach

**Planning Surgery**

- Careful pre op assessment
- Indication for surgery
  - Confirm diagnosis
  - Pain
  - Infertility
  - Facilitate access to oocytes at IVF OPU
- Assessment of ovarian reserve – will become more critical
  - Ultrasound to include – AFC
  - AMH (Anti-Mullerian Hormone)
    - AMH is produced by the follicles, it corresponds well with AFC and ovarian response to hyperstimulation in IVF, it is the only marker that is menstrual cycle independent and easily measurable (Chang HJ et al – 2010)

**AMH produced by small growing follicles**

- Initial recruitment
- Cycle recruitment

La Marca et al 2010
**AMH as marker of ovarian reserve**

![Graph showing AMH levels across different ages](image)

*Anderson et al 2012*

**Infertility and endometriomas**

- Time to treat – 6 – 12 months depending on age, symptoms, pain, male factor
- Need to individualize treatment
- Treatment of endometrioma dependent on a number of factors:
  - Ovarian reserve
  - Size of the endometrioma - 4cm or greater - ESHRE Guidelines(2005), WES Guidance(2013)
  - If IVF can we access oocytes at OPU
  - Reduce chance of infection at OPU
  - Associated pain and QOL issues
  - Appropriate access to trained surgeons and IVF specialists
  - Must not look at surgery and IVF as competing interests but rather as complementary therapeutic strategies

**Excision of endometriomas**

- Laparoscopic cystectomy by excisional surgery for endometrioma 4cm or greater improves fertility(spontaneous pregnancy rates) compared to drainage and coagulation (Beretta 1998, Alborzi 2004). Many other observational studies show an increased pregnancy rate after surgery for endometriomas with a weighted mean of 50%-summarized in Vercellini 2009 (see next slide)
- As well as improved fertility rates excision has lower recurrence of endometriomas and symptoms (Hart 2008 and updated 2011 – cochrane review) as compared to drainage and coagulation

**Issues related to treatment**

- Early studies suggested minimal if any damage to the ovarian reserve after surgical treatment for endometriomas – (Loh 1999, Donnez 2001, Canis 2001)
- Recent studies however have demonstrated damage to the ovarian reserve
  - Methodology to assess this includes D2 FSH, AFC, Ovarian reserve, response to gonadotrophins in IVF and AMH
  - (Somigliani 2003, Somigliani 2006, Chang 2010, Benaglia 2010, )
  - Damage may also relate to size of endometrioma being excised (Roman 2010)
  - Excellent paper to read - overview of published data – Somigliana et al 2013
  - “Aim is to develop innovative surgical measures aimed at preventing damage” – Xiajina M et al Fert & Steri 2013

**Is it all our fault?**

- Prospective assessment of the impact of endometriomas and their removal on ovarian reserve and determinants of the rate of decline in ovarian reserve (Gurkan Uncu et al Hum Rep 2013)
  - States endometriomas will themselves cause damage to the ovarian reserve – 30 patients with endometriomas and 30 matched controls
  - Surgery further compromises the problem
- In women with endometriosis anti-Mullerian hormone levels are decreased only in those with previous endometrioma surgery - Isabelle Streuli et al Hum Rep 2013
  - Do not believe endometriomas affect AMH levels but it is the surgery
- Obviously further work needs to be done
Reducing Risks

- Care with surgical technique
  - Excision is preferred method
  - Care with identification of planes (Canis Principle)
  - Minimize diathermy and conserve all ovarian tissue possible

- Recent small randomized clinical trial – shows potential less reduction in ovarian reserve when suturing is used for haemostasis – AFC outcome measure (Coric 2011)

- Minimize the amount of coagulation used – be very precise in its application

- Combined technique – excisional surgery and also ablative surgery for 10–20% of endometrioma wall next to hilus (Donnez 2010)

- Small study looked at reduction of postoperative adhesions by suture to close the ovary for haematomas compared to traditional (diathermy) endometrioma RCT – favored suturing – Pellicano 2008, Litta et al 2013

- Haemostatic aids in the ovary – ie Floseal with or without suturing (Angioli R eta l – 2009)

- AMH excellent marker
  - Should consider egg freezing prior to recurrent endometrioma surgery in young patient with low AMH not trying to conceive

- Should consider AMH in IVF cycles – now seems to be the best marker/predictor for oocyte yield and OHSS. It is however marker of quantity of eggs not quality. It now appears to be a better marker than D2 FSH, E2, Inhibin B, AFC or age (Arcic J et al Fert Steril 2013, Fleming R et al BioMedicine Online 2013)

- Some interesting information on AMH
  - In obese/overweight patients with PCO – losing weight – diet then exercise – reduces AMH levels and normalises cycles. May be due to a relationship between intraovarian testosterone and AMH in PCO pts (Nybacka eta l Fert & Stert 2013 – in press)

- OCP – studies suggested no change with the pill but recent study (Kallio S et al Fert & Steril 2013) suggest AMH drops with use of cont comb pill (regardless of route of admin) – this is important in counseling (consider retesting 3M after cease pill) the use of the pill in this way inhibits early phase of FSH development and perhaps even follicular growth in preceding phase.

