Clinical aspect of endometrial injury!

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Implantation Process

Good morphology embryo

Cross communication

Normal uterus & receptive endometrium
Why high quality embryos failed to implant?

Gamete quality
Embryo quality
Transfer technique
Luteal phase support
Time of implantation
What can we do?

What was suggested?

Is it possible to improve implantation?
Local endometrial stimulation (injury).
Intrauterine injections of oil to the rats uterus increased pregnancy rate.


The fertility rates among 109 patients following HSG were found to be 31%

Yang et al. Zhonghua Yi Xue Za Zhi (Taipei) 1989;44:293-7
How does the oil dye increase fertility?

- Clear mucus plugs.
- Break down peritoneal adhesions.
- Provide a stimulatory effect for the cilia.
- The iodine may exert a bacteriostatic effect.
- Washes the ovaries from local toxin.

Rasmussen et al. Radiology 1991;179:75
Improved pregnancy rate following HSG

Oil medium cause some irritation of the endometrium.
Dummy embryo transfer

Mansour and Aboulghar Hum Reprod 2002;17:1149
Embryo transfer under ultrasound

Treatable uterine cause for in-vitro fertilization failures

14 women

Implantation failure most probably due to uterine cause

Hysteroscopy + curettage + antibiotics + estradiol

With this treatment pregnancy rate was 43%

Friedler et al. Lancet 1993;341:1213
Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilization.

Endometrial expression of the gap junction protein Cx43

12 Patients, with mechanical infertility and repeated IVF failures, had multiple endometrial biopsies during spontaneous menstrual cycles

11 patients conceived at the following IVF cycles.

134 patients

Failed to conceive during one or more IVF cycles (Mean – 4)

Biopsies were taken on day 8, 12, 21 and 26 of spontaneous cycle before the IVF cycle.

Endometrial injury vs. control

Study group - 45  
Control - 89

Results

134 patients

<table>
<thead>
<tr>
<th>No. of Pat.</th>
<th>End. Biop.</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial injury vs. control</td>
<td>45</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Implant. %</td>
<td>27</td>
<td>14</td>
<td>0.00011</td>
</tr>
<tr>
<td>Clin. Preg.</td>
<td>66.7%</td>
<td>30.3%</td>
<td>0.00009</td>
</tr>
<tr>
<td>Live Birth</td>
<td>48.9%</td>
<td>22.5%</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Selected group of ICSI patients who failed >4 times (60 patients).
2 biopsies during the luteal phase.
30% conceived in the subsequent treatment cycle.

Raziel et al. Fertil Steril 2007:87;198-201
Local injury to the endometrium in controlled ovarian hyperstimulation cycles improves implantation rates

Prospective study

<table>
<thead>
<tr>
<th></th>
<th>End. biopsy 60 (patients)</th>
<th>Control 61 (patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation rate</td>
<td>33.3%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>48.4%</td>
<td>27.9%</td>
</tr>
<tr>
<td>Live birth</td>
<td>41.7%</td>
<td>22.9%</td>
</tr>
</tbody>
</table>

P < 0.05

Does a single endometrial biopsy regimen (S-EBR) improve ICSI outcome in patients with repeated implantation failure? A randomized controlled trial

210 p. repeated implantation failure (2) <39 y-o

A

Allocation

Hysteroscopy and curettage (n=105)

Follow-up

Follow-up (n=103)

Analysis

Analyzed (n=100)

B

Hysteroscopy only (n=105)

Follow-up

Follow-up (n=102)

Analysis

Analyzed (n=100)

## Treatment outcomes in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A (no. = 100)</th>
<th>Group B (no. = 100)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes retrieved (n)</td>
<td>11.6 ± 3</td>
<td>11.6 ± 2.8</td>
<td>0.787</td>
</tr>
<tr>
<td>Embryos transferred (n)</td>
<td>3.2 ± 0.6</td>
<td>3.3 ± 0.5</td>
<td>0.456</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>12%</td>
<td>7%</td>
<td>0.015*</td>
</tr>
<tr>
<td>Clinical pregnancy (%)</td>
<td>32 (32%)</td>
<td>18 (18%)</td>
<td>0.034*</td>
</tr>
<tr>
<td>Abortion (%)</td>
<td>4/32 (12.5%)</td>
<td>4/18 (22%)</td>
<td>0.618</td>
</tr>
<tr>
<td>Live birth rate (%)</td>
<td>28 (28%)</td>
<td>14 (14%)</td>
<td>0.024*</td>
</tr>
</tbody>
</table>

* P-value < 0.05 means statistical significance.
Endometrial injury in women undergoing ART:
a systematic review and meta-analysis

Nastri et al. The Cochrane Library 2012, Issue

Endometrial injury to overcome recurrent embryo
implantation failure: a systemic review and meta-analysis
Potdar et al.
Reproductive BioMedicine Online (2012) 25, 561–571

