

Individualising IVF: Introduction to the POSEIDON Concept



Introduction

The emergence of Personalized Medicine protocols for IVF.

- Differences between patients: age, ovarian reserve, BMI or presence of ovarian dysfunctions can impact IVF success
- IVF practice is currently extended to very diverse patient phenotypes and genotypes, *thus*
- Adapting the IVF procedure for each patient is crucial to optimise its efficacy and safety

**This represents the emergence of
Personalized Medicine for IVF.**

BMI, body mass index



Why Personalized Medicine in IVF?

Personalised medicine provides treatment protocols that are more specific, safer, targeted and cost-effective.



New More Detailed Stratification to Low Responders

Patient
Oriented
Strategies
Encompassing
Individualised
Oocyte
Number

A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept

The management of patients with impaired ovarian response (POR) remains a controversial and complex clinical issue, a topic of great interest for clinical practitioners. The concept of a different stratification of POR is, indeed, the number of oocytes retrieved was selected as a criterion of POR as one of the main, although not the final, marker of ovarian sensitivity during ovarian stimulation (1). To consider the definition of POR, several criteria (2) proposed new criteria. Based on the "response criteria" based on the number of oocytes retrieved, the concept of POR was defined as follows: (a) poor ovarian response (POR) and low ovarian response (LOR) were defined as <3 oocytes retrieved and <10 oocytes retrieved, respectively. (b) Moderate POR, which means with a low number of oocytes retrieved with a positive response of POR, was associated with a low number of oocytes retrieved and a low number of oocytes retrieved. (c) Moderate POR, which means with a low number of oocytes retrieved with a positive response of POR, was associated with a low number of oocytes retrieved and a low number of oocytes retrieved. (d) Moderate POR, which means with a low number of oocytes retrieved with a positive response of POR, was associated with a low number of oocytes retrieved and a low number of oocytes retrieved. (e) Moderate POR, which means with a low number of oocytes retrieved with a positive response of POR, was associated with a low number of oocytes retrieved and a low number of oocytes retrieved. (f) Moderate POR, which means with a low number of oocytes retrieved with a positive response of POR, was associated with a low number of oocytes retrieved and a low number of oocytes retrieved. (g) Moderate POR, which means with a low number of oocytes retrieved with a positive response of POR, was associated with a low number of oocytes retrieved and a low number of oocytes retrieved. 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The emergence of Personalized Medicine!



A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept, Alivaggi, Carlo et al., Fertility and Sterility, Volume 105, Issue 6, 1452 - 1453

POSEIDON Group Proposes...

- A more specific definition of the “low prognosis” patient ***introduces two new categories of impaired response:***
 - **Suboptimal response:** the retrieval of four to nine oocytes, at any given age, with a significantly lower live birth rate compared with normal responders
 - **Hypo-response:** higher dose of gonadotropins and more prolonged stimulation are required to obtain an adequate number of oocytes



Proposed New Stratification

- *Combines “qualitative” and “quantitative” parameters:*
 - Age of the patient and the expected aneuploidy rate
 - Biomarkers and functional markers (i.e., AMH and AFC)



Detailed Stratification of Low Responders

1

Patients <35 years, with sufficient ovarian reserve parameters (AFC \geq 5, AMH \geq 1.2 ng/mL), and with an unexpected poor or suboptimal ovarian response

Subgroup 1A: <4 oocytes and Subgroup 1B: 4-9 oocytes

2

Patients \geq 35 years, with sufficient ovarian reserve parameters (AFC \geq 5, AMH \geq 1.2 ng/mL), and with an unexpected poor or suboptimal ovarian response

Subgroup 2A: <4 oocytes and Subgroup 2B: 4-9 oocytes

3

Patients <35 years, with poor ovarian reserve parameters (AFC <5, AMH <1.2 ng/mL)

4

Patients \geq 35 years, with poor ovarian reserve parameters (AFC <5, AMH <1.2 ng/mL)

- The Poseidon group stratification of low responders to ovarian stimulation is more detailed than the Bologna criteria

Poseidon Group. Fertil Steril 2016

 Global Fertility Academy

Personalised Medicine requires that a range of treatment factors to be considered...