AMH

We will hear more

- AMH in IVF cycles – now seems to be the best marker/predictor for oocyte yield and OHSS. It is however marker of quantity of eggs not quality. It now appears to be a better marker than D2 FSH, E2, Inhibin B, AFC or age (Arcic J et al Fert Steril 2013, Fleming R et al BioMedicine Online 2013)

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Reducing recurrence

- Recurrence rates post surgery have been quoted at 12–30% after 2-5 year follow up (Seracchioli et al 2010)

- The length of use of the COCP post surgery is one of the critical factors related to recurrence

- Method of use is also critical

- Seracchioli’s study – divided patients into three groups:
  - 1: Continuous COCP
  - 2: Cyclical COCP
  - 3: No COCP

- Recurrence rate at 24 months:
  - 1: 8.2%
  - 2: 14.7%
  - 3: 29%

Conclusion

- Symptoms
- Diagnosis
- Indications for surgery
- Markers of ovarian reserve
- Preservation of ovarian tissue
- Consider surgical technique
- Post operative reduction in recurrence
- Egg freezing prior to recurrent surgery or even after primary surgery in young women – we will see more of this

References

- See Attached Word Document
Infertility and endometriosis

Basics
- Subtle lesions
- Typical endometriosis
- Cystic ovarian endometriosis
- Deep endometriosis

Conclusions

Disclosures
- Stockholder: EndoSAT NV, eSaturnus NV
- Other: CEO: EndoSAT NV

Teaching aims
- Surgery and IVF are complementary but surgery comes first.
- Treatment and results of surgery
  - Subtle
  - Typical
  - Cystic
  - Deep

Basics of infertility: MFR & CPR

Fertility basics
- Unexplained infertility: population model
  - 1 year: 20% conceive next year, 50% CPR
  - 3 years: <5% <20%
- This is the basis for initiating investigation & treatment
- Following surgery
  - Do not wait longer than 6-12 months
- IVF
  - It is a myth that the MFR remains constant
  - Real CPR, hardly exceeds 60% of the initial population

Surgery and IVF are complementary

Too liberal use of IVF
- Decreases CPR
- At a higher cost
- 1 IVF born child costs 20.000 $ median 3-4 cycles at $ 5000-6000/cycle
- Surgery: at least 4-5 times less for 5000 $ some 50% get pregnant more than once

Conclusion
- For endometriosis & infertility
- Surgery and IVF are complementary
- But surgery comes first
- Provided it is well done
- Quality control is necessary
Surgical treatment of Infertility

Introduction: the infertility work-up

Surgical treatment of endometriosis
Adhaesions
Myomectomy
Hydrosalpinx

Conclusions

Infertility: always a laparoscopy?

- Yes
  - if associated symptoms of pain
  - If cystic or deep endometriosis suspected

- ? When infertility is the only symptom
  - Calculated risk: overtreatment
  - missing treatable pathology
  - The exact place of THL is still unclear

- ? When IVF anyway indicated

Fertility Surgery

- Hysteroscopy
- Endometriosis
- Adhesions
- Oviduct
  - Hydrosalpinx
- Uterus
  - Myomectomy
- Ovary
  - Drilling under water?

Principles
Diagnostic laparoscopy during work-up
Surgery during this laparoscopy

Adhesions & Infertility

- Adhesions can cause infertility
  - Especially
  - Peritubal
  - Peri-ovarian

- Results of adhaesiolysis are poorly documented

Uterine septum

Hydrosalpinx

Salpingostomy

- Step 1: incision
  - Not too much
  - Collar keeps open

- Step 2: salpingoscopy
- Step 2: flowering
- Step 4: patency
Hydrosalpinx: Results

- Thinwalled Salpingostomy
  - Overall 60% cumulative pregnancy rate
  - Dependent on salpingoscopy
  - % EUP unclear

- Thickwalled hydrosalpinx
  - Pregnancy rate = 0: therefore salpingectomy

Symptoms vary with lesion

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Pain</th>
<th>Infertility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtle</td>
<td>80%</td>
<td>no</td>
</tr>
<tr>
<td>Typical</td>
<td>25%</td>
<td>in 50% +</td>
</tr>
<tr>
<td>Cystic</td>
<td>10%</td>
<td>in 80% +++</td>
</tr>
<tr>
<td>Deep</td>
<td>2-3%</td>
<td>in 95% +++++</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneal pockets—Müllerianosis-Choristoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ovarian Drilling for PCO

- A debated subject
  - Medical therapy
  - Versus drilling

- Results of drilling
  - 80% ovulations
  - 30% adhesions
  - Under water: THL
    - 0% adhesions?

Endometriosis and infertility

- In women trying to conceive, the MFR decreases rapidly to 10% within 1 year, which is similar to all endometriosis data
- This explains the increased endometriosis prevalence in infertile women

Mechanisms

- LUF and oocyte
- Sperm toxicity
- Transport and implantation
- Immune factors and endometrium
- Uterine contractility

Conclusions: Endometriosis and infertility

- The association of endometriosis and infertility is solid
- The chicken and the egg: It is unclear whether
  - Endometriotic lesions/mass causes infertility
  - Infertility causes endometriosis
- PK 1980—through LUF syndrome
  - Surgical removal will help
  - An Endometriotic constitution is associated with infertility
  - Surgical removal will not help

Endometriotic lesions and infertility

<table>
<thead>
<tr>
<th>Lesions</th>
<th>MFR</th>
<th>1y CPR</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtle lesions</td>
<td>nl</td>
<td>=UI</td>
<td>poor</td>
</tr>
<tr>
<td>Typical Lesions</td>
<td>10%</td>
<td>=UI</td>
<td>+++</td>
</tr>
<tr>
<td>Cystic Ovarian</td>
<td>10%</td>
<td>=UI</td>
<td>+++</td>
</tr>
<tr>
<td>Deep “Adenomyos”</td>
<td></td>
<td></td>
<td>Little data corrected for duration of infertility and age</td>
</tr>
</tbody>
</table>
Pregnancy rates: Endometriosis

Surgery & fertility

Subtle lesions

Fertility?

