Debate: Endometrial Evaluation for ALL?

Christos Coutifaris, MD, PhD
The Celso Ramon Garcia Professor of Obstetrics and Gynecology
Division of Reproductive Endocrinology and Infertility
Vice Chair for Faculty Development
Department of Obstetrics and Gynecology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Best of ESHRE and ASRM
New York, NY
March 16, 2019

LEARNING OBJECTIVES

At the conclusion of this debate, participants should be able to:

- Define the concept and clinical relevance of uterine/endometrial receptivity
- Discuss the clinical utility of tests in the evaluation of the endometrium in infertile patients
- Summarize current information about molecular approaches to determine the optimal timing for embryo transfer (personalized embryo transfer; pET)
- Discuss the endometrial contribution to the reproductive process

DISCLOSURES

- Nothing to disclose of relevance to the content of this presentation
- (NIH Research Grant support)
- (ASRM EC and Board member)
Frame the Question

➢ Should there be an evaluation of the endometrium for ALL women undergoing work-up and treatment for infertility?

Rationale

Phases of Human Implantation

Apposition  Adhesion  Intrusion  Invasion

Window of Implantation

Rationale

Window of Implantation (WOI)

19/20 24

LH surge  Window of Implantation (WOI)  Menses

14  19/20  24  28
A Description of 34 Human Ova within the First 17 Days of Development

- 1938 - 1954
- 211 Patients/hysterectomies
- 34 with fertilized ova in Fallopian tubes or uterus
  - 8 "free-lying" (7 in uterus and 1 in Fallopian tube)
  - Of the 34: 21 were (morphologically) normal and 13 were abnormal
  - Of the 21 morphologically normal
    - 4 non-implanted (histologic dating 17-19)
    - 17 implanted (histologic dating 20+)

Rationale

```
```

```
```
Window of Implantation (WOI)

Noyes RW, Hertig AT, Rock J
Dating the Endometrial Biopsy
*Fertil Steril* 1:3-25, 1950

- Observational Study
- Clinical Significance (?)
- Used routinely in the evaluation of infertility
- Significant controversy
  - Infertility
  - Recurrent Pregnancy loss
  - Luteal phase deficiency

NICHD Reproductive Medicine Network
Timed Endometrial Biopsy Study

Coutifaris et al., *Fertil Steril* 82: 1264, 2004
Results - “MID” secretory phase biopsy

<table>
<thead>
<tr>
<th></th>
<th>Fertile Women</th>
<th>Infertile Women</th>
<th>Ch-SQ p-value</th>
<th>Logistic regression p-value for group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=162</td>
<td>N=139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OOP2</td>
<td>49.4%</td>
<td>43.2%</td>
<td>.2810</td>
<td>.3343</td>
</tr>
<tr>
<td>OOP3</td>
<td>42.0%</td>
<td>30.9%</td>
<td>.0478</td>
<td>.0755</td>
</tr>
<tr>
<td>OOP4</td>
<td>22.2%</td>
<td>13.7%</td>
<td>.0556</td>
<td>.0595</td>
</tr>
</tbody>
</table>

NICHD Reproductive Medicine Network
Timed Endometrial Biopsy Study – Results

Results - “LATE” secretory phase biopsy

<table>
<thead>
<tr>
<th></th>
<th>Fertile Women</th>
<th>Infertile Women</th>
<th>Ch-SQ p-value</th>
<th>Logistic regression p-value for group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=170</td>
<td>N=148</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OOP2</td>
<td>35.3%</td>
<td>23.0%</td>
<td>.0163</td>
<td>.0218</td>
</tr>
<tr>
<td>OOP3</td>
<td>24.7%</td>
<td>11.5%</td>
<td>.0025</td>
<td>.0023</td>
</tr>
<tr>
<td>OOP4</td>
<td>17.6%</td>
<td>8.8%</td>
<td>.0211</td>
<td>.0166</td>
</tr>
</tbody>
</table>

Coutifaris et al., Fertil Steril 82: 1264, 2004
In conclusion, the timed endometrial biopsy followed by histological dating of the endometrium provides no clinically useful information as a screening test.

……it is strongly recommended that the histological evaluation of the endometrium be abandoned as a diagnostic tool in the routine evaluation of the infertile couple.

