Assessing and Improving Endometrial Competency

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Endometrial Competency

- Anatomy
- Implantation physiology
- Diagnostic modalities
- Uterine pathology
- Hormone supplementation
- Novel endometrial testing/treatment
- Conclusions
Implantation

3 stages
- Apposition
- Adhesion
- Invasion

Endometrium must secrete at least 3 cytokines for implantation

- Colony-stimulating factor 1 (CSF-1)
- Leukemia inhibitory factor (LIF)
- Interleukin 1 (IL-1)

Apposition

- Pinopodes in endometrium appear to absorb water from cavity, collapsing cavity and increasing contact between embryo and endometrium
- Occurs 2-4 days after morula enters uterine cavity

Adhesion

- Molecules on embryo and endometrium
- Integrins, laminin, fibronectin, etc.
- Molecules on embryo interact with integrin on endometrium
- Integrin: peak expression at implantation

Embryo secretes enzymes, mainly proteinases such as collagenase, plasminogen activator, etc. that digest endometrial intercellular matrix allowing embryo to grow into endometrium.

Cytotrophoblast invades uterine spiral arterioles, establishing hematologic connection.

Invasion into first 1/3 of myometrium.

Why do we Evaluate the Endometrial Cavity? Pathology

- 45% of infertile women have pathology affecting the cavity\(^1\)
- False negative rate for HSG before IVF is 37%\(^1\)
- Reduced clinical pregnancy rate with IVF in presence of endometrial pathology \(^2\)

HSG=hysterosalpingogram

\(^1\) Mooney & Milki. *Fertil Steril* 2003;79:637

Diagnostic Modalities
How Do We Evaluate the Endometrial Cavity?

- Transvaginal sonography
- HSG
- Saline sonography
- Hysteroscopy
- Endometrial biopsy
  - Endometrial function testing
  - Luteal phase adequacy/inadequacy

Transvaginal Sonography

- Midcycle examination
- Endometrial thickness
  - 7-8mm \(^1\)
  - 9.5 mm \(^2\)
  - Can be too thick... \(^3\)
- Endometrial pattern
  - Trilaminar

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Endometrial Pattern
Hysterosalpingogram (HSG)
HSG: The Good and the Bad

- Sensitivity (80.3%) and specificity (70.1%) for intrauterine abnormalities compared to H/S

- 43% of patients with normal HSG had abnormal H/S

- High false negative and false positive rates

H/S=hysteroscopy

Saline Sonography

- Office procedure
- No radiation
- Perhaps more accurate than HSG for polyps\(^1\)
- As good as office H/S for cavity visualization\(^2\)

\(^2\) van Dongen, et al. *Br J OBG* 2008;115;1232
Hysteroscopy

- Gold standard for cavity evaluation
- Simultaneously diagnostic and therapeutic
- 18% of patients with normal HSG and 2 failed IVF cycles have pathology
- Up to 1/3 of routine fertility patients have abnormality at H/S

1 La-Sala et al. *Fertil Steril* 1998;70:378
2 Koskas et al. *OBGYN International* 2010;1155
Uterine Pathology
Polyps
Fibroids
Adhesions
Mullerian anomalies
Functional abnormalities
Endometrial Polyps

- Overgrowth of uterine lining
- Estrogen dependent
- Theoretic sterile inflammatory reaction that impairs implantation
- Controversial association with both infertility and recurrent miscarriage\(^1\)-\(^2\)
  - No effect on PR, increase in SAb (n=83)\(^2\)
- No prospective, randomized studies re: polyps and IVF\(^3\)
- Polypectomy DOES improve PR in IUI (n=215)\(^4\)

Endometrial Polyp: Saline Sonogram
Most common benign tumor of the female pelvis¹

Affected women by age 35

- 40% Caucasians
- 60% African Americans

Submucosal fibroids significantly reduce pregnancy rates\textsuperscript{1-2}

Subserosal fibroids are essentially irrelevant\textsuperscript{1-2}

Intramural fibroids remain controversial\textsuperscript{2-3}

- Size\textsuperscript{3}
- Submucosal component\textsuperscript{1}

1. Parker W. Fertility and Sterility. 2007;87:725-736.
Conflicting data

Several studies suggest significant negative impact
  - 40% reduction in PR, 45% reduction in LBR if fibroids

Others suggest no adverse effect

Some suggest adverse effect if
  > 3-4 cm

Others suggest no difference
  (donor egg recipients, retrospective, n=94)
Fibroids & Infertility: Meta-analysis

- 347 studies 1998-2004
- 1 RCT, 9 prospective studies, 13 retrospective studies included
- Submucosal fibroids:

<table>
<thead>
<tr>
<th></th>
<th># Studies</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation Rate</td>
<td>2</td>
<td>.123-.649</td>
<td>.003</td>
</tr>
<tr>
<td>Live Birth Rate</td>
<td>2</td>
<td>.119-.850</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAb Rate</td>
<td>2</td>
<td>1.373-2.051</td>
<td>0.022</td>
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Fibroids & Infertility: Meta-analysis

Intramural Fibroids without cavity involvement

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<tr>
<td>Implantation Rate</td>
<td>14</td>
<td>0.696-.901</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Live Birth Rate</td>
<td>16</td>
<td>0.690-.883</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAb Rate</td>
<td>16</td>
<td>1.473-2.428</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Most studies do not include good evaluation of cavity...

