



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]

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Abstract

In reproductive medicine little progress has been achieved regarding the clinical management of patients with a reduced ovarian reserve or poor ovarian response (POR) to stimulation with exogenous gonadotropins -a frustrating experience for clinicians as well as patients. Despite the efforts to optimize the definition of this subgroup of patients, the existing POR criteria unfortunately comprise a heterogeneous population and, importantly, do not offer any recommendations for clinical handling. Recently, the POSEIDON group (**P**atient-**O**riented **S**trategies **E**ncompassing **I**ndividualize**D** **O**ocyte **N**umber) proposed a new stratification of assisted reproductive technology (ART) in patients with a reduced ovarian reserve or unexpected inappropriate ovarian response to exogenous gonadotropins. In brief, four subgroups have been suggested based on quantitative and qualitative parameters, namely, i. Age and the expected aneuploidy rate; ii. Ovarian biomarkers (i.e. antral follicle count [AFC] and anti-Müllerian hormone [AMH]), and iii. Ovarian response - provided a previous stimulation cycle was performed. The new classification introduces a more nuanced picture of the “low prognosis patient” in ART, using clinically relevant criteria to guide the physician to most optimally manage this group of patients. The POSEIDON group also introduced a new measure for successful ART treatment, namely, the ability to retrieve the number of oocytes needed for the specific patient to obtain at least one euploid embryo for transfer. This feature represents a pragmatic endpoint to clinicians and enables the development of prediction models aiming to reduce the time-to-pregnancy (TTP). Consequently, the POSEIDON stratification should not be applied for retrospective analyses having live birth rate (LBR) as endpoint. Such an approach would fail as the attribution of patients to each Poseidon group is related to specific requirements and could only be made prospectively. On the other hand, any prospective approach (i.e. RCT) should be performed separately in each specific group.

Open Peer Review

Referee Status:   

	Invited Referees		
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version 1			
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- Giuliano Bedoschi**, University of São Paulo (USP) Brazil
- Ariel Weissman**, Edith Wolfson Medical Center, Holon and Sackler Faculty of Medicine, Tel Aviv University (TAU) Israel, **Johnny S Younis**, Poriya Medical Center, Israel Faculty of Medicine, Bar-Ilan University Israel
- Colin M. Howles**, ARIES Consulting Switzerland

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Competing interests: PH, CA, RF, and SE are members of the POSEIDON group.

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The management of patients with an impaired ovarian reserve or poor ovarian response (POR) to exogenous gonadotropin stimulation has challenged reproductive specialists for decades. Apart from limited understanding of the pathophysiology, wide heterogeneity exists in the definition of the poor responder patient as well as overall disappointing outcomes in assisted reproductive technology (ART) (Papathanasiou *et al.*, 2016).

The POSEIDON group (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) was recently established to focus specifically on the diagnosis and management of low prognosis patients (Poseidon Group, 2016). Composed by reproductive endocrinologists and reproductive medicine specialists from 7 countries [Carlo Alviggi (Italy), Claus Y. Andersen (Denmark), Klaus Buhler (Germany), Alessandro Conforti (Italy), Giuseppe de Placido (Italy), Sandro C. Esteves (Brazil), Robert Fischer (Germany), Daniela Galliano (Spain), Nikolaos P. Polyzos (Belgium), Sesh K. Sunkara (United Kingdom), Fillipo M. Ubaldi (Italy), and Peter Humaidan (Denmark)] with long-standing clinical and/or research experience, the POSEIDON group in an opening paper proposed a new stratification to classify infertility patients with a reduced ovarian reserve or unexpected inappropriate ovarian response to exogenous gonadotropins (Poseidon Group, 2016). In brief, four subgroups have been suggested based on quantitative and qualitative parameters, namely, i. Age and the expected aneuploidy rate; ii. Ovarian biomarkers (i.e. antral follicle count [AFC] and anti-Müllerian hormone [AMH]), and iii. Ovarian response - provided a previous stimulation cycle was performed (Figure 1). The POSEIDON group also introduced a new measure for successful ART treatment, namely, the ability to retrieve the number of oocytes needed for the specific patient to obtain at least one euploid embryo for transfer.