Diagnosis and treatment during laparoscopy

• Is this a cause of infertility?

Typical Endometriosis

Fertility: MFR < 10%
CPR = unexplained infertility

Diaphragm
The LUF Syndrome

- Peritoneal fluid
- LUF Exists
- Associated
  - with typical E
  - not with subtle E
- A cofactor?

Results of treatment

- Infertility
  - Surgical treatment: Endocan study (R. Maheux et al)
    - Stage I and II and no other infertility factor
  - Discussion
    - Patient not blinded to treatment
    - Increase in treatment or decrease in non treatment?
    - LUF and stress
    - Trait anxiety and fertility

Results of treatment

- Infertility
  - Surgical treatment: Gruppo Italiano per lo studio dell’Endometriosi (Hum Reprod 99,14,1332-1334)
  - Stage I and II and no other infertility factor
  - RCT

Conclusion

- Subtle endometriosis
  - ? Whether it is a cause of infertility of pain
  - ? Whether treatment is useful
  - A physiologic condition occurring intermittently in all women
- Typical endometriosis
  - Cause of pain
  - Associated with infertility and with LUF
  - Unclear whether treatment is effective
  - Surgical excision – coagulation is technically unreliable
  - Recurrence rate around 20%
- Following laparoscopy & surgery CPR = 60%

Surgery & fertility

Cystic Ovarian Endometriosis

Fertility:
- MFR < 10%
- CPR = 60%

Cystic ovarian endometriosis

If you believe

Hughesdon

Focal treatment
**Vaporisation**

- Slow
- Incomplete
- Depth?
- Too deep bleeding

**Diagnosis and treatment during laparoscopy**

**Cystic ovarian endometriosis**

**Scissor excision**

**Excision**: protect the hilus

**Conclusion 4: cystic ovarian endo**

- Aspiration (ultrasound guided) is useless and dangerous (!!! IVF pucture)
- Vaporisation should be abandoned because higher recurrence rates around 20%

- Excision: careful + !!! hilus

**Conclusion: cystic ovarian endo**

- Surgery is mandatory
- 60% will get pregnant
- If well done

**Surgery & fertility**

**Deep Endometriosis**

- **Fertility**:
  - MFR < 10%
  - CPR = unexplained infertility

- if small without pain: ?
- in over 95%: surgery is necessary for pain
- impossible to know without laparoscopy
Deep endometriosis

• Adenomyotic nodule
  • Generally unique, Generally > 1 cm
  • Rarely Growing – rather an endpoint when diagnosed
• Infiltrating and metastatic in lymph nodes

• Following surgical excision
  • Low NK activity remains low – high CA125 decreases
  • Pain decreases: clinically not surprising
  • Fertility

Deep endometriosis and infertility

• When pain -> We do surgery
  • Removal of endometriosis
  • Creation of adhesions

• When only infertility -> ??
  • Nodule: no pain: 5%
  • Infertility: rare
  • Balance benefit for fertility <-> the adhesion formation

• Future = surgery + adhesion prevention

Pregnancies in deep endometriosis

N=2500

50% without children
50% with children

Full analysis with age
Diameter of lesion
Duration of surgery
Not done yet

Pregnancies in deep endometriosis

Journal of negative results: Massive adhesion formation after IVF punctures with deep nodules in RV septum

CONCLUSION: Extensive surgery for intraperitoneal and deep endometriosis in infertile women does not modify global fertility outcome but is associated with a higher complication rate


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Pregnancies in deep endometriosis


Live birth rate of 34% - lower in elder and after bowel problems
**Pregnancies in deep endometriosis**


*pregnancy rates (24% vs 41%, p = .004), n=178*


IVF n=64 does not expose women to a consistent risk of endometriosis-related symptoms progression-50% with children

---

**Conclusions**

Deep Endometriosis and infertility

- Huge variability in techniques
- Poorly documented fertility explorations
- Series too small for meaningful analysis eg size
- *spontaneous pregnancy rates of 25-60%*

- Prognostic factors ?
- Indication for surgery is pain not fertility

- Data suggest a negative effect upon fertility-MFR :
  - IVF data - our analysis

---

**Conclusion**

- Difficulty of surgery is difficult to predict
- Ureter
- bowel
- If too difficult: do not operate and refer
- Fertility surgery is one of the most demanding surgeries
- Some 60% become pregnant after extensive surgery for deep endometriosis

---

**Conclusions**

- No IVF without diagnostic laparoscopy (except severe male infertility)
- During diagnostic laparoscopy: fertility surgery
  - Adhesions
  - Endometriosis
    - Subtle
    - Typical
    - Cystic
    - Deep
  - Hydrosalpinx and fimbrosis
    - Thin-walled
  - Ovarian drilling
    - Under water ?
  - Myomectomy
- Adhesion prevention
Adenomyosis and fertility: surgical and medical management
George A Pistofidis MB.BS FRCOG

Disclosure
I have no financial relationships to disclose.