Donor recipients and IVF patients with either submucosal or intramural fibroids with submucosal component
N=101 total (15, 31, 26, 29) vs. 1448 controls (retrospective)
H/S if submucosal; X Lap if combo
Myomectomy affords excellent results

Donor Recipients

<table>
<thead>
<tr>
<th>OPR (%)</th>
<th>87 vs. 85 vs. 77 (control)</th>
<th>61 vs. 52 vs. 53 (control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant. Rates (%)</td>
<td>58 vs. 55 vs. 49 (control)</td>
<td>24 vs. 26 vs. 23 (control)</td>
</tr>
</tbody>
</table>

Surrey et al. *Fertil Steril* 2005;83:1473
Meta analysis – only 2 studies look at clinical pregnancy rates; only 1 evaluates LBR and SAb rates

Myomectomy does not improve outcome, but hard to get definitive conclusion with one study!

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<tr>
<td>Clin Preg Rate</td>
<td>2</td>
<td>.47-30.14</td>
<td>NS</td>
</tr>
<tr>
<td>Live Birth Rate</td>
<td>1</td>
<td>.75-3.7</td>
<td>NS</td>
</tr>
<tr>
<td>SAb Rate</td>
<td>1</td>
<td>.296-1.94</td>
<td>NS</td>
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Intrauterine Adhesions (Asherman’s Syndrome)

- Usually results from D&C related to pregnancy
- Incidence up to 27% (ASRM-1990)
- Diagnose with HSG, hysteroscopy
- Stellate, angulated defects
- Treat with H/S lysis

D&C=dilation and curettage

Mullerian Anomalies

- Unicornuate uterus
- Bicornuate uterus
- Uterine septum
- Uterine didelphis
- All associated with decreased reproductive potential

Hysteroscopy Before IVF

300 patients prospectively undergoing H/S before IVF

Control = 300 IVF patients with no H/S

40% unsuspected abnormalities at H/S

Pregnancy rate: 38% (study group) vs 18% (controls) (p<0.05)

Hormone Supplementation
Well established need

hCG used initially, but P4 used now due to ↓ incidence of OHSS

Start day: 1-3 days after retrieval

Progestosterone formulations

- Crinone, Prometrium, Endometrin, Vaginal progesterone suppository, IM

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# Efficacy of Vaginal Progesterone for Luteal Support Versus IM Progesterone

<table>
<thead>
<tr>
<th>Objective</th>
<th>Compare efficacy and patient satisfaction of Crinone® 8% (progesterone gel) versus IM progesterone in women under age 40 undergoing IVF-ET</th>
</tr>
</thead>
</table>
| Trial design | • Prospective randomized trial  
• Stratified by age (< 35 y, > 35- 39 y) before randomization  
• After positive pregnancy test, all patients switched to gel |
| No. of patients | 407 patients |
| Dosing | CRINONE (90 mg QD; n=206)  
IM progesterone (50 mg QD; n=201) |
| Administration | Vaginal gel: administered 2 days after oocyte retrieval  
IM progesterone: administered 1 day after oocyte retrieval |

Results

*Crinone® 8% (progesterone gel) Versus IM Progesterone*

Ongoing Pregnancy Rate

<table>
<thead>
<tr>
<th></th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRINONE (n=206)</td>
<td>45.2%</td>
</tr>
<tr>
<td>IM (n=201)</td>
<td>42.2%</td>
</tr>
</tbody>
</table>

\[ P = 0.56 \]

## Pregnancy Results, All Patients

<table>
<thead>
<tr>
<th></th>
<th>Crinone (n=172)</th>
<th>PIO (n=302)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Pregnancies</td>
<td>122 (70.9%)</td>
<td>194 (64.2%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Ongoing/Delivered</td>
<td>91 (52.9%)</td>
<td>144 (47.7%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>SAb</td>
<td>6 (3.5%)</td>
<td>13 (4.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Biochemical</td>
<td>22 (12.8%)</td>
<td>35 (11.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ectopic</td>
<td>3 (1.7%)</td>
<td>2 (0.7%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Efficacy is achieved across all vaginal preparations

Dosing requirements differ

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosing</th>
</tr>
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<tbody>
<tr>
<td>Capsule</td>
<td>TID</td>
</tr>
<tr>
<td>Inserts</td>
<td>BID/TID</td>
</tr>
<tr>
<td>Progesterone gel</td>
<td>Once daily</td>
</tr>
</tbody>
</table>
Estrogen (E2) falls after ovulation/retrieval
Possible association with diminished implantation
No difference in normal responders with GnRH antagonist (P,R study)\(^1\)
+ effect in meta-analysis of short and long down regulated GnRH agonist protocols\(^2\)
+ effect in P,R trial of long GnRH analog if peak E2 > 2500\(^3\)

