NEW APPROACHES OF OVARIAN STIMULATION IN POOR RESPONDERS

P Devroey
Poor Ovarian Response

- Poor
- Low
- Bad
- Slow
- Inadequate
- Suboptimal
First Description

- Decreased follicular response
- Low E2 levels
- Few oocytes
Definition of poor response

- Advanced maternal age (or other risk factor)
- Previous poor ovarian response (POR)
- Abnormal ovarian reserve test
- Two times of POR after maximal stimulation

Ferraretti AP et al. Hum Reprod 2011
Systematic review of RCT

- Randomized trials n=47
- 41 different definitions for POR
- Only 3 trials use the same definition
- Age and antral follicle count adopted in 9%
- Number of follicles retrieved adopted in 40%

Polyzos NP, Devroey P FS 2011
Risk factors associated with POR

- Chromosomal aberrations
- Ovarian endometriomas
- Ovarian surgery
- Chemotherapy
- Shortening of the menstrual cycle

De Vos et al. 2010
Gleicher et al. 2009
Garcia-Velasco and Somigliana 2009
Brodin et al. 2008
Is there an ideal protocol?

- Gonadotropins 300IU
- Increase of FSH starting dose does not result in higher pregnancy rates

Berkkanoglu and Ozgur FS 2010
Is there an ideal protocol?

- GnRH analogues
- GnRH antagonist
- Number gonadotropin ampoules (NS)
- Number of oocytes (NS)

Kyrou D et al. FS 2009
Pu D et al. Hum Reprod 2011
Alternative approaches

- Addition of estradiol in the luteal phase
- Meta-analysis showed increase of clinical pregnancy rate
- Important methodological pitfalls in this meta-analysis

Reynolds KA et al. Hum Reprod 2013
Polyzos NP and Tournaye H Hum Reprod 2014
Alternative approaches

- Addition of recombinant LH
- Recent meta-analysis of 40 RCT’s demonstrated significantly higher clinical pregnancy rates
- The addition of r-hLH may be beneficial

LH pretreatment Bologna POR

- **Study design**
  - Group A  FSH 400 IU
  - Group B  150 IU LH + FSH 400 IU

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Delivery rate per ET</td>
<td>1/10 (10%)</td>
<td>7/17 (41%)</td>
</tr>
<tr>
<td>Delivery rate per patients</td>
<td>1/21 (5%)</td>
<td>7/22 (32%)</td>
</tr>
</tbody>
</table>

Alternative approaches

• Addition of growth hormone (GH)
• Action of FSH on granulosa cells is modulated
• Two meta-analysis of 128 patients suggest in a significant increase in live birth rates
• The data are not robust

Kyrou D et al. FS 2009
Eftekhar M et al. Archives of Gynaecology and Reproduction 2013
Alternative approaches

- Addition of androgens
- Conversion of androgens to estrogens
- Administration of DHEA
- Meta-analysis demonstrated significantly higher ongoing pregnancy rates
- No robust data urgent need for multicentre RCT

Casson P.R. et al. FS 1998
Sunkara S.K. and Coomarasamy A. FS 2011
Sunkara S. K. et al. HR 2012
Alternative approaches

- Addition of aspirin
- Based on impaired ovarian blood flow
- RCT’s did not improve outcome
- Recent meta-analysis demonstrated no difference in the low dose aspirin group compared to the control group

Alternative approaches

• Natural cycles IVF
• Retrospective cohort trial
• 469 natural cycles
  • 390 cycles poor ovarian response
  • 79 cycles normal responders
• 2.6% Live birth rates in poor responders
• 8.9% Live birth rate in normal responders
• p = 0.006

## IVF versus IUI in Bologna POR

<table>
<thead>
<tr>
<th>Cycles n=461</th>
<th>Pregnancy Rates (%)</th>
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<tbody>
<tr>
<td></td>
<td>Age ≤ 40</td>
</tr>
<tr>
<td>IVF (n=184)</td>
<td>13 %</td>
</tr>
<tr>
<td>IUI (n=141)</td>
<td>2 %</td>
</tr>
<tr>
<td>Cancellation (n=136)</td>
<td>-</td>
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</table>

Quinquin M et al. FS 2014
Alternative approaches

• Oocyte cryopreservation
• It is a non experimental procedure
• The most important breakthrough in our decade
• Proposal vitrification of oocytes over several stimulation cycles
• Robust data are needed

Cobo A. et al. RBM Online 2012
Considerations

• Insufficient evidence exists
• Will long acting gonadotropins (corifollitropin alfa) be efficacious
• Need for properly designed studies
• Bologna Criteria are a step forward
• Oocyte vitrification for fertility preservation could be an option

Addition of highly purified HMG after corifollitropin alfa in POR

- **Stimulation protocol**
  - Elonva + 300 IU Menopur
  - GnRH antagonist from day 7 of the cycle

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<thead>
<tr>
<th></th>
<th>Patients &lt; 40 y</th>
<th>Patients ≥ 40 y</th>
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<tbody>
<tr>
<td>Number</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>8/29 (28%)</td>
<td>0/18 (0%)</td>
</tr>
</tbody>
</table>

Polyzos NP et al. Hum Reprod 2013
Strategy

• Expected POR
• Proven POR
• Expected and proven POR
Expected POR

- > 40 years of age
- ≤ 3 oocytes
- AFC low ( <5 )
- AMH low (<1.1 ng/ml)
- FSH increased (> 12 U/L)
Ovarian Sensitivity Index (OSI)

The number of retrieved oocytes is divided by the total dose of FSH (per 1,000IU)

Li HW et al. JAR 2014
Conclusions

• No therapy has proven to be efficient
• The concept of expected POR has to be developed
• RCT’s are mandatory