Objectives
After this course you will be able to:
• Define adenomyosis
• Identify epidemiology of adenomyosis and recognise how types of adenomyosis differ with age
• Diagnose and classify adenomyosis based on clinical observation, symptomology and macroscopic appearance
• Recognise the affects of adenomyosis on fertility mechanisms
• Compare medical and surgical therapies and be able to assess and implement the most appropriate treatment plan
• Choose the relevant fertility treatment in each case

What is adenomyosis?
• Histologically, adenomyosis is diagnosed when endometrial glands are found inside the myometrium

Etiology of adenomyosis
1) Invagination of endometrial glands into the myometrium
2) Embryonically misplaced tot potential Mullerian remnants
3) Endometrium invaginates and proceeds along the myometrial lymphatics
4) Misplaced bone marrow stem cells displaced through the vasculature

What is adenomyosis? - definition
Is adenomyosis a single disorder?

Adenomyosis, similarly to endometriosis, is a complex condition with multiple etiologies, and with variable clinical expressions.

In some publications, adenomyosis is found with endometriosis...
- The prevalence of adenomyosis in 160 women with endometriosis was 79%.
- And in women under the age of 34 with endometriosis 90%.
  
  G Kunz, D Beil, P Huppert et al. Hum Reprod 2005

- There is a high correlation of endometriosis and adenomyosis in first degree relatives.
- Possibly both are phenotypes of a single disorder rather than two distinct diseases.
  
  S Kennedy, R Hadfield et al. Lancet 1998

In other series, adenomyosis and endometriosis coincides in...
- Endometriosis is observed in 6%-22% of women with adenomyosis.
- Myomas are concurrently observed in 35%-55%.

Endometriosis and adenomyosis are first degree relatives

Endometriosis and adenomyosis share some common aetio-pathogenic mechanisms (genetic, environmental, immunological).

Apoptosis and bel2 expression in normal human endometrium, endometriosis and adenomyosis
  
  Rebecca K Jones et al 1998

Distribution in endometriosis of 3 loci mapping to regions linked to endometriosis and endo/metastatic breast cancer
  
  Mokdad OA et al 2002

Estrogen receptor alpha gene polymorphism is associated with endometriosis, adenomyosis and pelvic pain
  
  Jc Katsuki et al 2002

Association between genetic polymorphisms of transforming growth factor (TGF) and beta 2 and risk of endometriosis and adenomyosis in Chinese women
  
  Shen Kang et al 2010

Is adenomyosis an immune disease?
  
  Hirota Ota et al 1998

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Endometriosis is observed in 6%-22% of women with adenomyosis.

Myomas are concurrently observed in 35%-55%.
• It is important from what perspective you look at the problem.

Women with endometriosis - DIE also having adenomyosis…….

……or women with diagnosed adenomyosis also suffering from DIE-endometriosis

Yet, they have not received the same attention!!!

Med-Line Publications 1995 - 2013

- Endometriosis papers: 19784
- Myomas: 5686
- Adenomyosis: 2146
- Total: 31626 (6.7%) adenomyosis papers

Laparoscopy

- Endometriosis: 5485
- Myomas: 827
- Adenomyosis: 304
- Total: 4476 (<3.6%) adenomyosis papers

Over 90 years, various terms have been used to describe adenomyosis, but there has not been an official classification

- Adenomyoma-nodule & diffuse adenomyosis
- Diffuse adenomyosis of the posterior or anterior uterine wall
- Focal lesions
- Infiltrative lesions

Thomas Cullen 1920, Kasei O et al 1973, Novak ER & Woodruff JD 1979

Uterine adenomyosis

- A new classification of adenomyosis uteri based on clinical observation, symptomatology, macroscopic appearance and histological findings

- Distinct types of uterine adenomyosis based on laparoscopic and histopathologic criteria

G Pistofidis, E Makrakis, O Koukoura et al 2013 Clin Exp Obstet & Gynec

A classification system of uterine adenomyosis

- Diffuse
- Scirrhotic
- Nodular
- Cystic

• How frequent & what age groups?
Out of 558 women with uterine pathology, 36 (7%) had diagnosed adenomyosis.

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean (yrs)</th>
<th>St Dev (yrs)</th>
<th>Range (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>41.2</td>
<td>6.7</td>
<td>[27 – 59]</td>
</tr>
<tr>
<td>Diffuse (orange)</td>
<td>44.4</td>
<td>6.0</td>
<td>[27 – 59]</td>
</tr>
<tr>
<td>Sclerotic (dark blue)</td>
<td>40.1</td>
<td>6.4</td>
<td>[30 – 47]</td>
</tr>
<tr>
<td>Nodular (yellow)</td>
<td>37.7</td>
<td>5.2</td>
<td>[27 – 45]</td>
</tr>
<tr>
<td>Cystic (light blue)</td>
<td>30.7</td>
<td>2.5</td>
<td>[28 – 33]</td>
</tr>
</tbody>
</table>

Comparison of patients age between the 4 groups:
- Diffuse vs Nodular: Difference (yrs): 6.7 – P< 0.001
- Diffuse vs Cystic: Difference (yrs): 13.7 – P< 0.001
- Sclerotic vs Nodular: NS
- Diffuse vs Sclerotic: NS
- Nodular vs Cystic: NS
- Diffuse vs Cystic: NS

Which is the best diagnostic test?

