POSEIDON's stratification of 'Low prognosis patients in ART" and its new proposed marker of successful outcome: The WHY, the WHAT, and the HOW

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I. The WHY

The management of patients with an impaired ovarian reserve or poor ovarian response (POR) to exogenous gonadotropin stimulation has challenged reproductive specialists for a long time. Apart from our limited understanding of its pathophysiology, there is wide heterogeneity in the definition of the poor responder patient as well as overall disappointing outcomes in assisted reproductive technology (ART) cycles.

The Bologna criteria for poor responders (ESHRE, 2011) was introduced in 2011 with the main objective of selecting homogeneous groups of patients based on 'oocyte quantity' for testing in prospective randomized trials (RCT) for different strategies. Up to now, more than 70 RCT have compared interventions in poor responders using a wide range of patient inclusion criteria, including the Bologna criteria. Interestingly, among the trials registered in _clinicaltrials.gov_ (up to March 2017), 44 were specific to POR, but only 7 trials enrolled an adequate sample size to avoid a type II error. Analyzing results of the completed trials and published literature, the overall conclusion is that there is insufficient evidence to support the routine use of any particular intervention either for pituitary down-regulation, ovarian stimulation or adjuvant therapy. A possible explanation is that the analysis of whole populations of POR with different baseline characteristics and, therefore, different prognosis in a given RCT may dilute the effect size. It can be therefore concluded that little progress has been achieved with regard to the clinical management of POR, thus frustrating clinicians and patients alike.

A critical shortcoming of the existing POR criteria, which are largely based on ovarian biomarkers and number of oocyte retrieved after controlled ovarian stimulation (COS), is that women with POR may comprise subgroups with diverse baseline characteristics. The reasons stem from the wide biological variability in the number of non-growing and growing follicles within the same age group. Hereditable factors, genetic and medical conditions, as well as lifestyle and environmental exposure to toxicants impact not only the establishment of the primordial follicle pool during fetal life but also the reproductive function in adult women, thus contributing to the observed interindividual variability. Moreover, the ovarian sensitivity to exogenous gonadotropins used for COS is also variable and modulated by genetic factors involving both the gonadotropins and their receptors.

For these reasons, reduced ovarian reserves should be discriminated from poor/suboptimal ovarian responses to gonadotropins caused by inherent ovarian resistance (eg. genetic polymorphisms). However, at present it is not clear whether the Bologna criteria (or any other criteria) for POR can eliminate clinical heterogeneity within the poor responder population. It can be thus argued that analysis of whole populations of POR with different baseline characteristics and, therefore, different prognosis in a given RCT may dilute the effect size.

In clinical terms, counting the number of oocytes retrieved or estimating such numbers using ovarian biomarkers may not be enough for clinical management. Equally important is to determine the aforementioned ovarian sensitivity to gonadotropins and the age-related decrease in oocyte quality that largely depends on chromosomal abnormalities occurring prior to meiosis II. Indeed, the genetic competence of oocytes is paramount as it affects the implantation potential of resulting embryos. Whereas embryo euploidy rates of about 60% are observed in younger women (<35 years of age) undergoing IVF, these numbers fall to 50% in women aged 35-39, and to dramatically low rates of about 30% in those with 40-42 years old. As a result, the age-related embryo aneuploidy rate can dramatically change the prognosis in women that have the same oocyte yield. Consequently, age-related embryo aneuploidy rates can dramatically change the prognosis of women with same oocyte yield. It seems therefore essential to take these elements into account when defining any criteria for POR due to its marked effect on treatment outcome.

Unfortunately, the currently existing criteria for POR have not fully appreciated the multitude of factors mentioned above. This may explain the lack of scientific evidence supporting any effective intervention for this patient category when these criteria are used for designing clinical trials. As a result, practitioners have used different strategies –often not evidence-based- in clinical management since none of the POR criteria provide a clear path for management. In fact, a recent international survey among clinicians found that the most used criterion for identifying POR was the "number of follicles produced", which has rarely been included in the definition of POR by scholars (IVFonline.org). And due to the absence of efficient remedies, most practices do not use evidence-based treatment for this category of patients. Furthermore, according to RESOLVE, a not-for profit patient organization dedicated to providing education to couples suffering from infertility, POR are those women who require large doses of medication and who make less than an optimal number of oocytes (RESOLVE.org). This indicates that patients themselves have introduced a new element into the already complex POR equation, namely, suboptimal response to ovarian stimulation. As it stands, it was sound to assume that anyone -scholars, clinicians, and patients- has been fully satisfied with the existing criteria for the diagnosis of low responders because they fail to provide a clear path for management. These are the reason why the POSEIDON Group was created, i.e., to shed light into the definition and management of Low Prognosis Patients (LPP) undergoing Assisted Reproductive Technology (ART).