Following its publication earlier this year (Poseidon Group, 2016), the POSEIDON stratification system has sparked interest among

infertility practitioners. Here, we expand the discussion as to why the new concept has been proposed, providing new and important information as below.

First, it is clear that the major players involved in the complex POR equation are not fully satisfied with the existing classification criteria. Taking the scholarly perspective, for instance, until now more than 70 randomized controlled trials (RCTs) compared interventions in poor responders using a wide range of definitions, including the most recent Bologna criteria (Ferraretti *et al.*, 2011; Papathanasiou *et al.*, 2016). Among the trials registered in www.clinicaltrials.gov until November 2016, 44 were specific to POR. However, analyzing the results of completed trials and the published literature, the overall conclusion is that there is insufficient evidence to support the routine use of any particular intervention for POR. Thus, data indicate that the current classification criteria have been unable to discriminate patient subsets within the POR population who could benefit from specific interventions (Nagels *et al.*, 2015; Pandian *et al.*, 2010; Papathanasiou *et al.*, 2016). 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.

Along the same lines, but taking the perspective of the clinician, a recent international survey showed that the most frequently used criterion to identify POR was the “number of follicles produced”, which surprisingly has been rarely included in the scholarly definition of POR (Patrizio *et al.*, 2015). Moreover, due to the absence of efficient remedies, most practices do not use an evidence-based treatment for this category of patients (Patrizio *et al.*, 2015). Lastly, according to the standpoint of the patient, RESOLVE (www.RESOLVE.org), a non-for profit patient organization dedicated to providing education to couples suffering from infertility, classifies POR as women who require large doses of medication and who produce less than an optimal number of oocytes. This indicates that patients themselves have introduced

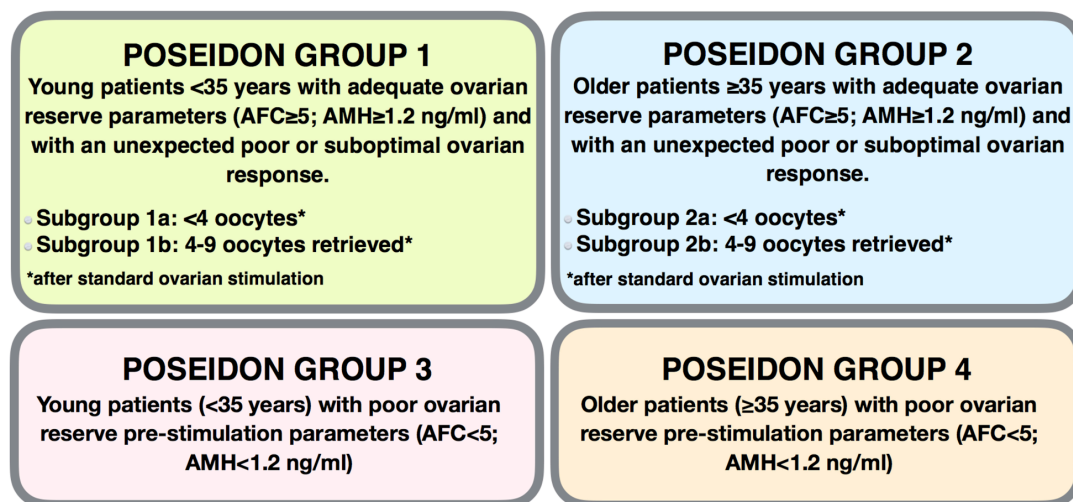


Figure 1. Four groups of ‘low prognosis patients’ in assisted reproductive technology according to the POSEIDON’s stratification based on oocyte quantity and quality. AFC: antral follicle count; AMH: anti-Müllerian hormone. Adapted with permission from Elsevier; Poseidon Group (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number), Alviggi C, Andersen CY, Buehler K, Conforti A, De Placido G, Esteves SC, Fischer R, Galliano D, Polyzos NP, Sunkara SK, Ubaldi FM, Humaidan P. A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept. *Fertil Steril.* 2016 Jun;105(6):1452–3.

a new element into the already complex POR equation, namely, suboptimal response to ovarian stimulation.

