From POR to low prognosis
New Poseidon Group stratification

Peter Humaidan
Overview

• Definition of POR

• Diagnosis and age related prognosis

• POSEIDON stratification of low prognosis

• Concluding remarks
DEFINITION OF POOR RESPONDER (LOW PROGNOSIS)
The poor responder patient

Agreeing about a definition...
The poor responder patient

A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the end of the tunnel?

Nikolaos P. Polyzos, M.D., Ph.D., and Paul Devroey, M.D., Ph.D.
Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium

Objective: To assess the definitions for “poor ovarian responders” used among randomized trials for the treatment of women with impaired response to stimulation.

Design: Systematic review.

Setting: None.

Patient(s): Poor ovarian responders.

Intervention(s): Treatment modalities for the management of poor ovarian responders.

Main Outcome Measure(s): Number and nature of the criteria used to define poor ovarian response to stimulation and threshold values used.

Result(s): Among 47 randomized trials, 41 different definitions for the patients with poor ovarian response have been used. No more than 3 trials used the same definition, whereas even trials from the same research groups used different definitions across different trials. None of the criteria used was adopted in more than 50% of the trials. Age and antral follicle count were adopted only in 9% of the definitions, whereas the criteria of number of follicles on the final stimulation day and number of oocytes retrieved were used in more than 40% of the trials; nonetheless, even for these criteria, the threshold values were consistently different.
Definitions of Poor responders (low prognosis)

A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the end of the tunnel?

Nikolaos P. Polyzos, M.D., Ph.D., and Paul Devroey, M.D., Ph.D.

- 47 RCT
- 41 Definitions

- Age
- Previous trials
- AFC
- FSH
- Follicles, n
- Oocytes retrieved, n
- E2
- Good quality embryos
- FSH consumption

Polyzos and Devroey, Fertil Steril 2011
The 2011 Bologna-ESHRE criteria for poor responders

At least two of the following three features must be present:

– Advanced maternal age (≥40 years) or any other risk factor for POR
– A previous POR (≤3 oocytes with a conventional stimulation protocol)
– An abnormal ovarian reserve test (i.e. antral follicle count < 5–7 follicles or AMH< 0.5 – 1.1 ng/mL)

– Poor responder if - Two previous episodes of POR after maximal stim
The 2011 Bologna-ESHRE criteria for poor responders

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Poor responder if:

- Two previous episodes of POR after maximal stim
Bologna criteria and clinical daily life

• Bologna POR are classified as a single population of patients – although they are not (heterogenous group)

• Confusion exists between real poor response to the treatment and potential causes of the poor response

• Bologna POR - mathematical model – does not take age related effect on oocyte quality into consideration
Confused on a higher level...
“Follicle output ratio”