**U/S**
- Heterogeneous myometrial area
- Globular asymmetric uterus
- Irregular cystic spaces
- Myometrial linear striations
- Poor definition of endometrial myometrial junction
- Myometrial anterior posterior asymmetry
- Thickening of anterior/posterior wall with increased/decreased echogenicity

*Sensitivity 0.79 and Specificity 0.85*

**MRI**
- Diffuse or local widening of junctional zones (JZ)
- JZ thickness of 15mm
- Subjective thickening of JZ, localized or diffuse
- Ill-defined low intensity lesion
- JZ wider than 12mm
- Uterine enlargement with small hypo-intense myometrial spots

*Sensitivity 74% and Specificity 91%*
Normal JZ thickness 7-8 mm maximum up to 10mm

Adenomyotic minor focal lesion

Larger focal adenomyosis of Ant Ut wall

Diffuse adenomyosis

How does it affect fertility?

Adenomyosis and fertility

Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes
A Maheshwari et al 2012 Hum Reprod

• Out of 410 studies only 20 were deemed adequate for analysis.

None was randomized controlled!
14 were case series
6 were case reports

Why so few and poor quality studies?

ADENOMYOSIS

Symptoms – Indication for surgery

Until 2008

Why infertility trials are few and far between...

A) Mostly older age groups
B) Infrequent condition
C) Infertility not the presenting symptom
Possible mechanisms of fertility impairment

Myometrial dysfunction
- Disruption of the specific uterine microenvironment in the basal endometrium may explain the structural and functional abnormalities of the junctional zone, such as hyper-peristalsis, dys-peristalsis and incoordinate smooth muscle proliferation associated with endometriosis and adenomyosis
- Impaired sperm transport

Implantation failure
1) Abnormal endometrial vascular patterns occurring throughout the menstrual cycle resulting in poor quality endometrium
   H Ota & T Tanaka 2003
2) Elevated amounts of antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase resulting in excessive reactive oxygen production
   A Agarwal, S Gupta, RK Sharma 2005
3) Pronounced aggregation of macrophages in superficial endometrial glands (TNFα & IL-1) may produce a hostile immune environment
   K Tremellen & P Russell 2011

Effect of adenomyosis on obstetric outcome
- In one study by Juang et al 2007, was found increased risk of preterm delivery and premature rupture of membranes
- Additional risks include: uterine rupture, post-partum atony-haemorrhage (PPH), ectopic pregnancy, red degeneration and PPH

Treatment options
Medical: IUD danazol-loaded devices, GnRH agonists
Conservative treatments: high intensity focused U/S, uterine artery embolization, electro-myolysis
Combination treatments: conservative surgery with GnRH agonists
Surgical treatments: laparoscopic resection with or without uterine artery occlusion
IUD danazol-loaded devices

- In two studies with IUD vaginal ring, the combined pregnancy rate following insertion and removal was 41%.
  M Igarashi. 1990 Asia Oceania Obstet Gynaecol
  M Igarashi et al 2000. Ferti Steril
- Levonorgestrol releasing IUD has been used but only as a relief method for dysmenorrhoea.
  L Fedele et al 1997. Fert and Ster
  J Sheng et al 2009. Contraception

High intensity focused MRI guided ultrasound

- One case reported in 2006 of a successful live birth after ultrasound thermal coagulation.
  C Robinovic et al. 2006 Hum Reprod

Uterine artery embolization

- One study, involving six patients, after 36 months of follow up 5 (83%) women conceived.

GnRH agonist treatment

- In two case series and one case report 6 out of 7 women (85%) became pregnant within two years of cessation of therapy.
  JR Nelson, S Carson. 1993 Fertil Steril
  FJ Huang et al. 1999 J Reprod Med Obstet Gyneco
  L Lin et al. 2000 Chin Med J

Conservative surgery with GnRH agonists-danazol

- One retrospective study comparing conservative surgery with GnRH agonist vs GnRH agonist alone. Live birth rates 32% vs 8%.
  PH Wang et al. 2009 Obstet Gynecol

Conservative surgery with GnRH agonists-danazol

- In 8 studies evaluating conservative surgery with or without GnRH agonist. Four were case series and four were case reports.
- Six used GnRH post-op whilst 2 danazol.
- The pooled live birth rate was 88.2%.
Conservative surgery alone

- Three case series, two reported live birth rates one reported pregnancy rate. Technique involved excision of adenomyotic tissue or adenomyoma, hysteropalsy by laparoscopy or laparotomy. Overall live birth rate 36.2%

AN Strizhakov, AI Davydov. 1995 Akush Ginecol
A TadjerounI et al. 1995 Gynecol Rev Gynecol
H Takeshi et al 2006 I Min Invasive Gynecol

Comparing two surgical methods

- Fujishita compared two adenomyomectomy techniques. The classic adenomyomectomy with a transverse incision step wise resection of abnormal tissue. The newer technique yielded 50% pregnancy rate compared with 0% of the older method.

A Fujishita et al 2004. Gynecol Obstet Invest

Inconclusive results

- Heterogeneous techniques and follow up periods varying from 6-69 months
- Type of adenomyosis not specified
- Most studies have been uncontrolled and outcomes reported in the form of case series
- Variable number of patients per study
- Only four out of 20 studies with larger numbers of patients (14, 35, 65 & 65) the rest 1-8, average 3 patients/study
- Pregnancy results varying from 8% - 88%

So...

- Which is the ideal method for treating adenomyosis related infertility?
- What fertility treatment is better and for which type of adenomyosis?

Adenomyosis and fertility: poorly studied and inconclusive data

No studies found on the impact of adenomyosis and natural conception

In seven studies assessing adenomyosis on IVF outcome, results were conflicting. Two studies suggested no effect of adenomyosis.

V Mijatovic et al. 2010 EJ OG RB, MR Costello et al. 2011 EJ OG RB

The other four reduced implantation rates with increased miscarriage rates.


