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Declared receipt of honoraria or consultation fee from Merck Serono
9th IVF Preceptorship: current practice in the 21st century

24-25 September 2015
Madrid and Alicante, Spain
PCOS vs Poor responders: the extremes of ovarian response

Professor Hakan Yaralı, MD
Anatolia IVF and Women’s Health Center
&
Hacettepe University, School of Medicine, Dept. of OB/GYN
Agenda-Poor Ovarian Responder

• Definition
• Which is the best COS protocol?
• Adjuvant treatment; oocyte/embryo accumulation; IVA; PGS
• Conclusions
Definition: ESHRE Consensus-Bologna Criteria

1. Advanced maternal age (≥ 40 y) or any other risk factor for POR
2. A previous POR (≤3 oocytes after a conventional stimulation protocol)
3. An abnormal ovarian reserve test (AFC: 5–7 or AMH: 0.5-1.1 ng/ml)

2/3 previous episodes of POR after maximal stimulation
... but is Bologna criteria ideal?

- Sallam et al-HR 2011
- Younis et al-HR 2011
- Papathanasiou A-HR 2014
- Venetis CA-HR 2014
- Ferraretti et al-HR 2014

Homogenous subgroups for live birth rates or not?
## Subgroups – Bologna ESHRE criteria

<table>
<thead>
<tr>
<th>Categories</th>
<th>Subgroups</th>
<th>ESHRE criteria fulfilled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No previous IVF attempt</strong></td>
<td>≥40 yr (± Risk factor for POR) + Abnormal ORT</td>
<td>1 + 3</td>
</tr>
<tr>
<td>1 previous IVF attempt with POR</td>
<td>≥40 yr (± Risk factor for POR)</td>
<td>1 + 2</td>
</tr>
<tr>
<td></td>
<td>Abnormal ORT</td>
<td>2 + 3</td>
</tr>
<tr>
<td></td>
<td>≥40 yr (± Risk factor for POR) + Abnormal ORT</td>
<td>1 + 2 + 3</td>
</tr>
<tr>
<td>2 previous IVF attempts with POR</td>
<td>No risk factor for POR and normal ORT</td>
<td>Supplemental criterion 4</td>
</tr>
<tr>
<td></td>
<td>≥40 yr (± Risk factor for POR) but normal ORT</td>
<td>1 + Supplemental criterion 4</td>
</tr>
<tr>
<td></td>
<td>Abnormal ORT but no risk factor for POR</td>
<td>3 + Supplemental criterion 4</td>
</tr>
<tr>
<td></td>
<td>≥40 yr (± Risk factor for POR) and abnormal ORT</td>
<td>1 + 3 + Supplemental criterion 4</td>
</tr>
</tbody>
</table>

8 Subgroups (even 13)
Bologna Criteria-Subgroups
(From the database of 14,775 patients; 2005-Jan 2014)

Cancellation & Live Birth/Cycle Rates

1,257 PORs-Bologna Criteria

- ≥ 40 yr
- ≤ 3 oocytes
- AFC<7

- 32.4% \(^{a,b}\) a, b, c: p<0.01
- 37.4%
- 50.0\(^{a}\)
- 2.3\(^{c}\)
- 47.0\(^{b}\)
- 6.3%
- 3.3%
- 8.7\(^{c}\)
Bologna Criteria- 5 Subgroups

**Similar live birth rates**

- **Busnelli et al. Hum Reprod 30; 315 – 322, 2015**
  - N=362; Live birth rate= 0-10%
- **La Marca et al. J Assist Reprod Genet May 2015**
  - N=210; Live birth rate= 5.5-7.4%
Agenda-Poor Ovarian Responder

• Definition
• Which is the best COS protocol?
  • Adjuvant treatment; oocyte/embryo accumulation; IVA; PGS
• Conclusions
What is your preferred COS regimen for Poor Responders? (45 countries; 196 centers; 124,700 cycles)

