ENDOMETRIOSIS AND THE STATE OF THE ART

LUIS S. NOBLE MD
WHAT IS ENDOMETRIOSIS?

• The presence of endometrial tissue (glands and stroma) in an extrauterine location.
ENDOMETRIOSIS

• Affects 7-10% of reproductive age women
• Associated with:
  - Pelvic pain, dysmenorrhea, dyspareunia.
  - Infertility
  - Ovarian cysts
  - Pelvic adhesions
  - Bowel dysfunction
  - Bladder dysfunction
  - Extra pelvic endometriosis
ETIOLOGY

- **RISKS FACTORS:**
  - Family history of endometriosis
  - Early age of menarche
  - Short menstrual cycles (< 27 d)
  - Long duration of menstrual flow (>7 d)
  - Heavy bleeding during menses
  - Inverse relationship to parity
  - Delayed childbearing
  - Defects in the uterus or fallopian tubes
ETIOLOGY

- Early in the 20th century (1927), Samson proposed his theory of retrograde menstruation through the fallopian tubes into the peritoneal cavity as a cause of endometriosis.
- Celomic metaplasia
- Vascular lymphatic spread
- Relatively recent research has suggested involvement of the immune system in the pathogenesis of endometriosis.
- Intriguing nonhuman primate studies have demonstrated a strong association between dioxin exposure and the development of endometriosis.
WHY?

• Retrograde menstruation is an almost universal event.
• Only 7-10% of all women get endometriosis
• Nearly 40% of infertile women have endometriosis
• *Uninterrupted menstruation...*
Family history of endometriosis
Early age of menarche
Short menstrual cycles (< 27 d)
Long duration of menstrual flow (>7 d)
Heavy bleeding during menses
Inverse relationship to parity
Delayed childbearing
Defects in the uterus or fallopian tubes

- Regular predictable menses= Normal
- Regular predictable menses= Normal...but not natural from evolutionary standpoint?
!Kung women
Average age of 1st pregnancy 15
15 years lactational amenorrhea
4 years of pregnancy
48 menstrual cycles
“Intellectual evolution”

“Biological evolution”
Endometriosis
Eutopic Endometrium

• Eutopic endometrium should have enhanced ability of proliferation, implantation and angiogenesis, and greater probability of escaping the unfavorable conditions of the ectopic environment.
CYP 19

Expression of the CYP19 (aromatase) gene: an unusual case of alternative promoter usage

EVAN R. SIMPSON, M. DODSON MICHAEL, VEENA R. AGARWAL, MARGARET M. HINSHELWOOD, SERDAR E. BULUN, AND YING ZHAO
The Cecil H. and Ida Green Center for Reproductive Biology Sciences, The University of Texas Southwestern Medical Center, Dallas, Texas, 75235-905 1, USA 1997
Endometriosis (super eutopic endometrial cells)?

• The Eutopic endometrium of women with endometriosis. Is it biochemically different?
CYP 19 GENE EXPRESSION

- RT PCR for CYP 19 gene
- Peritoneum
- Eutopic endometrium (no endometriosis)
- Eutopic endometrium (endometriosis)
- Endometriotic implants

Result:
- Negative
- Negative
- POSITIVE
- POSITIVE

Noble et al 1995 JCMN
Molecular expression

• Aromatase present in Endometrium of women with endometriosis. (Noble et al 1995)
• B-3 integrin expression is aberrant in endometrium of women with endometriosis (Lessey et al 1996)
Recent proteomic analysis revealed molecular dysregulation of more than 70 proteins in the proliferative phase of eutopic endometrium in stage IV and secretory phase of stage II, III and IV endometriosis. Using mass spectrometry, 48 proteins spots which were consistently differentially expressed from stage II to IV endometriosis were identified. (Rai et al 2010)
Aromatase expression

![Graph showing Aromatase activity for different conditions: CONTROL, IL-2 + DEX, PGE2 10^-8 M, cAMP, IL 1b + DEX, IL-15+ DEX.