Secondly, it is important to further discuss the issue of quantity versus quality regarding oocytes. It is difficult to deny that counting the number of oocytes retrieved or estimating their numbers using ovarian biomarkers may not be sufficient for clinical management. Equally important is the age-related decrease in oocyte quality, which largely depends on chromosomal abnormalities occurring prior to meiosis II (Sakakibara *et al.*, 2015). Despite recognizing that other biochemical processes are also relevant to oocyte quality, the genetic competence of the oocyte is paramount as it affects the implantation potential of the resulting embryo. For instance, blastocyst euploidy rates of about 60% are observed in younger women (<35 years of age) undergoing ART whereas these numbers fall to 30% or lower in patients aged 40–42 (Ata *et al.*, 2012). As a result, the age-related embryo aneuploidy rate dramatically changes the prognosis of women with the same oocyte yield as well as those with different oocyte yields.

Lastly, and most importantly we wish to stress the new POSEIDON marker of successful outcome, i.e., the ability to retrieve the number of oocytes necessary to achieve at least one euploid embryo 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). This is essential to avoid any misunderstanding regarding the POSEIDON concept, as the intention of the concept is to help guide clinicians through the medical management, and as such it should not to be used in retrospective analyses having live birth rate (LBR) as an endpoint.

While LBR is more appropriate for counseling purposes and designing RCTs, the POSEIDON concept is based on (i) a better stratification of women with “low prognosis” in ART, and (ii) individualized therapeutic approaches in each group, having as endpoint the number of oocytes required to have at least one euploid embryo for transfer in each patient. Essentially, the

POSEIDON concept was designed to offer a practical endpoint to clinicians as it may help set a clear goal for management.

Obviously, retrospective analyses of previously structured databases can match patients to fit into POSEIDON subgroups. As an example, from an existing database (pre-POSEIDON) one might analyze the LBR of women ≥ 35 years with low ovarian reserve (i.e., POSEIDON group 4). However, assuming 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%), approximately 12 oocytes are needed to obtain at least one euploid blastocyst for transfer in a given 36 year old patient. Nevertheless, it is unlikely that this hypothetical patient was treated according to the POSEIDON concept, using an individualized therapeutic plan, based on the number of oocytes to obtain at least one euploid blastocyst. Hence, any analysis, using LBR as an endpoint to be valid should ensure that patients were prospectively stratified as per POSEIDON groups and treated with the mindset of achieving the proposed POSEIDON marker of success.

In conclusion, in comparison with previously suggested models to define POR patients from a rigid standpoint and without any clinical guidance, the POSEIDON concept contemplates clinical recommendations with a new pragmatic endpoint, the number of oocytes needed to obtain one euploid embryo for transfer in each patient. We see this novel initiative as an important working – and counseling tool for the ART specialist who handles the low prognosis patient.

Author contributions

All authors contributed equally to the preparation and revision of the draft manuscript and have agreed to the final content.

Competing interests

PH, CA, RF, and SE are members of the POSEIDON group.

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Colin M. Howles

ARIES Consulting, Geneva, Switzerland

This initiative to provide further clarity by stratifying 'Low Prognosis' ART patients into 4 main groupings is a valuable step forward in assisting clinicians and organisations considering clinical trials in such individuals.

There is one point that I would urge the authors to consider in their future deliberations on this topic. If a patient in Poseidon Group 1 or 2 had a suboptimal response, following an individualised FSH dosing scheme based upon for example AMH, should this be checked again in a subsequent stimulation cycle where a higher incremental FSH starting dose is used, prior to categorising the patient in these groupings? R. Fleming has recently referred to the existence of an 'iatrogenic poor response' (ESHRE Annual meeting 2016 Helsinki, sponsored symposium). In his dataset, a higher FSH starting dose given in a subsequent cycle (within 9 months of the poor response cycle), increased the oocyte yield. On the contrary, ART patients already identified by low AMH to be 'poor responders' did not benefit from an increase in the FSH dose.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 30 January 2017

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Five years have passed since the publication of the Bologna criteria for the definition of poor ovarian response (POR) ¹ and evidence is continuing to accumulate to assess their employment as well as limitations in the ART setting. This has been recently encapsulated in a contemporary critical appraisal ².