Gallot et al., Hum Reprod 2012
Number of oocytes and cumulative live birth rates

Drakopoulos et al., 2016

**Table 1** IVF outcome for groups of women with different ovarian response.

<table>
<thead>
<tr>
<th>Ovarian response groups</th>
<th>Group A 1–3 oocytes</th>
<th>Group B 4–9 oocytes</th>
<th>Group C 10–15 oocytes</th>
<th>Group D &gt;15 oocytes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 83</td>
<td>n = 471</td>
<td>n = 327</td>
<td>n = 218</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.8 (3.9)</td>
<td>31.6 (4.1)</td>
<td>30.5 (3.8)</td>
<td>30.3 (3.5)</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 (4.9)</td>
<td>23.9 (4.8)</td>
<td>23.2 (4.3)</td>
<td>22.9 (3.7)</td>
<td>0.11&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indication of IVF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (7.4%)</td>
<td>222 (39.3%)</td>
<td>175 (30.1%)</td>
<td>126 (22.3%)</td>
<td>0.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>6 (18.8%)</td>
<td>16 (50%)</td>
<td>5 (15.6%)</td>
<td>5 (15.6%)</td>
<td></td>
</tr>
<tr>
<td>Tubal</td>
<td>7 (8.3%)</td>
<td>39 (46.4%)</td>
<td>25 (29.8%)</td>
<td>13 (15.5%)</td>
<td></td>
</tr>
<tr>
<td>Ovulatory</td>
<td>6 (7.6%)</td>
<td>35 (44.3%)</td>
<td>23 (29.1%)</td>
<td>15 (19%)</td>
<td></td>
</tr>
<tr>
<td>Unexplained</td>
<td>22 (6.5%)</td>
<td>159 (46.9%)</td>
<td>99 (29.2%)</td>
<td>59 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>Duration of stimulation</td>
<td>9.2 (2.2)</td>
<td>9.3 (1.8)</td>
<td>8.9 (1.6)</td>
<td>8.9 (1.3)</td>
<td>0.018&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Insemination method</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVF</td>
<td>12 (9.7%)</td>
<td>55 (44.3%)</td>
<td>38 (30.7%)</td>
<td>19 (15.3%)</td>
<td>0.6&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ICSI</td>
<td>59 (7.8%)</td>
<td>322 (42.5%)</td>
<td>219 (28.9%)</td>
<td>158 (20.8%)</td>
<td></td>
</tr>
<tr>
<td>IVF + ICSI</td>
<td>12 (5.5%)</td>
<td>94 (43.3%)</td>
<td>70 (32.3%)</td>
<td>41 (18.9%)</td>
<td></td>
</tr>
<tr>
<td>Fertilization rate</td>
<td>60.64% (34.6%)</td>
<td>63.4% (24.7%)</td>
<td>60.5% (20.3)</td>
<td>56.9% (20.5)</td>
<td>0.003&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>2.3 (0.7)</td>
<td>6.6 (1.6)</td>
<td>12.1 (1.7)</td>
<td>22 (7.6)</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Day of embryo transfer in the fresh cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>43 (10.9%)</td>
<td>189 (48%)</td>
<td>113 (28.7%)</td>
<td>49 (12.4)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Day 5</td>
<td>22 (3.6%)</td>
<td>241 (38.9%)</td>
<td>205 (33.1%)</td>
<td>152 (24.5%)</td>
<td></td>
</tr>
<tr>
<td>No embryo transfer in the fresh cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Moderate-severe OHSS</td>
<td>19 (22.9%)</td>
<td>45 (9.6%)</td>
<td>11 (3.4%)</td>
<td>24 (11%)</td>
<td></td>
</tr>
<tr>
<td>Live birth in the fresh cycle*</td>
<td>14 (16.9%)</td>
<td>140 (29.7%)</td>
<td>111 (33.4%)</td>
<td>70 (32.1%)</td>
<td>0.02&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cumulative live birth*</td>
<td>18 (21.7%)</td>
<td>187 (39.7%)</td>
<td>165 (50.5%)</td>
<td>134 (61.5%)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Strong association between number of oocytes and cumulative LBR (fresh+frozen)

*Age adjusted (OR: 0.9; 95% CI: 0.9-1.01); Drakopoulos et al HR 2016; Published Online Jan 2
Influence of age on oocyte yield

“ANDROFERT”, January 2008 to December 2015; N=5,892

Mean ± SD Number of oocytes per age group

“ANDROFERT”, January 2008 to December 2015; N=5,892

Courtesy of Dr Sandro Esteves,
Influence of age on oocyte quality

Mitochondrial function impaired (less energy)

Granulosa cell apoptosis increased (quality)

Oxidative stress increased (quality)

Ben-Meir et al. Aging Cell 2015
Weall et al. Reproduction 2015
Age related euploidy rate in oocytes

Euploidy rate in oocytes (N=1776) aCGH

- 60
- 50
- 40
- 30
- 20
- 10
- 0

≤30Y  31-35Y  36-37Y  38-40Y  ≥41Y

- euploid
- balanced oocytes

Courtesy of Dr. R. Fischer, Hamburg Fertility Center
Aneuploidy rates in embryos increase with age