AROMATASE ACTIVITY
pmol/mg protein/4h

Noble, Bulun JCNM 1996]
Prostaglandins, such as PGE2 and PGF2α, are secreted in significantly higher levels from eutopic and ectopic endometrial cells in women with endometriosis (Dmowski et al., 1998; Gazvani & Templeton, 2002). Higher levels of PGE2 increase estrogen biosynthesis (Noble et al., 1997) by creating a positive feedback system favoring continuous estrogen production (Bulun et al., 1999; Bulun, Zeitoun, Takayama, & Sasano, 2000; Gazvani & Templeton; Noble et al.; Ulukus et al., 2006; Zeitoun & Bulun, 1999).
Endometriosis
It is a riddle wrapped in a mystery inside an enigma.

Winston Churchill
Clinical Aspects

• **DIAGNOSIS:**
  - Symptoms (pelvic pain, infertility, dysmenorrhea)
  - Physical findings
  - Imaging
  - Laboratory testing
Uterosacral nodularity
Alogrithm in infertile couples

• History (dysmenorrhea, pelvic pain, dyspareunia)
• Semen analysis
• HSG
• Endocrine evaluation (mid-luteal progesterone, ovarian reserve testing)
• Physical exam

Current data being analyzed for publication by Dr. Park and Dr. Ramirez
Chronic pelvic pain and endometriosis

- More complex history
- Look for signs of psychological suffering
- Not as clear cut as infertile couples
- 20-25% will have endometriosis
- Infertility couples (asymptomatic) up to 50% will have endometriosis.
Diagnosis

• Imaging: (Limited to advance stages) MRI can be used to detect up to 82 percent of endometriomas greater than or equal to 1 cm and 50 percent of hemorrhagic lesions less than or equal to 5 mm due to the small implant size and variable appearance (Brosens et al., 2004).

• CA-125 testing unreliable

• beta-3 integrin, aromatase PCR or immunostaining with EMB promising

• Laparoscopy/Laparotomy
SPLIT ROADS

PAIN

INFERTILITY

SURGERY
MEDICAL MANAGEMENT OPTIONS

• Almost all medical management options are contraceptive:
MEDICAL MANAGEMENT OPTIONS

• Danazol
• GnRh analogs + NSAIDS
• Continuous oral contraceptives + NSAIDS
• Progestins, oral, (IUD), injectable
• Aromatase inhibitors: Anastrozole (Arimidex), Letrozole (Femara) in combination with progestin or GnRH analogs
• Experimental: Inhibitors of VGEF
Laparoscopy

- Laparoscope
- Uterus
- Gas Filled Area
Endometriosis appearance
**American Society for Reproductive Medicine Revised Classification of Endometriosis**

### Patients' Name: [Blank]  Date: [Blank]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Severity</th>
<th>Description</th>
<th>Laparoscopy</th>
<th>Laparotomy</th>
<th>Photography</th>
<th>Recommended Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Minimal)</td>
<td>1-5</td>
<td>Laparoscopy</td>
<td></td>
<td></td>
<td></td>
<td>Photograph</td>
<td></td>
</tr>
<tr>
<td>II (Mild)</td>
<td>6-15</td>
<td>Laparoscopy</td>
<td></td>
<td></td>
<td></td>
<td>Photograph</td>
<td></td>
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<tr>
<td>III (Moderate)</td>
<td>16-40</td>
<td>Laparoscopy</td>
<td></td>
<td></td>
<td></td>
<td>Photograph</td>
<td></td>
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<tr>
<td>IV (Severe)</td>
<td>&gt; 40</td>
<td>Laparoscopy</td>
<td></td>
<td></td>
<td></td>
<td>Photograph</td>
<td></td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
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### Prognosis: [Blank]

<table>
<thead>
<tr>
<th>Pelvis</th>
<th>ENDOMETRIOSIS</th>
<th>&lt; 1cm</th>
<th>1-3cm</th>
<th>&lt; 3cm</th>
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<tbody>
<tr>
<td>Superficial</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Deep</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>R Superficial</td>
<td>4</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>L Superficial</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Deep</td>
<td>4</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Posterior Culdesac Obliteration</td>
<td>Partial</td>
<td>Complete</td>
<td>4</td>
<td>40</td>
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</tbody>
</table>