- **Type of gonadotrophin suppression**
 - Antagonist compared with long GnRH agonist protocols associated with a large reduction in OHSS
 - No evidence of a difference in live-birth rates
- **Dose of FSH**
 - An individualised FSH dose regimen in 'standard' patient population: \uparrow proportion of appropriate ovarian responses, \downarrow need for dose adjustments during COS
- **Administration of LH activity (LH, hMG, hCG)**
 - No specific biomarker for LH requirement
- **Choice of alternative protocols**

COS, controlled ovarian hyperstimulation; OHSS, ovarian hyperstimulation syndrome

Ah-Nany et al., Cochrane Database Syst Rev 2011
Popovic-Todorovic et al., Hum Reprod 2003

 Global Fertility Academy

Personalised Medicine *requires that a range of treatment factors to be considered...*

- Type of gonadotrophin suppression
 - Antagonist compared with long GnRH agonist protocols associated with a large reduction in OHSS
- **BUT WHY LH SUPPLEMENTATION?**
- Dose of FSH
 - An individualised FSH dose regimen in 'standard' patient population: ↑ proportion of appropriate ovarian responses, ↓ need for dose adjustments during COS
- **Administration of LH activity (LH, hMG, hCG)**
 - No specific biomarker for LH requirement
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Ah-Nany et al., Cochrane Database Syst Rev 2011
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The Role of Luteinizing Hormone in Follicular Phase

Since early follicular phase

Induction of androgens production in the theca cells



FSH receptor induction in granulosa cells-responsiveness

Act synergistically with IGF-1—growth
Increase in pre-antral and antral follicles—recruitability

Since intermediate follicular phase

- Expression of LH receptors in the granulosa
- Sustain of FSH-dependent granulosa activities, including aromatase induction and growth factors release
- IGF-1, EGF etc...
- Regulation of final follicle/oocyte maturation
- Optimization of steroidogenesis

Jeppesen et al., JCEM, 2012

Weil et al., 1999; Vendola et al., 1999; Vendola et al., 1998; 1999; Spinder et al., 1989; Jeppesen et al, JCEM, 2012.



The Valuable Role of LH in COS

- “ LH supplementation started:
 - Before COS; 1^o day of COS; Antagonist day; day 6^o - 8^o

- “ Subgroups of women
 - . Normo-responder; poor responder; hypo/suboptimal responder

- “ Dosing used
 - . 75 IU/day; 150 IU/day; 2:1 ratio

- “ Analogs regimen
 - Antagonist; Agonist

COS, controlled ovarian hyperstimulation;



Conclusions

- LH supplementation of GnRH antagonist stimulation improves IVF outcomes in subgroups of patients

- Must close the evidence gap and disseminate knowledge base supporting LH supplementation

- Incorporate LH supplementation within theme of personalized medicine



Conclusions (con't.)