- **GnRH agonist short protocol**: 53%
- **GnRH agonist long protocol**: 15%
- **GnRH antagonist**: 20%
- **GnRH agonist using flexible regimen**: 9%
- **Short protocols microdose**: 2%
- **No analogues**: 1%

GnRH\textsubscript{ant} vs GnRH\textsubscript{a} - Meta-analysis (12 RCT’s)

- **Cycle cancellation**
  - Antagonist vs Long Agonist Protocol
    - OR = 1.34 (0.86–2.11)
  - Antagonist vs Short Agonist Protocol
    - OR = 1.08 (0.75–1.57)

- **Clinical Pregnancy Rate**
  - Antagonist vs Long Agonist Protocol
    - OR = 0.79 (0.54–1.14)
  - Antagonist vs Short Agonist Protocol
    - OR = 1.33 (0.88–2.01)

- **Significantly less duration of stimulation and FSH dose with GnRH\textsubscript{ant} use compared to GnRH\textsubscript{a}long protocol**
# Poor Responders Interventional Trial (PRINT)-RCT

<table>
<thead>
<tr>
<th></th>
<th>Long agonist (n=31)</th>
<th>Short agonist (n=31)</th>
<th>GnRH-ant (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total FSH consumption (IU)</td>
<td>5540±1216&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>4819±1145&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4740±1131&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cycles reaching ET (%)</td>
<td>24 (77.4)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>17 (54.8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13 (43.3)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>No. of oocytes</td>
<td>4.42±3.06&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.71±1.60&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.30±2.91</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>1.7±0.5</td>
<td>1.6±0.5</td>
<td>1.8±0.6</td>
</tr>
<tr>
<td>Ongoing pregnancy, %</td>
<td>8.1%</td>
<td>8.1%</td>
<td>16.2%</td>
</tr>
</tbody>
</table>

<sup>a</sup>: p=0.02; <sup>b, c</sup>: p=0.01
### 300 vs 450 vs 600 IU FSH-Any difference in outcome?

<table>
<thead>
<tr>
<th></th>
<th>300 IU (n=38)</th>
<th>450 IU (n=39)</th>
<th>600 IU (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of oocytes</td>
<td>5.2 ± 0.4</td>
<td>6.3 ± 0.7</td>
<td>6.6 ± 0.6</td>
</tr>
<tr>
<td>No. of embryos trans.</td>
<td>2.5 ± 0.3</td>
<td>2.5 ± 0.3</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>ET cancellation</td>
<td>9%</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Live birth / cycle</td>
<td>11%</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Live birth / ET</td>
<td>13%</td>
<td>12%</td>
<td>13%</td>
</tr>
</tbody>
</table>

All non-significant
What if conventional protocol fails..

Since gonadotropins cannot manufacture follicles de novo..

Let’s reduce patient burden and...

Mild IVF

Modified Natural Cycle IVF

With/without Adjuvant treatment
## Mild IVF/Modified Natural Cycle IVF-RCTs

<table>
<thead>
<tr>
<th>Author</th>
<th>Minimal Stimulation / Natural cycle</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Protocol</td>
</tr>
<tr>
<td>Ragni et al-2012</td>
<td>145</td>
<td>CC-150 mg/d</td>
</tr>
<tr>
<td>Revelli et al-2014</td>
<td>355</td>
<td>CC-100 mg/d+150 IU FSH+GnRHant</td>
</tr>
<tr>
<td>Mohsen et al-2013</td>
<td>30</td>
<td>Natural cycle + hCG</td>
</tr>
<tr>
<td>Morgia et al-2004</td>
<td>59 (114 cycles)</td>
<td>Natural cycle + hCG</td>
</tr>
</tbody>
</table>

<sup>a</sup>: p<0.01
Modified Natural Cycle-PORs fulfilling Bologna Criteria

**Outcome**

- **Polyzos et al-2012**
  - 136 patients; 390 cycles; No sub-group distinction was made
  - Live birth/cycle= 2.6% (10/390)
  - Did not differ among age groups (≤35 y, 36–39 y and ≥40 y)