### Adhesions

<table>
<thead>
<tr>
<th>Ovary</th>
<th>ADHESIONS</th>
<th>&lt; 1 Enclosure</th>
<th>3-4 Enclosure</th>
<th>&gt; 3 Enclosure</th>
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</thead>
<tbody>
<tr>
<td>R Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dense</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>L Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dense</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Tube</td>
<td>R Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dense</td>
<td>4*</td>
<td>8*</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>L Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dense</td>
<td>4*</td>
<td>8*</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

*If the fimbriated end of the fallopian tube is completely closed, change the point assignment to 16.
Denote appearance of superficial implant types as red (R), red-pink, flame-like, vesicular blob, clear vesicles, white (W), opacifications, peritoneal defects, yellow-brown, or black (B) black, hemosiderin deposits, blue. Denote percent of total described as R__%, W__% and B__%. Total should equal 100%.

Denote appearance of superficial implant types as red (R), red-pink, flame-like, vesicular blob, clear vesicles

<table>
<thead>
<tr>
<th>Additional endometriosis:</th>
<th>Associated pathology:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>L</th>
<th>To be used with normal tubes and ovaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>L</th>
<th>To be used with abnormal tubes and/or ovaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>
Staging

• Endometriosis staging has no relationship to severity of pelvic pain, however, is inversely correlated to fertility potential
Surgical management

• Resection superior than fulguration/vaporization

• For pain, presacral neurectomy or LUNA procedure.
Cytoreduction is the name of the game...

Resection vs Fulguration/ablation (vaporization)

1- Fulguration versus resection of experimental endometrial peritoneal implants in the rat. (Wilson et al)

2- Winkel CA et al study observed that at 12 months, 96% of excision patients and 69% of vaporization patients were pain-free, falling to 69% and 23%, respectively, at 24 months.

3. Findings from a study of 135 patients with a mean follow-up of 3.2 years revealed reductions in pain scores related to dysmenorrhea, no menstrual pelvic pain, and dyspareunia (Winkel CA et al).
Cytoreduction is the name of the game

• These studies suggest that converting from ablative to excisional therapy will refine diagnosis, reduce disease burden and morbidity, lengthen the time to recurrence, and improve outcomes overall.
Endometriosis and Infertility

- Distorted Pelvic Anatomy.
- Altered Peritoneal Function.
- Hormonal and Ovulatory Abnormalities.
- Impaired Implantation (challenged based on b-3 integrin research)
- Oocyte and Embryo Quality.
- Abnormal Uterotubal Transport.
TABLE III.—*Possible negative effects of cytokine rich peritoneal fluid on gamete function and embryonic development.*

- **Spermatozoa**
  1. Impairment of acrosome reaction
  2. Impairment of sperm motility

- **Oocyte**
  1. Impaired folliculogenesis
  2. Impaired oocyte quality

- **Sperm-oocyte interaction impairment**

- **Impaired embryonic development**
  1-2. Cell stage block
  2. Decreased blastulation
Peritoneal environment in endometriosis

- Randomized clinical trials on the use of surgery for infertility or pain associated with endometriosis have shown a clear benefit. This clearly shows that the peritoneal environment is a critical part of the pathogenesis and treatment of the disease.
Infertility and Endometriosis

BYPASS OR EXCISE?

Bypass → ART

Excise → Laparoscopy
Laparoscopy/Endometriosis and Infertility

- Excision of endometriotic lesions (cytoreduction) favorably affects fertility.
- Pelvic pain improves after laparoscopic excision of endometriosis.
Endometriomas and surgery before ART

• Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case–control study☆
  Juan A. Garcia-Velasco, M.D., Neal G. Mahutte, M.D., José Corona, M.D., Victor Zúñiga, M.D., Juan Gilés, M.D., Aydin Arici, M.D., Antonio Pellicer, M.D.
  Received: February 11, 2003; Received in revised form: April 30, 2003; Accepted: April 30, 2003;

• Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas
  Mauro Busacca, MDa, b, Jennifer Riparini, MDb, c, Edgardo Somigliana, MD, Giulia Oggioni, MDa, b, Stefano Izzo, MDb, c, Michele Vignali, MD, PhDa, b, Massimo Candiani, MDb, c
  Received 19 November 2005, Revised 1 February 2006, Accepted 18 March 2006, Available online 8 May 2006