Local endometrial injury and IVF outcome:
a systematic review and meta-analysis
Tarek El-Toukhy, SeshKamal Sunkara, Yakoub Khalaf
Reproductive BioMedicine Online (2012) 25, 345–354
Local endometrial injury and IVF outcome: a systematic review and meta-analysis
Tarek El-Toukhy, SeshKamal Sunkara, Yakoub Khalaf
Reproductive BioMedicine Online (2012) 25, 345–354

Prospective – 5
Retrospective – 2
Randomized - 2
Clinical pregnancy rate

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (fixed)</th>
<th>Weight</th>
<th>RR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>Randomised controlled trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karimzadeh et al 2009</td>
<td>13/48</td>
<td>4/45</td>
<td>37.57</td>
<td>2.05</td>
<td>[1.07, 8.66]</td>
</tr>
<tr>
<td>Narvekar et al 2010</td>
<td>16/49</td>
<td>7/51</td>
<td>62.43</td>
<td>2.38</td>
<td>[1.07, 5.28]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>97</td>
<td>96</td>
<td>100.00</td>
<td>2.63</td>
<td>[1.39, 4.96]</td>
</tr>
<tr>
<td>Non-randomised controlled studies</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Borash et al 2003</td>
<td>30/45</td>
<td>27/89</td>
<td>19.53</td>
<td>2.20</td>
<td>[1.51, 3.20]</td>
</tr>
<tr>
<td>Li et al 2004</td>
<td>24/35</td>
<td>5/36</td>
<td>5.31</td>
<td>4.94</td>
<td>[2.12, 11.48]</td>
</tr>
<tr>
<td>Raziel et al 2007</td>
<td>18/60</td>
<td>7/57</td>
<td>7.73</td>
<td>2.44</td>
<td>[1.10, 5.41]</td>
</tr>
<tr>
<td>Zhou et al 2008</td>
<td>29/60</td>
<td>17/61</td>
<td>18.16</td>
<td>1.73</td>
<td>[1.07, 3.01]</td>
</tr>
<tr>
<td>Bonavita et al 2011</td>
<td>31/49</td>
<td>43/98</td>
<td>30.87</td>
<td>1.44</td>
<td>[1.06, 1.96]</td>
</tr>
<tr>
<td>Guven et al 2011</td>
<td>27/56</td>
<td>18/62</td>
<td>18.40</td>
<td>1.66</td>
<td>[1.03, 2.67]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>305</td>
<td>403</td>
<td>100.00</td>
<td>1.95</td>
<td>[1.61, 2.35]</td>
</tr>
</tbody>
</table>

Total events: 29 (Treatment), 11 (Control)
Test for heterogeneity: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%
Test for overall effect: Z = 2.99 (P = 0.003)

Total events: 159 (Treatment), 117 (Control)
Test for heterogeneity: Chi² = 9.65, df = 5 (P = 0.09), I² = 48.2%
Test for overall effect: Z = 6.88 (P < 0.00001)

Favours control  Favours treatment
### Ongoing pregnancy rate

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised controlled trial</td>
<td>11/49</td>
<td>5/51</td>
<td>2.29 [0.86, 6.11]</td>
<td>100.00</td>
<td>2.29 [0.86, 6.11]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>49</td>
<td>51</td>
<td></td>
<td>100.00</td>
<td></td>
</tr>
<tr>
<td>Total events: 11 (Treatment), 5 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for heterogeneity: not applicable</td>
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<tr>
<td>Test for overall effect: Z = 1.65 (P = 0.10)</td>
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</tr>
</tbody>
</table>

### Non-randomised controlled studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barash et al 2003</td>
<td>22/45</td>
<td>21/89</td>
<td>2.07 [1.28, 3.34]</td>
<td>38.06</td>
<td></td>
</tr>
<tr>
<td>Li et al 2004</td>
<td>17/35</td>
<td>4/36</td>
<td>4.37 [1.63, 11.70]</td>
<td>10.64</td>
<td></td>
</tr>
<tr>
<td>Raziel et al 2007</td>
<td>13/60</td>
<td>5/57</td>
<td>2.47 [0.94, 6.49]</td>
<td>13.84</td>
<td></td>
</tr>
<tr>
<td>Zhou et al 2008</td>
<td>25/60</td>
<td>14/61</td>
<td>1.82 [1.05, 3.14]</td>
<td>37.46</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>200</td>
<td>243</td>
<td></td>
<td>100.00</td>
<td></td>
</tr>
<tr>
<td>Total events: 77 (Treatment), 44 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 2.51, df = 3 (P = 0.47), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.99 (P &lt; 0.000001)</td>
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</tbody>
</table>
Conclusions

Endometrial injury increase success rate in the following cycle.
Possible mechanisms

Local injury might induce rapid growth of the endometrium.

Local injury might provoke wound healing involving secretion of cytokines and growth factors.
Questions need to be answered?!

Patients selection

Timing

Technique

Number of biopsies needed