IVF - adenomyosis

Two series showed no difference

In two recent retrospective studies were long and ultra-long (mean 5.3 months) down regulation protocols were used. Implantation rates between the adenomyosis-endometriosis and the healthy group were similar.


Study weaknesses...

Both retrospective studies, adenomyosis diagnosed only by U/S, in one adenomyosis and endometriasis patients were grouped together. Long and ultra long GnRH protocols were used. Adenomyosis treated separately.
IVF - adenomyosis

Four studies showed reduced implantation and viable pregnancy rates.

In four recent studies comparing viable pregnancies in women undergoing IVF, with (Group A) and without (Group B) adenomyosis, implantation outcome was less in women with adenomyosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group A (%)</th>
<th>Group B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V. Thaluri 2012 HR</td>
<td>23.6%</td>
<td>44.6%</td>
</tr>
<tr>
<td>J. Ballester 2012 HR</td>
<td>10%</td>
<td>42.2%</td>
</tr>
<tr>
<td>A. Maubon 2010 JGGR</td>
<td>22.2%</td>
<td>47.2%</td>
</tr>
<tr>
<td>R. Salim 2012 RBOC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study weaknesses:
- First and second retrospective studies, adenomyosis diagnosed only by U/S, short protocols used, adenomyosis type and extension not known. Third prospective study with MRI assessment.

IVF - adenomyosis

One study showed similar implantation but increased miscarriage rate.

J. A. Martinez-Conejero et al compared implantation and miscarriage rates in three groups: (Group A) with adenomyosis, (Group B) with endometriosis, (Group C) normal.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group A (%)</th>
<th>Group B (%)</th>
<th>Group C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation</td>
<td>29.6%</td>
<td>33%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>13.1%</td>
<td>6.1%</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

Study weaknesses:
- Retrospective study on older age group women undergoing oocyte donation. Similar implantation rates between groups but with higher miscarriage rate in the adenomyosis group.

Surgical correction

Is surgery for adenomyosis related infertility correct?

This is a vague question.

The correct question is, which type of adenomyosis is amenable for surgical management?

Four types of uterine adenomyosis

A. Adenomyotic nodule
B. Sclerotic myometrial adenomyosis
C. Diffuse adenomyosis
D. Adenomyotic cyst or cystic adenomyosis

Nodular Adenomyosis
Sclerotic adenomyosis

Difused adenomyosis

Adenomyotic cyst or cystic adenomyosis

A classification system of uterine adenomyosis

<table>
<thead>
<tr>
<th></th>
<th>Adenomyomectomy</th>
<th>Hysterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100% (37)</td>
<td>100% (19)</td>
</tr>
<tr>
<td>Cystic</td>
<td>16% (5)</td>
<td>16% (3)</td>
</tr>
<tr>
<td>Nodular</td>
<td>100% (19)</td>
<td>100% (19)</td>
</tr>
<tr>
<td>Sclerotic</td>
<td>89% (8)</td>
<td>11% (1)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>19% (7)</td>
<td>81% (30)</td>
</tr>
</tbody>
</table>
Surgery for adenomyosis

- Nodular and cystic can has been removed in all cases laparoscopically
- In eight cases of sclerotic adenomyosis (89%) the major part of the lesion was resected. In some cases Complete Uterine Reconstruction Surgery was necessary (CURS)
- In only 7 (19%) was cyto-reduction of the lesion feasible.

RECOMMENDATIONS FOR SURGERY in women requesting fertility

- As 1st line option, nodular, cystic and sclerotic adenomyosis can and should be surgically removed
- A) A younger women
- B) Dysmenorroe-a-menorrhagia most common
- Diffused adenomyosis should be best treated by long pre IVF down regulation therapy
- A) Older age groups
- B) Long recovery following surgery
- C) Incomplete removal of the disease or surgery too destructive of uterine anatomy

Conclusions: endometriosis-adenomyosis

There is a strong association between adenomyosis and endometriosis.

Some authors believe that the two conditions represent different stages of the same disease whereas others identify them as separate entities.

However it is important from what angle you look at the problem. Women with diagnosed IVF also having adenomyosis (more frequent) or women with diagnosed adenomyosis also suffering from endometriosis (less frequent)

In women treated with prolonged down-regulation, adenomyosis in addition to endometriosis does not impair the outcome of assisted reproduction

Conclusions adenomyosis-fertility

Adenomyosis types differ with age

Adenomyosis patients present primarily with dysmenorrhoea, and menorrhagia

There is little data on the epidemiology of adenomyosis associated with subfertility

In patients with localized adenomyosis in, nodular, sclerotic or cystic, surgery should be offered first

In patients requesting fertility with diffused adenomyosis, prolonged down-regulation with GnRH analogues is the best option

IN OUR SERIES

1) Not accurate follow up, mostly referrals from elsewhere
2) Only natural fertility after laparoscopic surgery alone, up to 3 years follow up
3) None of the patients had pre-op or post-op down-regulation therapy

Cystic 2 (66%)
Nodular 7 out of 19 (37%)
Sclerotic 3 (37%)
Diffuse 0%

Italian multicenter study on complications of laparoscopic myomectomy

Sizzi O et al 2007

1) 1998-2004 four centres
2) 2050 laparoscopic myomectomies
3) Myoma size 1-20 cm

Complications in 38 (2.02%) women

- 14 cases of haemorrhage (3 blood transfusion)
- 10 postoperative haematomas
- 1 bowel injury
- 1 postoperative kidney failure
- 2 unexpected carcinomas
- 7 converted to laparotomy
- 2 readmitted for surgery
- 1 laparoscopic hysterectomy
- 386 pregnancies, 1 case (0.26%) of ruptured uterus at 33 weeks
- The one case had adenomyosis!
The end

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A New Approach to Endometrioma Laparoscopic Combined Technique

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President of the Turkish-German Gynecology Association (TAJEV)
Editor of the Journal of the Turkish-German Gynecology Association (JTGGA)

Disclosure
I have no financial relationships to disclose.