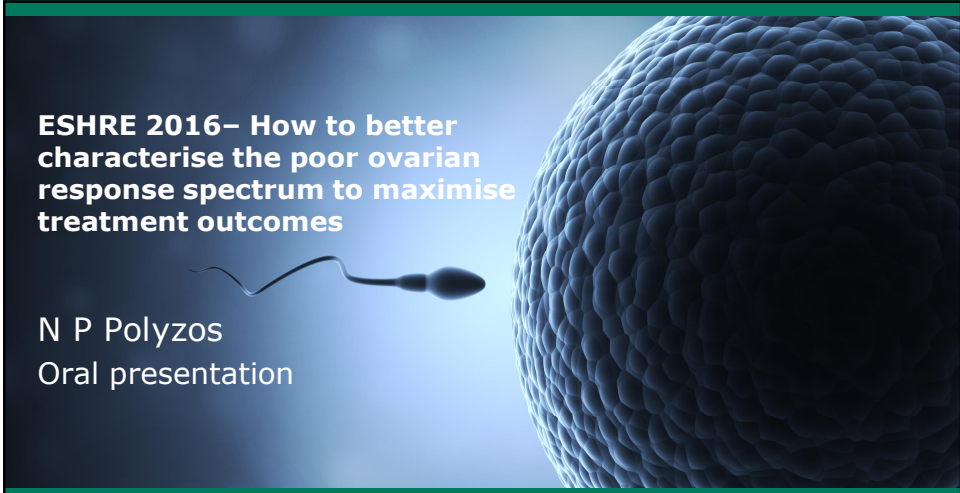
- Use the POSEIDON concept of low prognosis to collectively improve the management of patients undergoing assisted reproductive technologies
- Promote tailored approach to patient handling
- Identify more homogeneous populations for clinical trials



Conclusions (con't.)

- Provide better tools to maximize IVF success rates
- Optimize outcomes for the broadest base of IVF patients





ESHRE 2016– How to better characterise the poor ovarian response spectrum to maximise treatment outcomes

N P Polyzos
Oral presentation



Introduction

POSEIDON predicts presence of suboptimal responders and that LH supplementation is of value within certain subgroups.

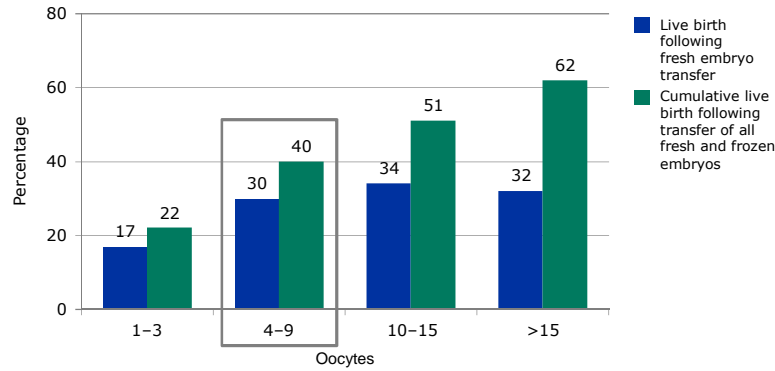
- The Bologna criteria defines women who are poor responders, *but*
 - Predicts no benefit of treatment in poor responders
- To better characterise the poor ovarian response spectrum and maximise treatment outcomes
 - Focus on intermediate prognosis groups of patients ('suboptimal responders')
 - 4–9 oocytes after conventional stimulation

BUT DO THEY EXIST?

Polyzos N P. Merck symposium. Presentation 2



Studies have demonstrated that suboptimal responders do exist



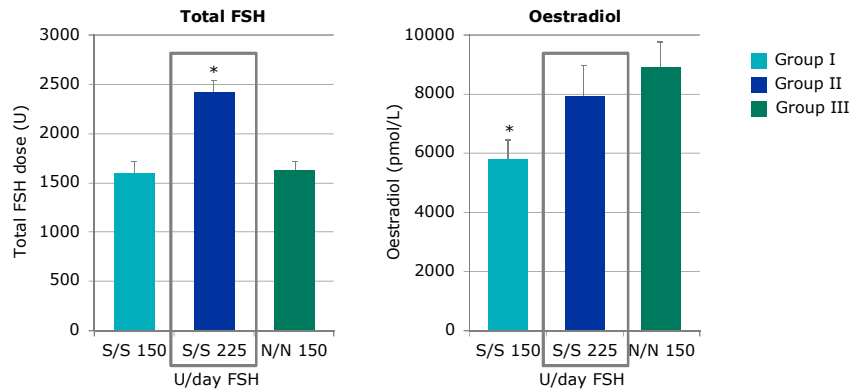
Drakopoulos et al., Hum Reprod 2016

- FSH receptor polymorphisms might be one reason that some patients respond suboptimally