…… In parallel, continued research on the emerging molecular markers of endometrial development should be encouraged.
**Endometrial Receptivity Analysis (ERA) – Accuracy**

In a blinded study the ERA classified better than Noyes criteria

<table>
<thead>
<tr>
<th>Pathologist 1 (P1)</th>
<th>Pathologist 2 (P2)</th>
<th>P1 vs P2</th>
<th>ERA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.618</td>
<td>0.685</td>
<td>0.622</td>
<td>0.922</td>
</tr>
<tr>
<td>(0.446-0.791)</td>
<td>(0.545-0.824)</td>
<td>(0.435-0.839)</td>
<td>(0.815-1.000)</td>
</tr>
</tbody>
</table>

- 0.61 - 0.80 - Good Concordance
- 0.81 - 1.00 - Very Good Concordance

**Clinical Results**

- 55,000 PATIENTS
- 70% Receptive
- 30% Non-receptive
- 79.5% Pre-receptive
- 10.5% Post-receptive / Refractory
- >70 Countries  
  >1,500 Clinics

**Conclusion**

In conclusion, the timed endometrial biopsy followed by histological dating of the endometrium provides no clinically useful information as a screening test. Given the data from this study and the high cost of the procedure, it is strongly recommended that the histological evaluation of the endometrium be abandoned as a diagnostic tool in the routine evaluation of the infertile couple. Although the $53 to $75 million annual savings can be considered modest, the channeling of these funds to support infertility treatments of high efficacy, such as IVF, can be of great benefit to infertile couples. In parallel, continued research on the emerging molecular markers of endometrial development should be encouraged. However, as proven in this study, it is clear that rigorous evaluation of any tests based on new parameters needs to be undertaken before their routine application to clinical practice and their proclamation as “gold standards” for the evaluation of the luteal phase.
Conclusions and Questions

• Question to answer: Endometrial evaluation for ALL?
  (Histology is OUT)
• Key points to consider:
  • Endometrial dysfunction (molecular/genetic) is rare (mostly iatrogenic?)
  • WOI is wide
• Excellent and insightful molecular work
• BUT:
  • Is the work convincing enough for widespread clinical application?
  • Personalized embryo transfer for ALL?
• NEED:
  • Convincing data that molecular endometrial dysfunction is a major problem
  • Is there a validated test to evaluate such dysfunction?
  • What is the cycle to cycle variability of the test?

REBUTTAL

Debate: Endometrial Evaluation for ALL?
Rebuttal

Best of ESHRE and ASRM
New York, NY
March 16, 2019

Christos Coutifaris, MD, PhD
The Celso Ramon Garcia Professor of Obstetrics and Gynecology
Division of Reproductive Endocrinology and Infertility
Vice Chair for Faculty Development
Department of Obstetrics and Gynecology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania
How about the RCT????

### Recurrent Implantation Failure

**A. Clinical outcome of non-responsive RF and control patients that underwent pGT**

<table>
<thead>
<tr>
<th></th>
<th>Non-Response</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>No. of previously failed cycles RF Patients</td>
<td>5.0±0.8</td>
<td>6.4±1.1</td>
</tr>
<tr>
<td>No. of previously failed cycles Control Patients</td>
<td>6.5±0.8</td>
<td>5.4±1.0</td>
</tr>
<tr>
<td>E2A Progression</td>
<td>Pre-receptive</td>
<td>Post-receptive</td>
</tr>
<tr>
<td></td>
<td>21.7±0 (4.4)</td>
<td>4.7±1 (1.0)</td>
</tr>
<tr>
<td>Months between 1st and 2nd E2A</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>2nd E2A at the specified day (9.2±1.4 vs 11.1±0.8)</td>
<td>8.5±0.8</td>
<td>10±1.3</td>
</tr>
<tr>
<td>Patients with pGT after 2nd REPRODUCTIVE E2A</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Months between 2nd REPRODUCTIVE E2A and pGT</td>
<td>1.8±0.7</td>
<td>3.0±0.8</td>
</tr>
<tr>
<td>Implantation rate using pGT</td>
<td>39.4±0.6</td>
<td>41.3±0.8</td>
</tr>
<tr>
<td>Clinical abortion (%)</td>
<td>12±0.6</td>
<td>10±0.8</td>
</tr>
</tbody>
</table>

Ruiz Alonso et al., Fertil Steril 100:818, 2013

**B. Principal component analysis with E2A complexes**

![Principal component analysis with E2A complexes](image)

Ruiz Alonso et al., Fertil Steril 100:818, 2013

### Recurrent Implantation Failure

**Still need an RCT!!**

![Still need an RCT!!](image)

Ruiz Alonso et al., Fertil Steril 100:818, 2013
Concepts to think about

- Uterine (endometrial) receptivity
- Permissive endometrial environment
  - Attachment
  - Implantation
  - Placentation
- The future
  - Proteome
  - Secretome
  - Functional significance
- The ideal test
  - Quick
  - Inexpensive
  - Guide timing on transfer IN THE CYCLE OF TREATMENT