- **Kedem et al-2014**
  - N=111; ≤ 3 oocytes with FSH> 300 IU daily
  - Live birth/cycle= 0.9% (1/111)

- **Lainas et al-2015**
  - Modified NC (161 cycles) vs High-Dose-FSH GnRN-ant (164 cycles)
  - Live birth rate of 7.5% vs 3.1%
  - OR= 4.01; 95% CI: 1.14-14.09
Agenda-Poor Ovarian Responder

• Definition
• Which is the best COS protocol?
• Adjuvant treatment; oocyte/embryo accumulation; IVA; PGS
• Conclusions
Adjuvant treatment

• Androgens & Androgen Modulating Drugs
  • LH
  • Transdermal testosterone
  • DHEA
  • Aromatase inhibitors
• Growth Hormone
• Luteal E/GNRH-ant treatment
• Other: Pyridostigmine; Aspirin; L-arginine
ACCUMULATION OF OOCYTES/EMBRYOS
What number is a good number to accumulate?

Decisional making model based on recursive partitioning analysis

<table>
<thead>
<tr>
<th>Delivery</th>
<th>%</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.000</td>
<td>71.6</td>
<td>322</td>
</tr>
<tr>
<td>&gt; 0.000</td>
<td>28.4</td>
<td>128</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
<td>450</td>
</tr>
</tbody>
</table>

Number of vitrified MIL phase oocytes

Female age

<table>
<thead>
<tr>
<th>Delivery</th>
<th>%</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.000</td>
<td>77.4</td>
<td>263</td>
</tr>
<tr>
<td>&gt; 0.000</td>
<td>22.6</td>
<td>77</td>
</tr>
<tr>
<td>Total</td>
<td>75.6</td>
<td>340</td>
</tr>
</tbody>
</table>

Day of transfer

<table>
<thead>
<tr>
<th>Delivery</th>
<th>%</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.000</td>
<td>87.4</td>
<td>97</td>
</tr>
<tr>
<td>&gt; 0.000</td>
<td>12.6</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>24.7</td>
<td>111</td>
</tr>
</tbody>
</table>

Blastocyst

<table>
<thead>
<tr>
<th>Delivery</th>
<th>%</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.000</td>
<td>59.3</td>
<td>48</td>
</tr>
<tr>
<td>&gt; 0.000</td>
<td>40.7</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>18.0</td>
<td>81</td>
</tr>
</tbody>
</table>

Rienzi et al, HR. 2012
How many eggs should be frozen to obtain one live birth?

The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophotoderm biopsies evaluated with comprehensive chromosomal screening

How many eggs should I freeze?

To the Editor: We read with great interest the recent publication by Fransasiak et al. (1). They retrospectively report the largest published series to date of blastocysts screened for aneuploidy. It brings to mind a question that often is presented to the infertility specialist with regard to elective oocyte cryopreservation to defer childbearing. How many oocytes should be frozen at a given age to obtain one live birth? Using data from the Fransasiak et al. article, additional data from the same subjects, and some arithmetic extrapolation, perhaps we can make an informed estimate of this number as follows:

Patients when counseling them in response to a question that we will inevitably hear more and more frequently in the coming years.

Edward J. Nejat, M.D., M.B.A.
Janelle Luk, M.D.
John Zhang, M.D., Ph.D., H.C.L.D.
New Hope Fertility Center, New York, New York

April 17, 2014

http://dx.doi.org/10.1016/j.fertnstert.2014.05.008

Estimated number of oocytes needed per live birth (stratified by age)

\[
\text{Mean number of oocytes required to obtain one blastocyst} = \frac{\text{Percentage of blastocysts biopsied that are euploid} \times \text{Live birth rate per euploid blastocyst transfer}}{\text{Percentage of patients with live birth}}
\]
Accumulation of Oocytes: Advantages and Disadvantages

• **Advantages**
  - Less ET cancellations
  - Will reduce significant drop-out rate (over 75%)
  - Palliate the psychological distress caused by repeated failures
  - Higher live birth rate per intention-to-treat patient

