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The New POSEIDON Criteria: The WHY, the WHAT, and the HOW

Announcer: Welcome to ReachMD! This activity, The New POSEIDON Criteria: The WHY, the WHAT, and the HOW, is provided by TOPEC Global and supported by an independent educational grant from Merck KGaA, Darmstadt, Germany.
Here is your speaker, Dr. Sandro Esteves.

Dr. Esteves: Hello everyone. First of all, I want to thank the Global Women's Health Academy for the opportunity to talk about the new POSEIDON criteria and discuss its new marker of success in Assisted Reproductive Technology. My name is Sandro Esteves, and I am the Medical and Scientific Director of ANDROFERT Center in Campinas, Brazil. I am also one of the POSEIDON's group founding members.

In this talk, I will first tell you why we developed the POSEIDON criteria. Then, I will explain what is new in this system and why it offers a better way to classify and provide care to the so-called poor ovarian responder patient undergoing assisted reproductive technology. Lastly, I will inspire you to embrace innovation by using the POSEIDON criteria. I am delighted with it because of the excellent results I have had since I started to use these criteria about one year ago. It is simple, easy to explain to our patients and it helps to guide us on how to most optimally manage patients undergoing IVF and ICSI treatments as we will see.

Now, let us get started with the why. It all started because of the difficulties we as reproductive medicine specialists face when handling patients with a poor ovarian response. 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 cycles regarding of the intervention utilized. The peculiarities of this group of patients and diversity in the definition of the poor responder patient represent major limitations of interventional trials because most of such studies compare patients with different characteristics.

In an attempt to shed light on this problem, the Bologna criteria for poor responders was developed with the primary objective of selecting homogeneous groups of patients based on the oocyte quantity for testing in prospective randomized trials. Despite becoming quite popular in research studies involving poor responders, the Bologna criteria achieved little about the clinical management of this patient category. Here I depict three patients who, despite having distinct clinical characteristics, fit the criteria of poor responders according to Bologna.

The problem of placing these patients in the same box is their probability of delivering a baby following IVF or ICSI is entirely different, despite the similar number of oocytes retrieved. In clinical terms, counting the number of oocytes retrieved or estimating such numbers using ovarian biomarkers is not enough for clinical management and counseling. We also need to account for the age-related decrease in oocyte quality that is intrinsically related to oocyte chromosomal abnormalities. Consequently, the age-related aneuploidy rates of resulting embryos dramatically change the prognosis of women with the same oocyte yield as clearly shown in this graph.

Let's now consider the case of a patient with a good ovarian reserve but poor or suboptimal ovarian response to ovarian stimulation with FSH. This phenomenon can happen, for example, to women with genetic polymorphisms affecting gonadotropins or their receptors. The clinical picture of this patient is completely different than a patient with reduced ovarian reserve, despite the fact that both are classified as poor ovarian responders. Notably, the existing criteria do not discriminate these types of patients, although their prognosis concerning pregnancy can be drastically different.

To shed light on this problem, the POSEIDON Group, created in 2015 under the initiative of Professor Alviggi from Italy, discussed and elaborated practical solutions concerning the diagnosis and management of the poor responder patient undergoing ART. POSEIDON, as you may know, is the God of the Sea and other waters in Greek mythology. In our case, POSEIDON is an acronym for Patient-

Oriented Strategies Encompassing Individualized Oocyte Number. It may look complicated, but I will show you how simple it is.

First, I invite you to appreciate its meaning as a light that provides patients new hope for a successful IVF treatment and a guide for clinicians to most optimally manage the group of patients I will describe to you now. You should care about the new POSEIDON criteria because they propose a unique and more detailed stratification of low responders to ovarian stimulation, which represent a significant proportion of patients we treat in our daily practice.

The group proposes a paradigm shift from the long-term used concept of poor ovarian response to the new concept of low prognosis. We feel that low prognosis is a better terminology because it not only allows to group the patients who have a reduced probability of pregnancies in ART but also stratify the low prognosis patients into four categories based on quantitative and qualitative parameters, namely: First, the age of the patient and the expected embryo aneuploidy rate; Second, ovarian biomarkers; and third, the ovarian response of the patient provided a previous cycle of stimulation had been carried out. Let's now look in detail at how these patient groups differ and the reasons why we used these parameters to develop the four-group categories.

We included the AFC and AMH to discriminate patients of POSEIDON's groups 1 and 2 from those of POSEIDON's groups 3 and 4 because both markers can predict with fair accuracy and better than FSH and age, the risk of achieving low oocyte quantity after ovarian stimulation; however, since neither AMH nor AFC can identify patients with ovarian resistance to gonadotropin stimulation, we included the number of oocytes retrieved in a previous cycle of conventional ovarian stimulation to classify patients as POSEIDON groups 1 and 2. In this case, we defined a suboptimal response as retrieval of four to nine oocytes, despite adequate pre-stimulation ovarian parameters and a poor ovarian response as retrieval of fewer than four oocytes despite adequate pre-stimulation ovarian parameters.