Learning Objectives

- Endometrioma and infertility
- Endometrioma surgery and infertility
- Endometrioma surgery and ovarian reserve
- Combined technique

Endometriosis: An ancient disease

- Endometriosis: one name, many diseases.
- It has been seen nearly 4000 years, but we are still years away from introducing an accurate, noninvasive diagnostic test and treatment.
- Four thousand years is long enough; the time has come to end the empire of endometriosis.

Ovarian Endometriomas

Ovarian follicles are present at the base of the endometriotic pseudocyst

Dronne J.
Endometriosis: enigmatic in the pathogenesis and controversial in its therapy

Ovarian follicles are present at the base of the endometriotic pseudocyst

Endometrioma
Chocola
tec fluid
Capsul

Residual Ovarian Cortex
Endometrial Epithelium and Stroma

Dronne J.
Endometriosis: enigmatic in the pathogenesis and controversial in its therapy
• Despite extensive studies, the cause and result relationship between endometriosis and infertility is not clearly understood.


• Follicular density in cortex from ovaries with endometriomas less than 4 cm in size is significantly lower than in cortex from contralateral normal ovaries.


• We know that decreased AMH levels in patients with mild/minimal endometriosis


• and negative effects of endometriotic cysts on the rate of spontaneous ovulation.


Ovarian Endometrioma Surgery

improves FERTILITY

Who prefer surgery for endometrioma?

<table>
<thead>
<tr>
<th>Hospital setting</th>
<th>Expectant</th>
<th>Medical</th>
<th>Surgical</th>
<th>Medical followed by surgical</th>
<th>Surgical followed by medical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>District general hospital</td>
<td>14 (13.3)</td>
<td>3 (3.7)</td>
<td>3 (3.3)</td>
<td>59 (55.1)</td>
<td>6 (5.6)</td>
<td>107 (100%)</td>
</tr>
<tr>
<td>University teaching hospital with IVF set up</td>
<td>1 (11.1)</td>
<td>0</td>
<td>0</td>
<td>1 (11.1)</td>
<td>9 (90%)</td>
<td></td>
</tr>
<tr>
<td>University teaching hospital with no IVF set up</td>
<td>1 (11.1)</td>
<td>0</td>
<td>0</td>
<td>1 (11.1)</td>
<td>9 (90%)</td>
<td></td>
</tr>
</tbody>
</table>

Total: 16 (15.5) | 3 (3.3) | 3 (3.3) | 68 (62.8) | 6 (5.6) | 117 (110%) |


Removal of endometriomas improve fertility

Pregnancy rates in the first year after LS

Donnez J. Hum Reprod 1996

---

70
Removal of endometriomas does not improve fertility outcomes: a matched, case-control study


We need to remove endometriomas before IVF?

**NO**
- Endometriomas do not affect pregnancy rates in IVF

Pouly 2003
Calhaz-Jorge 2004
Garcia-Velasco 2004
Suzuki 2005
Kumbak 2008

**YES**
- Pregnancy rates are decreased in the advanced stage

Kivilcami 2005

- ESHRE Guidelines: Pregnancy rates are lower in the endometrioma groups than the patients of tubal factor infertility

Kennedy 2005

- Risk of PID

Younis 1997
Wei 1998

Do we need to remove endometriomas before IVF?

Endometrioma surgery before IVF treatments are recommended.
- Oocytes quality
- COH responsiveness
- Fertilisation and implantation failure
- Rule out malignancies
- Reduction of the risk of PID after oocyte pick-up

Surgical management of endometriomas has no significant effect on IVF pregnancy rates and ovarian response to stimulation compared with no treatment.


Endometriosis and infertility: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

- There is insufficient evidence to indicate that resection of endometriomas prior to IVF improves outcomes.
Endometriosis and ART Outcome

<table>
<thead>
<tr>
<th>Stage</th>
<th>Implantation rate</th>
<th>PR per ET</th>
<th>Birth/ongoing pregnancy per started cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASRM I-II (n=724)</td>
<td>27.8% (204/1058)</td>
<td>39.4% (261/662)</td>
<td>25.8% (157/724)</td>
</tr>
<tr>
<td>ASRM III-IV (n=100)</td>
<td>25.0% (133/533)</td>
<td>36.7% (115/312)</td>
<td>24.3% (85/350)</td>
</tr>
<tr>
<td>TUBAL FACTOR (n=1171)</td>
<td>24.9% (471/1895)</td>
<td>37.9% (406/1072)</td>
<td>25.3% (296/1171)</td>
</tr>
</tbody>
</table>


Endometrioma: A different entity

Outcome of the first cycle in patients with ASRM stage III-IV without and with endometrioma.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Implantation rate</th>
<th>PR per ET</th>
<th>Birth/ongoing pregnancy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without endometrioma (n=164)</td>
<td>26.9% (83/308)</td>
<td>40.2% (66/164)</td>
<td>30.5% (50/164)</td>
</tr>
<tr>
<td>Endometrioma (n=186)</td>
<td>20.9% (66/316)</td>
<td>26.3% (49/186)</td>
<td>18.8% (35/186)</td>
</tr>
</tbody>
</table>