• **Disadvantages**
  - Unnecessary stimulations if the pregnancy is achieved from the 1\textsuperscript{st} cycle
  - Cost
Double stimulation (Shanghai Protocol)
Double stimulation (*Shanghai Protocol*)

- 38 POR’s (Bologno criteria)
- No. of oocytes harvested (167)
  - Stage I: 1.7±1.0; Stage II: 3.5±3.2
- 26/38 (68.4%) succeeded in producing 1-6 viable cryopreserved embryos
- 21 underwent 23 frozen ET’s resulting in 11 ongoing pregnancies (*47.8%*)
Quantity and Quality-Interlinked?

• Yes
  • Unilateral oophorectomy results in an immediate increase in the rate of oocyte aneuploidy (Brook et al-1984; Eichenlaub-Ritter et al-1988)
  • Increased chance of conceiving a genetically abnormal pregnancy or having a miscarriage for women with diminished OR (Freeman et al-2000; van Montfrans et al-2001; Sahu et al-2010; Grande et al-2014)

• No
  • No increase in the rate of embryo aneuploidy in women with low OR (Lie Fong et al-2008)
  • No increase in miscarriage (Tremellen and Kolo-2010)

Ongoing RCT (SOLAIRE) for PGS..
In Vitro Activation
Different courses of development of primordial follicles

1. Primordial follicles (sleeping, surviving)
2. Death of primordial follicles
3. Activation of primordial follicles

Ovarian aging
Fertility

PI3-Kinase Pathway

PI3-Kinase = Gas
PTEN = Brake
Ovarian Fragmentation and IVA promote follicle growth via different mechanisms.
Ovarian Fragmentation & IVA Treatment

- 27 patients with ovarian failure
- Duration of amenorrhea of $6.8 \pm 2.1$ y without spontaneous pregnancy
- 13/27 had residual follicles at histological examination
- 8/13 had successful growth secondary to ovarian fragmentation and IVA
- 5/8 had mature oocytes
- 2 had successful pregnancy following FET
- 1 healthy baby

Hsueh et al.  Endoc Rev Feb 2015  
Kawamura et al-2015
Conclusions-PORs

- Bologna criteria, while being a step forward, may still not be perfect
- Most studies are underpowered ("miniature") and single-center based
- No evidence for any particular COS protocol to improve treatment outcome. GnRH$_{ant}$ protocols may reduce treatment burden
- Insufficient evidence for most of the adjuvants to improve outcome
- Role of PGS?
- IVA may be promising in selected patients
Agenda-PCOS

- Which is the best COS protocol?
- Adjuvant treatment
- Conclusions
**HYPER-RESPONDER**

**Definition**
- > 15 oocytes

**Profile**
- AMH > 4 ng/mL
- AFC > 20
- PCOS type; mostly younger
- History of OHSS/multiple oocytes harvested in previous therapy

**Therapy**
- Antagonist
- 75-150 IU/d starting dose of rFSH
- GnRH-agonist trigger

**Incidence 15 %**

---

**Hyper-responder**
- Definition
- Profile
- Therapy
Haiyan Lin, Yu Li, Lin Li, Wenjun Wang, Dongzi Yang, Qingxue Zhang*
Department of Gynecology & Obstetrics, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China