It is important to identify these patients because retrieval of a lower number of oocytes than expected is associated, at any given age, with a significantly lower cumulative live birth rate than that achieved in normal or high responders. Identification of POSEIDON's groups 1 and 2 patients is only possible after ovarian stimulation and oocyte retrieval. These patients may be those with ovarian resistance to gonadotropin stimulation due to the existence of genetic polymorphisms involving gonadotropins and their receptors.

Lastly, we included age to distinguish younger from older patients in group categories because maternal age is critical to oocyte genetic competence and it affects the implantation potential of resulting embryos. Therefore, a patient classified as POSEIDON's group 4 is likely to have a lower probability of achieving a live birth than a POSEIDON's group 3. This is so because of the higher embryo aneuploidy rate in group 4 category, despite the fact that both groups include patients with abnormal ovarian biomarkers. The same reasoning applies when comparing patients of groups 2 and 1.

We used 35 years of age to distinguish younger from older patients because the percentage of aneuploidy embryos is, on average, lower than 50% in women younger than 35 years old. On the contrary, embryo aneuploidy rates are higher than 50% in women older than 35 years of age, increasing steadily after this age.

In addition to providing a system for identifying and classifying low prognosis patients in ART, the POSEIDON group introduced a new measure of success in ART, namely the ability to retrieve the number of oocytes needed to potentially obtain at least one euploid blastocyst for transfer in each patient. This is the POSEIDON endpoint which has been discussed in detail in a subsequent publication by the POSEIDON group.

We know that the transfer of euploid blastocysts dramatically decreases the negative impact of age on implantation. The problem is that the older the patient, the higher the risk of having no transferable embryos due to the increased frequency of aneuploidy embryos in this patient category. To overcome this problem, a possible solution would be to estimate the number of oocytes needed to achieve at least one euploid blastocyst in the patient embryo cohort.

The solution we found was to develop a predictive model in which the input variables, adjusted by other critical predictive factors, allows estimation of the number of oocytes needed to achieve at least one euploid blastocyst for transfer in each patient. This predictive model is the ART calculator, a tool developed to estimate POSEIDON's endpoint.

In this movie, I will show you how easy it is to use the ART calculator. All you need to do is input the variables. Let's consider, for instance, an infertile couple of 36 and 38 years old, respectively, which due to the severe male factor has to use testicular sperm for ICSI. The ART calculator allows adjustment by co-variables known to affect estimates such as sperm and oocyte status and also the type of planned transfer, fresh or frozen-thawed for instance. Then, with a single click, the calculator provides an estimation of the number of oocytes needed to obtain at least one blastocyst for transfer, thus saving us a lot of time. To sum up, the new POSEIDON criteria allows identification and stratification of low prognosis patients in the ART settings, and we feel that the estimation of the POSEIDON's marker of success represents a logical endpoint to guide clinicians to develop a working treatment plan.

Now, let me move on to my last point that is how POSEIDON can be used in clinical practice. As a clinician, I feel that with a clear goal

in mind, we can use the most suitable remedies to each POSEIDON group with the objective of achieving the POSEIDON's endpoint. For instance, we can use a pharmacological approach in POSEIDON groups 1 and 2 patients with the objective of increasing the follicular output rate. This is so because patients classified as POSEIDON groups 1 and 2 may harbor genetic polymorphisms affecting ovarian sensitivity to gonadotropin stimulation; therefore, strategies such as the use of more potent gonadotropins preparations, adding LH to the stimulation regimen and avoiding the use of prolonged pituitary suppression may be beneficial for this group of patients.

In POSEIDON groups 3 and 4, a pharmacological intervention alone may not be enough to change the fate of this category of low prognosis patients. In this group, oocyte and embryo accumulation programs and the use of dual stimulation in the follicular phase and luteal phase of the same cycle, combined with pharmacological interventions are the strategies to be considered.

These are just some examples of how the POSEIDON criteria may open new horizons to clinicians to most optimally manage the low prognosis patients, and ultimately providing new hope for success and aiming at reducing the time to pregnancy.

In conclusion, I want to express five points that the POSEIDON groups have made available to new clinicians and to me as well. First, the POESIDON group proposes a change in the definition of the poor responder patient from the heterogeneous criteria to the concept of low prognosis. Second, the POSEIDON criteria combine quality and quantity for the stratification of patients with a confirmed or expected inappropriate ovarian response to ovarian stimulation. Third, using POSEIDON, the clinician can both classify their patients with a low prognosis in ART and estimate the number of oocytes needed to obtain at least one euploid blastocyst for transfer in each patient. Fourth, the doctor can design an individualized therapeutic plan with the mindset to achieve the target number of oocytes for the patient's clinical scenario. Lastly, the new concept can also identify more homogeneous populations for testing in clinical trials.

Before I end my presentation, just one more thing; I want to take this opportunity to introduce the recently launched POSEIDON website to you. The POSEIDON website is a dedicated platform where you will find unique information about the POSEIDON criteria and its marker of success in ART, including a variety of educational material. Most importantly, you can sign up and become a POSEIDON member today. The POSEIDON website is intended to be a platform to discuss and share ideas and much more. Our platform has just started and we have big plans for making it a fantastic resource for all of us.

Last but not least, we made the ART calculator available for all who sign up and become members of the POSEIDON group. Please visit us at www.groupposeidon.com and sign up today. Thank you very much.

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