II. The WHAT

The POSEIDON (**P**atient-**O**riented **S**trategies **E**ncompassing **I**ndividualized **O**ocyte **N**umber) group was created in 2015, envisaging discussing and elaborating practical solutions with regard to the diagnosis and management of POR. The group comprises 12[1] opinion leaders in reproductive medicine from 7 countries with large clinical/research experience and robust publication record. Its name also reflects the place chosen for its first meeting in the Italian island of Ischia.

The POSEIDON group has proposed a new stratification for classifying infertility patients with confirmed or expected inappropriate ovarian response to exogenous gonadotropins. Specifically, four subgroup categories have been created based on quantitative and qualitative parameters, namely, i. The age of the patient and the expected aneuploidy rate; ii. Ovarian biomarkers (i.e. AFC and AMH), and iii. The ovarian response of the patient provided a previous cycle of stimulation had been carried out. In the latter, a 'suboptimal response' was defined as the retrieval of four to nine oocytes despite adequate pre-stimulation ovarian parameters, as it is associated at any given age with a significantly lower live birth rate compared with normal responders, i.e., those with 10–15 oocytes. And a 'poor response' was defined as the retrieval of less than four oocytes despite adequate pre-stimulation ovarian parameters. Furthermore, the group introduced a new measure for successful ART treatment, namely, the ability to retrieve the number of oocytes necessary to obtain at least one euploid blastocyst for transfer in each patient.

We strongly believe this represents a more pragmatic endpoint for clinicians providing care to infertility patients. Furthermore, it opens the possibility of developing prediction models to help clinicians counsel and set patient expectations and establish a working plan to reduce the time-to-pregnancy (TTP).

The aim of this new system was to introduce a more nuanced picture of POR using clinically relevant criteria to guide the physician in the management of such patients. Essentially, the POSEIDON group proposes a change in the definition of POR from heterogeneous criteria to the concept of low prognosis, which may better reflect the fate of these patients in ART. Different remedies could then be applied to each patient category with the objective of achieving the proposed measure of success.

III. The HOW

The POSEIDON stratification system combines quality and quantity for the stratification of patients with confirmed or expected inappropriate ovarian response, and allow clinicians to estimate the number of oocytes needed to achieve a new marker of successful outcome, i.e., at least ONE euploid embryo for transfer in each patient.

As an example, a woman with 36 years with low ovarian reserve (i.e., POSEIDON group 4) may need up to 12 oocytes to obtain at least one euploid blastocyst for transfer, based on the commonly reported metaphase II rates (e.g. 75%), 2PN fertilization rates (e.g. 70%), blastulation rates (e.g. 45%), and blastocyst euploidy rates (e.g. 50%).

Clinicians can therefore classify this hypothetical patient according to the POSEIDON criteria and estimate the number of oocytes needed to obtain at least one euploid blastocyst. Then, an individualized therapeutic plan with the mindset to achieve the target number of oocytes may be designed to most optimally manage the patient clinical scenario.

It is suggested that the new concept of low prognosis helps to improve the management of patients undergoing ART, promotes a tailored approach to patient handling, and identifies more homogeneous populations for clinical trials, thereby providing better tools with which to maximize IVF success rates.

Using the POSEIDON criteria, clinicians would be able to set patient expectations and establish a workable plan to reduce the time-to-pregnancy. This can be achieved by pharmacological and/or laboratory approaches that need to be elaborated in full detail.

5 Reasons to use POSEIDON

1. POSEIDON combines quality and quantity for the stratification of patients with confirmed or expected inappropriate ovarian response.

2. POSEIDON may allow clinicians to estimate the number of oocytes needed to achieve a new marker of successful outcome, i.e., at least ONE euploid embryo for transfer in each patient.

3. By using POSEIDON, clinicians would be able to set patient expectations and establish a workable plan to reduce the Time-to-Pregnancy.

4. POSEIDON concept of low prognosis can help to improve the management of patients undergoing ART by promoting a tailored approach to patient handling

5. POSEIDON concept may help identifying more homogeneous populations for clinical trials, thereby providing better tools with which to maximize IVF success rates.

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