• Damage to ovarian reserve associated with laparoscopic excision of endometriomas: A quantitative rather than a qualitative injury
  Guido Ragni, MD, Edgardo Somigliana, MD, Francesca Benedetti, MD, Alessio Paffoni, BS, Walter Vegetti, MD, Liliana Restelli, BS, Pier Giorgio Crosignani, MD

• Endometrioma Excision and Ovarian Reserve: A Dangerous Relation
  Mauro Busacca, MD, Michele Vignali, Received 8 August 2008, Accepted 18 December 2008, Available online 3 March 2009
Endometriosis and ART

What should come first?
Endometriosis and ART

- Is the endometrium less receptive in endometriosis?
- Oocyte quality lower?
- Fertilization rates impacted?
### Endometriosis and ART

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Endometriosis (N=78)</th>
<th>Tubal (N=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.7±3.5</td>
<td>31.9±3.7</td>
<td>0.166</td>
</tr>
<tr>
<td>BMI</td>
<td>24.3±3.5</td>
<td>25.1±4.2</td>
<td>0.178</td>
</tr>
<tr>
<td>D2 FSH</td>
<td>6.9±2.1</td>
<td>6.3±1.9</td>
<td>0.652</td>
</tr>
<tr>
<td>D2 LH</td>
<td>5.3±2.4</td>
<td>5.02±2.4</td>
<td>0.442</td>
</tr>
<tr>
<td>AMH</td>
<td>2.9±1.4</td>
<td>2.7±1.5</td>
<td>0.382</td>
</tr>
<tr>
<td>AFC</td>
<td>11.1±5.1</td>
<td>10.9±3.8</td>
<td>0.722</td>
</tr>
<tr>
<td>Combined ovarian</td>
<td>11.8±5.8</td>
<td>10.3±4.3</td>
<td>0.043</td>
</tr>
</tbody>
</table>

SD=Standard deviation; BMI=Body mass index; FSH=Follicle-stimulating hormone; LH=Luteinizing hormone; AMH=Anti-müllerian hormone; AFC=Antral follicle count

**Effect of endometriosis on implantation rates when compared to tubal factor in fresh non donor in vitro fertilization cycles**

## Endometriosis and ART

<table>
<thead>
<tr>
<th></th>
<th>Endometriosis group (N=78)</th>
<th>Tubal group (N=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocyte retrieved</td>
<td>6.2±3.6</td>
<td>7.9±5.5</td>
<td>0.016</td>
</tr>
<tr>
<td>M2 oocyte(^a)</td>
<td>69.5</td>
<td>69.3</td>
<td>0.944</td>
</tr>
<tr>
<td>Fertilization rate(^a)</td>
<td>64.8</td>
<td>70.2</td>
<td>0.044</td>
</tr>
<tr>
<td>Cleavage rate(^a)</td>
<td>94.9</td>
<td>96.4</td>
<td>0.298</td>
</tr>
<tr>
<td>Grade 1 embryo(^a)</td>
<td>49.6</td>
<td>50.4</td>
<td>0.767</td>
</tr>
<tr>
<td>No of embryo transferred</td>
<td>2.4±1.1</td>
<td>2.68±1.2</td>
<td>0.276</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>19 (19/78)(^b)</td>
<td>34 (34/100)(^c)</td>
<td>0.222</td>
</tr>
</tbody>
</table>

\(^a\)percentage.  \(^b\)Embryo transfer not done in 12 cases.  \(^c\)Embryo transfer not done in 11 cases.
Endometriosis and ART

• There is insufficient evidence to indicate that resection of endometriomas prior to IVF improves outcomes.
• IVF success rates in women with endometriosis appear to be diminished compared to women with tubal factor infertility; however, IVF likely maximizes cycle fecundity for those with endometriosis.
• Women with endometriosis have higher incidences of preterm delivery, pre-eclampsia, antepartum bleeding/placental complications, and cesarean section when compared to women without endometriosis.
Endometriosis treatment decision making

• Not so easy and clear cut
• Each patient should be individualized
• Decision making should encompass all potential avenues