The POSEIDON group is making a sincere effort to introduce a more specific and higher resolution set of criteria in an attempt to guide the physician to most optimally manage this group of patients (³ and current F1000Research paper). There are, however, several reservations regarding the proposed stratification system and some clarifications that need to be made.

Since age is perhaps the most important criterion for oocyte quality, embryo ploidy and therefore also prognosis, it is now used as a major criterion in the POSEIDON stratification, with 35 years being the age cut-off used. Thirty five years is indeed the age where both aneuploidy rates begin to rise, and pregnancy rates begin to decline in many large ART data sets. The choice of 35 years as a cut-off should be briefly explained and backed up by references.

A large amount of research has established antral follicle count (AFC) and anti-müllerian hormone (AMH) as the most reliable and accurate ovarian reserve tests (ORT) in predicting ovarian response. Specific cut-off values of <1.2 ng/mL and <5 antral follicles have been selected for AMH and AFC, respectively, in contrast to the less clearly defined values in the Bologna criteria, ≤5-7 follicles for AFC and ≤0.5-1.1 ng/mL for AMH. How were the cutoffs of AMH and AFC reached/decided?

The standardization of measurement of both markers is still underway. AMH assays are in a constant process of precision improvement and automation. It is unclear for AMH whether "one size fits all", for example, should two patients, one with AMH levels of 1 ng/mL and the other with undetectable AMH levels, be counseled and managed the same way? Furthermore, currently, a 36 years old patient with regular cycles and POR, may have the same undetectable AMH levels as a 50 years old menopausal woman. Ultra-sensitive AMH levels are currently being developed, and whether they will have a role in better discrimination and prognostication of POR patients, remains to be seen. Similarly, there is yet a lack of standardization of AFC measurements. The performance and resolution of ultrasound machines is being constantly improved, and standards should be set for optimal imaging requirements. The fact that the techniques for measurement of both AMH and AFC are still under development should be mentioned. The POSEIDON group classifies the retrieval of 4-9 oocytes as a suboptimal response. For many, including ourselves, 8-10 oocytes is considered a goal and a successful outcome of COS, in terms of both safety and efficacy, especially in young patients. Furthermore, Cai et al. ⁴ have recently demonstrated that similarly aged patients have similar pregnancy prospects after fresh embryo transfer when the same number and quality of embryos are replaced, irrespective of their number of oocytes retrieved. It is therefore questionable whether the range of 4-9 oocytes is again not too broad in terms of prognostication of outcome.

The authors claim that the Bologna classification criteria have been unable to discriminate patient subsets within the POR population who could benefit from specific interventions. This is still premature to decide, as there are many studies based on the Bologna criteria that are still underway. Furthermore, a recent well performed multi-center study has shown that in normal responders the individualized treatment has similar efficacy to conventional ovarian stimulation ⁵. Whether the same is true in the POR population employing the Bologna or other criteria has yet to be explored.

The POSEIDON group also suggests that stimulation should be tailored according to "the age-related embryo/blastocyst aneuploidy rate" with the intention "to retrieve the number of oocytes necessary to obtain at least one euploid embryo for transfer in each patient. The corresponding references and nomograms should be brought and constructed, respectively, in order for the stratification to become practical and for clinicians to be able to proceed with its use.

Having an euploid blastocyst as a goal may be too simplistic, since many (in some publications >50%) euploid blastocysts never implant. Do the authors suggest to extend embryo culture to the blastocyst stage, or just use having one blastocyst as an end-point for calculation of the desired oocyte number per

age group? It is questionable whether embryos in POR patients should be cultured at all to the blastocyst stage, or transferred as early as possible in the cleavage stage ⁶.