<table>
<thead>
<tr>
<th># Day 5 embryos</th>
<th>egg</th>
<th>&lt;35</th>
<th>35–39</th>
<th>40–42</th>
<th>&gt;42</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3</td>
<td>30%</td>
<td>40%</td>
<td>50%</td>
<td>70%</td>
<td>85%</td>
</tr>
<tr>
<td>4–6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7–10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

7753 embryos from 900 IVF cycles and 60 clinics
One more oocyte makes a **clinical** difference in live birth rate for all age groups


Stimulation does not increase the aneuploidy rate

**TABLE 2.** Results of the PGS of 46 donors who fulfilled both the unstimulated and ovarian stimulated cycles

<table>
<thead>
<tr>
<th></th>
<th>Unstimulated cycle</th>
<th>Stimulated cycle</th>
<th>Relative risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of biopsied embryos</td>
<td>46</td>
<td>307</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of informative embryos</td>
<td>46</td>
<td>303</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blastomeres on d 3 (mean ± sp)</td>
<td>7.4 ± 1.4</td>
<td>7.9 ± 0.9</td>
<td>1.17 (0.77–1.77)</td>
<td>0.45</td>
</tr>
<tr>
<td>Fragmentation on d 3 (mean ± sp)</td>
<td>7.4 ± 6.2</td>
<td>9.1 ± 4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of chromosomally abnormal embryos/</td>
<td>16/46 (34.8%)</td>
<td>123/303 (40.6%)</td>
<td>1.17 (0.77–1.77)</td>
<td>0.45</td>
</tr>
<tr>
<td>informative embryos [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean chromosomally abnormal embryos rate per subjecta (%)</td>
<td>34.8 (95% CI = 20.5–49.1)</td>
<td>38.2 (95% CI = 30.5–45.8)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>No. of blastocysts on d 5/biopsied embryo [n (%)]</td>
<td>31/46 (67.4%)</td>
<td>238/307 (77.5%)</td>
<td>1.15 (0.93–1.42)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Data are presented as mean ± sp or n (percent). P value <0.05 is considered statistically significant.

*a* Paired-samples t test.

**FIG. 3.** Type of chromosome involved in the aneuploid embryos group. No statistically significant differences (P > 0.05) were observed in any of the analyzed chromosomes between the unstimulated and the stimulated cycle. Chrom., Chromosome.
DIAGNOSIS & PROGNOSIS
AFC and AMH roughly estimate ovarian reserve

Who has the highest chance of pregnancy?

Age 28
AMH 0.70 ng/ml
2 episodes POR

Age 42
AMH = 1.2 ng/ml
1 episode POR
Age and delivery rate
20 years’ experience - the Swiss ART registry

Swiss Med Wkly. 2015;145:w14087
POSEIDON STRATIFICATION
A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept

Poseidon Group (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number), Carlo Alviggi, M.D., Ph.D., Claus Y. Andersen, D.M.Sc., Klaus Buehler, M.D., Alessandro Conforti, M.D., Giuseppe De Placido, M.D., Sandro C. Esteves, M.D., Ph.D., Robert Fischer, M.D., Daniela Galliano, M.D., Ph.D., Nikolaos P. Polyzos, M.D., Ph.D., Sesh K. Sunkara, M.D., M.R.C.O.G., Filippo M. Ubaldi, M.D., Peter Humaidan, D.M.Sc.

OPINION ARTICLE
The novel POSEIDON stratification of ‘Low prognosis patients in Assisted Reproductive Technology’ and its proposed marker of successful outcome [version 1; referees: 2 approved, 1 approved with reservations]

Peter Humaidan¹,², Carlo Alviggi³, Robert Fischer⁴, Sandro C. Esteves ⁵
Poseidon: From poor response to low prognosis

**Poor reserve**

- **Group 3:**
  - < 35 years poor reserve predicted
  - AFC < 5, AMH < 1.2 ng/ml

- **Group 4:**
  - > 35 years poor reserve predicted
  - AFC < 5, AMH < 1.2 ng/ml

**Poseidon group**

- Group 1:
  - < 35 years good reserve – unexpected poor response
  - 1a: < 4 oocytes
  - 1b: 4-9 oocytes