\(^1\) Ceyhan et al. *Fertil Steril* 2008;89:1827
\(^2\) Pritts and Atwood *Hum Reprod* 2002;17:2287
\(^3\) Farhi et al. *Fertil Steril* 2000;73:761
Sildenafil (Viagra®)

- Selective cGMP phosphodiesterase inhibitor
- Increases cGMP levels leading to vascular relaxation, increased blood flow
- Cleared within 48 hours of D/C
- Safety not established
- Not FDA approved for use in women
- No prospective, randomized trials
Sildenafil and Delivery Rates in Patients with Previous IVF Failure

- Retrospective trial (n=105): at least 2 consecutive IVF failures and endometrium < 9mm
- Sildenafil 25 mg vaginal suppositories QID starting with FSH start
- 73/105 had endometrial thickness ≥ 9 mm (69.5%)
- Delivery rate 41% vs. 0% if < 9mm (p<0.01)
- Implantation rate 29% vs. 2% if < 9mm (p<0.01)

Sher G, Fisch J. Fertil Steril 2002;78:1073
Sildenafil Effect on Endometrial Thickness in Women with RPL

- 38 recurrent aborters, 37 controls
- Baseline peak endometrial thickness was less in RPL patients (8.06 vs. 9.03 mm, p<0.05)
- Sildenafil significantly increased peak thickness in study patients (9.25 vs. 8.06 mm, p<0.05)
- Sildenafil increased uterine artery blood flow

Aspirin

Low dose (81 mg) significantly improves uterine blood flow, implantation rates\textsuperscript{a}

- prospective, randomized, double blind placebo controlled trial

Other data suggest similar conclusions

Acupuncture

- Conflicting data
- Conflicting prospective, randomized (small) trials
- Herbs??
Novel Endometrial Testing
Endometrial Function Testing: MAG

- Mouse-associated golgi (MAG) protein
- Abnormal expression in natural cycle is highly predictive of IVF failure
  - 1/17 (5.9%) if abnormal vs 24/61 (39.4%) (p=.01) if normal expression¹
  - 96% specificity and 94% predictive value for predicting IVF failure
  - Low (30%) sensitivity for IVF success

¹ Catalonitti et al. *Fertil Steril* 2006;85:255
Endometrial Function Testing: Integrins

- Cell surface adhesion molecules
- Multiple types, but 3 appear to increase during window of implantation
  - $\alpha v \beta 3$, $\alpha 4 \beta 1$, $\alpha 1 \beta 1$
- Decreased expression with endometriosis, hydrosalpinges, unexplained infertility\(^1\)
- No clear predictive ability for pregnancy

\(^1\) Thomas et al, *Fertil Steril* 2003;80:502
What Can We Potentially Do If We Find An Abnormality?

- Resect polyps, fibroids, septa
- Lyse adhesions
- Consider increasing progesterone supplementation for MAG deficiency
- What about intentionally “injuring” the endometrium?
Intentional Endometrial Injury Before IVF

- Prospective trial, n=134
- Previous failed IVF
- 45 patients randomized to endometrial biopsy on cycle days (EMBx CD) 8, 12, 21, 26 before IVF cycle

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<tr>
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<th>+ BX</th>
<th>-BX</th>
<th>P Value</th>
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<tr>
<td># embryos/ET</td>
<td>3.4</td>
<td>3.1</td>
<td>NS</td>
</tr>
<tr>
<td>IR (%)</td>
<td>27.7</td>
<td>14.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LBR (%)</td>
<td>48.9</td>
<td>23.6</td>
<td>&lt;0.05</td>
</tr>
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ET=embryo transfer; IR=implantation rate; LBR=live birth rate

Intentional Endometrial Injury Before IVF

- 2 other prospective trials, n=63, n=60
- Previous failed IVF
- EMBx CD 21 & 26 before IVF cycle, or once CD 5-22

<table>
<thead>
<tr>
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<th>Raziel, n=63</th>
<th>Zhou, n=60</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td># embryos/ET</td>
<td>3.3</td>
<td>2.25</td>
<td>NS</td>
</tr>
<tr>
<td>IR (%)</td>
<td>11 vs. 4</td>
<td>33.33 vs. 17.78</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LBR (%)</td>
<td>22 vs 8</td>
<td>41.67 vs. 22.96</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Raziel et al. *Fertil Steril* 2007;87:198
Local injury may enhance synchrony between endometrium and embryo

Injury may promote decidualization, improving receptivity

Does this really make sense?

- Menses occurs anyway before cycle of implantation
- Menses initiates regeneration without injury...

No direct basic science support of mechanism

Sometimes it’s not so clear...
Conclusions

- Evaluation of the endometrial cavity before IVF is critical
- Hysteroscopy remains the gold standard, although expense & logistics make universal application impractical
- HSG and sonohysterography are reasonable surrogates despite diminished accuracy
Conclusions (cont)

- *All* endometrial pathology should be corrected prior to IVF
  - Data suggests all fibroids with submucosal component
  - Some controversy remains re: intramural
- Progesterone supplementation provides luteal support
- Estrogen supplementation in certain circumstances may be beneficial
- Novel diagnostic testing may play an eventual role
- Pros vs. Cons of intentionally injuring endometrium before IVF...