The POSEIDON stratification aims not only to define poor ovarian response but also to establish the prognosis for patients. It is likely that by using these criteria more homogenous populations can be established for clinical trials. However, it remains to be seen whether the management and outcome of POR patients undergoing ART can be also improved by their incorporation. It is possible that unless we will witness major breakthrough in the management of POR patients, the lay definition "women who require large doses of medication and who produce less than an optimal number of oocytes" used by patient organization Resolve (www.resolve.org) will be as good as any stratification system.

In summary, it is clear that the POSEIDON group offers an improved stratification for POR patients, which has the potential to improve study designs and fine tune prognostication. It remains to be seen whether the reproductive outcome of POR patients will also be improved following the new classification system. Perhaps it is time to set an international expert meeting in order to revise the Bologna criteria and establish new consensus criteria that would enhance both diagnosis and prognosis.

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We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Author Response (Member of the F1000 Faculty) 21 Mar 2017

Sandro Esteves, ANDROFERT - Andrology and Human Reproduction Clinic Referral Center for Male Reproduction, Brazil

The Poseidon stratification of 'Low Prognosis patients' in Assisted Reproductive Technology is on the right track.

Response to: Weissman A and Younis JS. Referee Report For: 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].

F1000Research 2016, **5**:2911 (doi: 10.5256/f1000research.11186.r19119)

Dear Editors,

We thank doctors Weissman and Younis for their insightful commentary on our most recent publication in *F1000 Research* (Humaidan *et al.* 2016). First of all, we are pleased to see that our colleagues agree in the fact that the novel proposed Poseidon stratification of 'Low prognosis patients in Assisted Reproductive Technology (ART)' is a "sincere effort to introduce a more specific and higher resolution set of criteria" and that in comparison with the Bologna criteria this new classification system offers "an improved stratification for poor ovarian response (POR) patients which has the potential to improve study designs and fine-tune prognostication". Moreover, that this stratification system also has the potential to help guide the clinician to most optimally manage a heterogeneous and challenging group of ART patients.

Importantly, the Poseidon stratification is based on the concept that although POR is very relevant, it is not the only variable for defining prognosis. In fact, the Poseidon group's proposal is to move from a strict view of POR to the "low prognosis" concept. In particular, two new prognostic indicators have been introduced: i) the hypo-sensitivity to standard doses of gonadotrophins, and ii) the ovarian "quality". The former is related to Poseidon's groups 1 and 2 and is based on the principle of the 'Follicle Output RaTE' (FORT). In brief, patients classified as Poseidon's groups 1 and 2 have an oocyte yield lower than expected and can be probably retreated with different OS regimens. The latter is based on the age-related aneuploidy rate, which might offer the possibility of exploring different stimulation strategies and treatments, including an oocyte/blastocyst accumulation program.

As regards the clarifications requested by Weissman and Younis, we are delighted to have the opportunity to provide the answers to help the authors as well as clinicians with interest in the matter concerned to view the Poseidon concept in the correct perspective.

Firstly, the cut-off of 35 years of maternal age is a generally accepted and well-recognized limit to distinguish the young and the ageing patient, as it overall determines the initiation of age-related changes in not only oocyte quantity (Ferraretti *et al.*, 2011; Ata *et al.* 2012) but also oocyte quality (Ben-Meir *et al.* 2015; Weall *et al.* 2015). As for the specific cut-off values of AFC and AMH set at < 5 antral follicles and < 1.2 ng/ml, we certainly agree that these limits are more clearly defined than those suggested by the Bologna criteria ($\leq 5-7$ and $\leq 0.5 - 1.1$ ng/ml, respectively). For AMH, the best cut-off values reported in the literature are in the range from 0.5 to 1.1 ng/ml, whereas for AFC the values range from less than 5 to less than 7 (Broekmans *et al.*, 2006; Broer *et al.*, 2010; La Marca *et al.*, 2010). Thus, the cut-off levels used for the Poseidon stratification are well within the accepted criteria to define POR, but more clearly defined to make them applicable to daily clinical practice as well as research.