- Group 2:
  - > 35 years good reserve – unexpected poor response
  - 2a: < 4 oocytes
  - 2b: 4-9 oocytes

**Good reserve**

- Group 1:
  - < 35 years good reserve – unexpected poor response
  - 1a: < 4 oocytes
  - 1b: 4-9 oocytes

- Group 2:
  - > 35 years good reserve – unexpected poor response
  - 2a: < 4 oocytes
  - 2b: 4-9 oocytes

Fertil Steril 2016
Treatments will be based on these low prognosis categories

**Good Ovarian Reserve**

**UNEXPECTED LOW RESPONSE**
- **YOUNG**

**Reasons for low Response:**
- FSH dose does not reach threshold
- Genetic polymorphism of FSH-R; LH-R; V-LH -β
- (Asynchronous development)

**UNEXPECTED LOW RESPONSE**
- **OLD**

"Good reserve - good quality"

**iCOS Treatment:**
- GnRH Antagonist
- Increase rFSH dose
- Add LH activity
- Synchronize follicle wave before COS (E2, OCP)
- Fresh transfer

Poseidon Group, Fertil Steril 2016
Treatments will be based on these low prognosis categories

**Good Ovarian Reserve**
- 
- Increase rFSH and add rLH
- HCG or GnRHa trigger
- Blastocyst culture
- Synchronize follicle wave before COS (E2, OCP)
- Fresh transfer or segmentation

**UNEXPECTED LOW RESPONSE YOUNG**

**UNEXPECTED LOW RESPONSE OLD**

**Reasons for low Response:**
- FSH dose does not reach threshold
- Genetic polymorphism of FSH-R; LH-R; V-LH –β
- Asynchronous development

Poseidon Group, Fertil Steril 2016
Treatments will be based on these low prognosis categories

Good Ovarian Reserve

Unexpected Low Response
Young

Old

Unexpected Low Response
Old

Young

Poor Ovarian Reserve

Poseidon Group, Fertil Steril 2016
Treatments will be based on these low prognosis categories

“Poor reserve - good quality”

iCOS Treatment:
- Long GnRHa protocol
- GnRH antagonist (E2, OCP)
- Stimulation up to 300 IU/d rFSH
- DuoStim (Ubaldi et al., 2015)
- Androgens? (DHEA, testosterone)

- Fresh transfer
- Oocyte/embryo accumulation and FET

Reasons for low Response:
- Poor ovarian reserve
- Asynchronous development
- (Genetic polymorphism of FSH-R; LH-R; V-LH –β)

Poseidon Group, Fertil Steril 2016
Treatments will be based on these low prognosis categories

Good Ovarian Reserve

- UNEXPECTED LOW RESPONSE
  - YOUNG

- OLD

Poor Ovarian Reserve

- UNEXPECTED LOW RESPONSE
  - OLD

- YOUNG

Poseidon Group, Fertil Steril 2016
Treatments will be based on these low prognosis categories

**Reasons for low Response:**
- Poor ovarian reserve
- Asynchronous development
- (Genetic polymorphism of FSH-R; LH-R; V-LH –β)

**Poor Ovarian Reserve**

*iCOS Treatment:*
- Long GnRHa protocol
- GnRH antagonist (E2, OCP)
- Stimulation up to 300 IU/d rFSH and LH
- Androgens (DHEA, testosterone)?
- GH?
- DuoStim (Ubaldi et al., 2015)
- Fresh transfer
- Segmentation – oocyte/embryo accumulation and FET
- (Oocyte donation)

“Poor reserve – poor quality”

Poseidon Group, Fertil Steril 2016
What is the number of oocytes necessary to obtain at least one euploid embryo for transfer in each patient

Humaidan et al., F1000Res, 2016 dec 23
CONCLUSIONS
Poseidon Principles for Low Prognosis patients
Individualized approach including all steps of IVF

• GnRH analogue regimen
• Gonadotropin dose and drug type
• Trigger strategy
• Combined strategies (Duostim)
• Adjuvant therapies
• Personalization in lab technologies
Thank You
peter.humaidan@midt.rm.dk