Laparoscopic Management of Endometriomas

- Capsule of the Cyst
  - Excision
  - Ablation

- Which technique is the optimal one?
  - With only drainage, 80% recurrence at the end of 6 months

Saleh A, Tulandi T. Fertil Steril 1999

- Endometriomas are best stripped from the ovary and completely excised
  - This has been shown to give better symptomatic relief than drainage and ablation
  - It also provides histology to exclude rare malignancies
- The potential downside is a greater loss of ovarian tissue and follicle reserve

- Regarding ovarian reserve, several reports have suggested that vaporization or fenestration is favorable compared with cystectomy for endometriomas.

But,

- Laparoscopic cystectomy results in a lower recurrence rate and a higher cumulative pregnancy rate than fenestration, and therefore concluded that laparoscopic cystectomy is a better choice than fenestration.
The post-operative decline in serum anti-Mullerian hormone correlates with the bilaterality and severity of endometriosis.

Hirokawa W et al. Hum Reprod. 2011

Laparoscopic Management of Endometriomas Effects on Ovarian Reserve

Surgical intervention and surgical modality may decrease the ovarian reserve

Laparoscopic excision of endometriomas is associated with permanent, quantitative damage to the ovarian reserve.


All things considered,

• Although removal of endometriotic lesions of the ovary using a surgical approach is recommended, it will be necessary to determine what type of surgery should be selected each for different types of endometriosis and for individual patients.

Hirokawa W et al. Hum Reprod. 2011

Surgical Risk

• Exsision of the normal ovarian cortex

• Recurrence

Solution: Combined Technique
**Combined Technique**

- Start with excision
- Then ablation

<table>
<thead>
<tr>
<th>Total Cystectomy</th>
<th>Combined Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clip</td>
<td>Clip</td>
</tr>
</tbody>
</table>

**Reproductive Outcomes of Combined Technique**

- The volume of the ovary after the combined technique was similar to that of the contralateral normal ovary.
- The AFC on day 2-5 showed the same number of antral follicles in all subgroups.
- Histopathology of the excised part of the endometrioma revealed the presence of follicles in only one case (2%).
- The pregnancy rate was 41% at a mean follow-up of 8.3 months.
- Recurrence of a small endometrioma was observed in only one case (2%).

**Recurrence Rates after Combined Technique**

- n: 12 patients with endometrioma operated by combined technique
- Follow up 6 months after surgery, and no cyst recurrence was observed.
- Pain relief was complete in all patients.
- Sonographic evaluation of ovarian volumes and antral follicle count on day 2 or 3 of the menstrual cycle at 6 months after surgery were not significantly different between the operated and the contralateral non-operated ovary.
Conclusion

• L/S Cystectomy
  – Histopathologic diagnosis
  – Decreased risk of infection
  – Increased ovarian responsiveness

– Multiple or inappropriate attempt → decreased ovarian reserve

– Solution: Seems to be Combined Technique

References
CULTURAL AND LINGUISTIC COMPETENCY

Governor Arnold Schwarzenegger signed into law AB 1195 (eff. 7/1/06) requiring local CME providers, such as the AAGL, to assist in enhancing the cultural and linguistic competency of California’s physicians (researchers and doctors without patient contact are exempt). This mandate follows the federal Civil Rights Act of 1964, Executive Order 13166 (2000) and the Dymally-Alatorre Bilingual Services Act (1973), all of which recognize, as confirmed by the US Census Bureau, that substantial numbers of patients possess limited English proficiency (LEP).

California Business & Professions Code §2190.1(c)(3) requires a review and explanation of the laws identified above so as to fulfill AAGL’s obligations pursuant to California law. Additional guidance is provided by the Institute for Medical Quality at http://www.imq.org

Title VI of the Civil Rights Act of 1964 prohibits recipients of federal financial assistance from discriminating against or otherwise excluding individuals on the basis of race, color, or national origin in any of their activities. In 1974, the US Supreme Court recognized LEP individuals as potential victims of national origin discrimination. In all situations, federal agencies are required to assess the number or proportion of LEP individuals in the eligible service population, the frequency with which they come into contact with the program, the importance of the services, and the resources available to the recipient, including the mix of oral and written language services. Additional details may be found in the Department of Justice Policy Guidance Document: Enforcement of Title VI of the Civil Rights Act of 1964 http://www.usdoj.gov/crt/cor/pubs.htm.

Executive Order 13166, “Improving Access to Services for Persons with Limited English Proficiency”, signed by the President on August 11, 2000 http://www.usdoj.gov/crt/cor/13166.htm was the genesis of the Guidance Document mentioned above. The Executive Order requires all federal agencies, including those which provide federal financial assistance, to examine the services they provide, identify any need for services to LEP individuals, and develop and implement a system to provide those services so LEP persons can have meaningful access.

Dymally-Alatorre Bilingual Services Act (California Government Code §7290 et seq.) requires every California state agency which either provides information to, or has contact with, the public to provide bilingual interpreters as well as translated materials explaining those services whenever the local agency serves LEP members of a group whose numbers exceed 5% of the general population.

If you add staff to assist with LEP patients, confirm their translation skills, not just their language skills. A 2007 Northern California study from Sutter Health confirmed that being bilingual does not guarantee competence as a medical interpreter. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2078538.