Secondly, the Poseidon stratification classifies 4-9 oocytes as a suboptimal response, based on the results of the largest analysis until now including a total of 400 135 IVF cycles showing that live

birth rates (LBR) within this population were ~20–30% lower compared with women of the same age with 10–15 oocytes retrieved (Sunkara *et al.*, 2011). These observations were recently confirmed by Drakopoulos *et al.* (2016) in a retrospective cohort study involving 1099 women 18-40 years old subjected to IVF/ICSI. The cumulative LBR, i.e. the sum of all live births obtained in the first fresh IVF/ICSI including those achieved by utilization of all cryopreserved embryos available, varied as a function of the number of oocytes retrieved, being 21.7% among patients with 1-3 oocytes, 39.7% in those with 4-9 oocytes, 50.5% in the group with 10-15 oocytes, and 61.5% among the patients with greater than 15 oocytes. In particular, suboptimal responders (4-9 oocytes) had a significantly lower cumulative LBR ($P=0.02$) than normal (10-15 oocytes) responders (Drakopoulos *et al.* 2016). Whether or not this range is too broad needs to be determined in future prospective trials applying the Poseidon criteria.

Thirdly, as regards tailoring of ovarian stimulation to obtain at least one euploid blastocyst for transfer in each individual patient – the new proposed measure of a successful ART treatment by the Poseidon group (Humaidan *et al.* 2016; Alviggi *et al.* 2015)- and the corresponding nomograms and references, we are happy to announce that these are on their way, and that a “Poseidon Calculator” is currently being developed, using mathematical and statistical models, to provide the clinician a useful tool to calculate with a few clicks the number of oocytes needed for each specific patient – also taking the results of the individual ART laboratory into account. Although it might still be debated whether an embryo should be transferred at the cleavage or blastocyst stages in the ‘Low prognosis’ ART patient, we are convinced that in a well-functioning ART laboratory blastocyst transfer is the correct way to go.

Lastly, we concur with Weissman and Younis that like all other criteria set in medicine prospective trials are needed to explore the efficacy of the Poseidon criteria in each specific sub-group to evaluate whether the incorporation of the new stratification improves the management and outcome of low responder patients. Along these lines, we would certainly welcome an initiative to set a larger international board to further improve the diagnosis and prognosis of the ‘Low prognosis patient’.

The response to Weissman and Younis commentary as above is authored by Humaidan P, Esteves SC, Fischer R and Alviggi C.

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Manuscript Review

The novel POSEIDON stratification of 'Low prognosis patients in Assisted Reproductive Technology' and its proposed marker of successful outcome

F1000 Research

The premise of this opinion article was to expand the discussion on the POSEIDON stratification system, including new and important information about this new concept.

First, the authors demonstrated the researchers' dissatisfaction with the existing criteria for the definition

of poor ovarian response (POR). As discussed in the article, dozens of randomized clinical trials have been published using different criteria for the diagnosis of POR. This demonstrates the importance of elaborating new stratification criteria that takes into account relevant prognosis information for POR patients. As discussed by the authors, the fact that the different strategies proposed by the clinical trials do not show improvement of in vitro fertilization cycles outcomes could be related to the dilution of the effect size when using a broad POR classification. Strategies developed for more specific groups of patients may demonstrate different reproductive outcomes. This information is of utmost relevance, especially in patients diagnosed with POR. The division of patients in subgroups would allow a more refined and individualized strategy for specific groups of patients.

Secondly, age criterion is essential to estimate the prognosis of in vitro fertilization cycles, due to the increase in the rates of aneuploidy as the maternal age advances. The inclusion of this criterion for dividing patients' subgroups is of great value.

The POISEDON marker of successful outcome, based on the number of oocytes necessary to achieve euploid embryo transfer, may assist reproductive specialists for counseling purposes.

In conclusion, the POSEIDON stratification concept presents several advantages when compared to previously described models. This facilitates the evaluation of strategies that could result in increased success of in vitro fertilization cycles for specific subgroups of patients. In addition, reproductive specialists would be able to better advise patients about their treatment prognosis.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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