Oocyte in vitro maturation (IVM) in clinical practice?

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IVM - introduction

- Is a "new" method of ART
- The basis of IVM is the maturing in vitro of oocytes from germinal vesicle (GV) stage to metaphase II stage, fertilization of mature oocytes and transfer of embryos into uterus

IVM history

First pregnancies

- **1983**: Veeck et al. Two pregnancies from ET of immature oocytes from stimulated cycles.
- **1991**: Cha et al. First pregnancy from immature oocytes from unstimulated ovaries.
- **1994**: Trounson et al. First pregnancy from immature oocytes from PCOS patient.

The main **difference** between IVM and IVF/ICSI methods

- IVM patients don’t receive medications for conventional COH!
Advantages of IVM

- Avoid the side effects of aGnRH and gonadotrophins
- Avoid the risks of ovarian hyperstimulation syndrome - OHSS
- Safe treatment for PCOS patients
- Costs are reduced compared with conventional IVF
- Easy for the woman, less invasive treatment

Application of human oocyte maturation in vitro

- Patients with PCOS
- Patients with high risk of OHSS
- Regular cycling patients
- Maturation of GV oocytes recovered from superovulation cycles
- Oocyte donation
- In vitro culture of follicles
- Possibility to rescue cancer patients' fertility

Different Priming in IVM

- No priming (Mikkelsen et al. HR 1999)
- Priming with low dose FSH (Mikkelsen and Lindenberg HR 2001) (Lin et al. HR 2003)
- Priming with hCG (Chan et al. FS 1999)
- Priming with FSH+hCG (Lin et al. HR 2003)
Different Priming in IVM

- **PCOS/PCO**
  - FSH PRIMING (Mikkelsen et al., 1999)
    - Improved MR
    - Improved PR
  - hCG PRIMING (Chian et al., 2000)
    - Maturation was hastened
    - Improved clinical pregnancy rate
- **NORMAL OVARIIES**
  - NO PRIMING
  - FSH PRIMING

Success of IVM

- In last years PR was improved according to early studies!

<table>
<thead>
<tr>
<th>Centre</th>
<th>No. of cycles</th>
<th>PR/ET (%)</th>
</tr>
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<tbody>
<tr>
<td>Chian '99</td>
<td>25</td>
<td>32.0</td>
</tr>
<tr>
<td>Chia '00</td>
<td>94</td>
<td>24.5</td>
</tr>
<tr>
<td>Chia '01</td>
<td>24</td>
<td>29.0</td>
</tr>
<tr>
<td>Child '99</td>
<td>121</td>
<td>28.0</td>
</tr>
<tr>
<td>Child '00</td>
<td>107</td>
<td>21.5</td>
</tr>
<tr>
<td>Lin '00</td>
<td>68</td>
<td>33.0</td>
</tr>
<tr>
<td>Li et al. '03</td>
<td>43</td>
<td>26.0</td>
</tr>
<tr>
<td>Halmahem A '03</td>
<td>48</td>
<td>23.0 (IVF)</td>
</tr>
<tr>
<td>Mikkelsen '01</td>
<td>36</td>
<td>29.0</td>
</tr>
</tbody>
</table>

(Chian et al. RBM Online 2005)
Perinatal outcome and IVM

Congenital abnormalities

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>IVM</td>
<td>1.42</td>
<td>0.52 – 3.91</td>
</tr>
<tr>
<td>IVF</td>
<td>1.21</td>
<td>0.63 – 2.62</td>
</tr>
<tr>
<td>ICSI</td>
<td>1.69</td>
<td>0.88 – 3.26</td>
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(Buckett et al. Obstet Gynecol 2007)

Perinatal outcome and IVM

Pregnancy outcomes after IVM, IVF and ICSI

(Buckett et al. Fertil Steril 2008)
Numerous factors have been identified which influence the maturation of human oocytes:
- nature of women – age, PCOS or non PCOS women,
- length of menstrual cycle,
- follicle size and atresia,
- treatment with gonadotrophins and ovarian steroids,
- cumulus cell and granulose cell function (Trounson, 2003)
- endogenous endocrine background?

PCOS

- Heterogeneous endocrine disorder
- Affect 1 in 15 women worldwide
- The most frequent cause of hyperandrogenism and oligo-anovulation
- Psychological, social, economic consequences

PCOS

- Endocrinological irregularities:
  - elevated LH in 40% of women
  - insulin resistance in 40% of obese women
  - obesity in ~ 50% women
  - hyperandrogenism
- Follicular endocrine environment is related to oocyte quality!
  (Tissier et al., 2000)
Hyperinsulinemia and IR play an important role in the pathogenesis of PCOS. (Dunaif, 1997)

Obesity has a synergistic effect, thus increasing hyperinsulinemia and IR. (Homburg et al., 2001)

The consequent hiperandrogenism leads to abnormal folliculogenesis and endometrial development. (Stadtmauer et al., 2002)

The prevalence of IR in PCOS women is high!

Does the developmental potential of immature oocytes obtained from IR-PCOS women differ from non-IR PCOS women?

Material and Methods

The study included 41 PCOS women undergoing IVM.

IR was assessed by calculating the HOMA index (fasting serum insulin [\(\mu U/ml\)] x fasting serum glucose [mMol/L] / 22.5).

36 hours prior to immature oocyte retrieval all women were primed with 10,000 IU of hCG.
Material and Methods

- All immature oocytes were cultured in IVM medium (MediCult) supplemented with 75 mIU/ml FSH + 75 mIU/ml LH (Menogon) and 10% heat inactivated maternal serum, for 24 to 30 hours.

- ICSI was performed in all matured oocytes and the embryos were transferred on day 2 after ICSI.

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Differences in clinical and embryological parameters between HOMA-IR positive and HOMA-IR negative group of PCOS patients undergoing IVM.

<table>
<thead>
<tr>
<th></th>
<th>HOMA-IR +</th>
<th>HOMA-IR -</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>No. of oocytes retrieved</td>
<td>21.1 ± 4.4</td>
<td>6.6 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>36.8 ± 4.9</td>
<td>24.7 ± 4.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Maturation rate (%)</td>
<td>47.01</td>
<td>58.98</td>
<td>0.051</td>
</tr>
<tr>
<td>Embryos</td>
<td>5.8 ± 1.9</td>
<td>4.1 ± 2.6</td>
<td>0.04</td>
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</tbody>
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Differences in clinical and embryological parameters between group of PCOS women with BMI ≥ 30 kg/m² and group of PCOS women with BMI <30 kg/m² undergoing IVM.

<table>
<thead>
<tr>
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<th>BMI ≥ 30</th>
<th>BMI &lt; 30</th>
<th>p</th>
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<tbody>
<tr>
<td>No. of oocytes retrieved</td>
<td>19.05 ± 6.14</td>
<td>6.87 ± 3.53</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Conclusions**

- Our study indicates the importance of evaluating insulin metabolism and BMI prior to infertile PCOS women enter IVM procedure.

- Pretreatment with insulin sensitizers?
- Weight – loss interventions?
Challenges of IVM

- Process of oocyte maturation is still poorly understood!
- Less effective than IVF
- Lower implantation rate!
- Risk of congenital abnormalities?
- Imprinting problems?
- Long term follow up is needed!

Summary

- IVM offers elimination of the risk of OHSS!
- So far, there have been no alarming reports on the safety of the IVM procedure or on the normality of the babies born!
- Improvement of clinical management (endometrium receptivity, embryo quality) and culture techniques will lead to improvement in clinical pregnancy!