### Ongoing pregnancy rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>GnRHa long protocol</th>
<th>GnRH antagonist protocol</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiann-Loung Hwang, 2004</td>
<td>23.4 2.9 24</td>
<td>23.2 2.8 25</td>
<td>11.0% 0.20 [-1.40, 1.80] 2004</td>
</tr>
<tr>
<td>Mahnaz Ashrafi, 2005</td>
<td>30.45 6.09 22</td>
<td>27.97 6.71 22</td>
<td>2.3% 2.48 [-1.31, 6.27] 2005</td>
</tr>
<tr>
<td>Trifon G, 2007</td>
<td>23.6 0 52</td>
<td>23.2 0 26</td>
<td>Not estimable 2007</td>
</tr>
<tr>
<td>Rafal Kurzawa, 2008</td>
<td>22.3 1.6 37</td>
<td>23.1 1.3 33</td>
<td>32.8% -0.80 [-1.48, -0.12] 2008</td>
</tr>
<tr>
<td>Marzieh Agha, 2010</td>
<td>0 0 0</td>
<td>0 0 0</td>
<td>Not estimable 2010</td>
</tr>
<tr>
<td>Ensieh, 2010</td>
<td>30.43 5.08 45</td>
<td>28.99 6.12 45</td>
<td>5.8% 1.44 [-0.88, 3.78] 2010</td>
</tr>
<tr>
<td>Trifon G, 2010</td>
<td>23.2 0 110</td>
<td>24.6 0 110</td>
<td>Not estimable 2010</td>
</tr>
<tr>
<td>Chung-Hoon Kim, 2012</td>
<td>22.7 2.9 103</td>
<td>22.9 3.1 103</td>
<td>27.5% -0.20 [-1.02, 0.62] 2012</td>
</tr>
<tr>
<td>Bulet, 2012</td>
<td>24.97 4.36 140</td>
<td>25.74 4.37 131</td>
<td>20.7% -0.31 [-0.90, 0.27] 2012</td>
</tr>
</tbody>
</table>

Total (95% CI) 533 497 100.0% -0.31 [-0.90, 0.27]

Heterogeneity: Tau² = 0.15; Chi² = 7.21, df = 5 (P = 0.21); I² = 31%
Test for overall effect: Z = 1.04 (P = 0.30)

OR: 1.05 (0.01-1.37)
**Agonist vs Antagonist-PCOS; Meta-analyses Severe OHSS**

- **Al-Inani et al-2011**
  - RD: **-0.10 %** (95%CI: -0.07 to -0.14)
    - Cancellation or coasting 53% less with antagonist (95% CI, 36-78)
- **Pundir et al-2012** a
  - RR: **0.60** (95% CI: 0.48-0.76)
- **Lin et al-2014**
  - OR: **1.56** (95% CI: 0.29-8.51)

a: Moderate or severe
Fertility management in the PCOS population: results of a web-based survey at IVF-worldwide.com

Paul R. Brezina · Virginia Mensah · Adam Balen · Milton Leong · Ariel Weissman · Yulian Zhao · Zeev Shoham

- 68 Nations; 262 centers
- Agonist (51%)
- Antagonist (46%)!
- Other (IVM, Natural cycle) (3%)
GnRHa Trigger: Benefits beyond OHSS...

- Avoidance of premature and massive stimulation in the early luteal phase by hCG
- Avoidance of prolonged hCG exposure which would rescue the ability of endometrial epithelial cells to respond to hCG (Evans et al-2013)
GnRH-a Trigger - OHSS

• With 1500 IU hCG rescue
  • Seyhan et al-2013

• Without hCG rescue (Cryo-all)
  • Fatemi et al-2014; Ling et al-2014; Gürbüz et al-2014; Santos-Ribeiro et al-2015
Metformin for IVF in PCOS – Meta-analysis

(10 RCTs; n=845)

• Live birth (7 RCT’s)
  – OR= 1.69 (95% CI: 0.85-3.34)

• OHSS (9 RCT’s)
  – OR= 0.27 (95% CI: 0.16-0.46)

• Miscarriage
  – OR= 0.50 (95% CI: 0.30-0.83)

Palomba et al. BJOG 2013; 120: 267-76
Cabergoline-Meta-analysis

• 8 RCT’s

• Moderate-Severe OHSS
  • RR= 0.38 (95% CI 0.29 to 0.51)

• Clinical pregnancy rate
  • RR= 1.02 (95% CI 0.78 to 1.34)
Conclusions – Hyper-responders

• GnRH$_{\text{ant}}$ is the protocol of choice

• Agonist trigger
  • Significant reduction of OHSS
  • Benefits beyond OHSS in fresh transfers

• Metformin and cabergoline co-treatment may lessen OHSS