Polyzos N P. Merck symposium. Presentation 2



Increased rFSH dose was found to be beneficial in poor responders



P < 0.05 between group II and group I + III
Behre et al., Pharmacogenet Genomics 2005

P < 0.05 between group I and group II + III

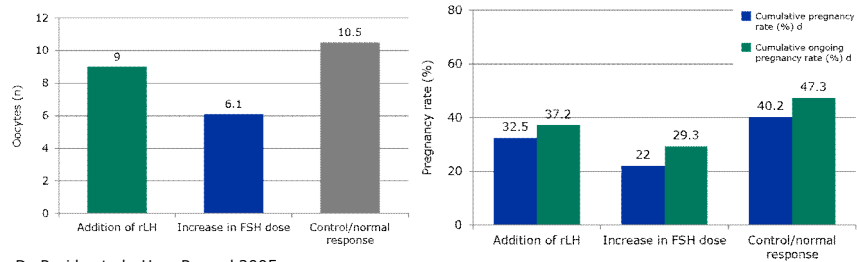
- Increasing the FSH dose from 150 to 225 U/day overcame the lower oestradiol response in women with Ser/Ser FSH receptor

N, asparagine; rFSH, recombinant follicle stimulating hormone; S, serine;

Polyzos N P. Merck symposium. Presentation 2



rLH supplementation was found to be more effective than increased rFSH dose



De Pacido et al., Hum Reprod 2005

- The initial ovarian response to rFSH can be suboptimal
- rLH supplementation is more effective than increasing rFSH dose in patients with an initial inadequate ovarian response to rFSH alone
- The findings are in keeping with the POSEIDON working group's new definition of low prognosis patients (Fertil Steril 2016)

rLH, recombinant luteinising hormone

Polyzos N P. Merck symposium. Presentation 2



Conclusions

- The Bologna criteria were a first step towards a uniform definition for poor ovarian response

Polyzos N P. Merck symposium. Presentation 2



Conclusions

- The Bologna criteria were a first step towards a uniform definition for poor ovarian response

The POSEIDON Group's "new definition" of low prognosis patients will be useful in segmenting patients into the most beneficial, patient-oriented ovarian stimulation approach.

Polyzos N P. Merck symposium. Presentation 2



P-671 – Majority of young females with occult POI menstruate regularly: why we should not rely on menstrual status as a marker of ovarian reserve

Y Güzel

Poster presentation



Introduction

To determine if there is a characteristic menstrual history that signals the onset of occult POI in young females.

- Diminished ovarian reserve or occult POI may develop spontaneously and insidiously in young females
- Its exact prevalence is unknown, but it is thought to affect around one in 250 women under the age of 35
- Further studies are needed to determine the prevalence of POI and to determine whether there are any menstrual irregularities or other symptoms that are related to occult POI

POI, premature ovarian insufficiency
Güzel Y. Poster. P-671



Menstrual status was not a reliable marker for occult POI

Outcome measure	Females with occult POI n=35
Age (years), mean	24.5
Menstrual irregularity in the previous year, %	14.3
≥1 skipped menses in the previous 6 months, %	14.3
Family history of premature ovarian failure in mothers or other first degree relatives, %	20

- All cases of POI were confirmed by early follicular elevated FSH (22 ± 2.5 mIU/mL) and lower antral follicle counts (2.6 ± 0.4)

POI, premature ovarian insufficiency; FSH, follicle stimulating hormone
Güzel Y. Poster. P-671



Study Conclusions

- The majority of young females with occult POI continue to menstruate regularly and do not report any menstrual abnormalities in the preceding year
- Menstrual status is not a reliable marker of ovarian reserves
- Other biomarkers of ovarian reserve/response should be utilized, as suggested in the POSEIDON's working group new definition

POI, premature ovarian insufficiency
Güzel Y. Poster. P-671



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