



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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v1 First published: 23 Dec 2016, 5:2911 (doi: [10.12688/f1000research.10382.1](https://doi.org/10.12688/f1000research.10382.1))
 Latest published: 23 Dec 2016, 5:2911 (doi: [10.12688/f1000research.10382.1](https://doi.org/10.12688/f1000research.10382.1))

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		
	1	2	3
version 1			
published 23 Dec 2016	report	report	report

- Giuliano Bedoschi**, University of São Paulo (USP) Brazil
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How to cite this article: Humaidan P, Alviggi C, Fischer R and Esteves SC. **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: [10.12688/f1000research.10382.1](https://doi.org/10.12688/f1000research.10382.1))

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Grant information: This work is supported by institutional funding of Androfert Center to the Poseidon group.

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

First published: 23 Dec 2016, **5**:2911 (doi: [10.12688/f1000research.10382.1](https://doi.org/10.12688/f1000research.10382.1))

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

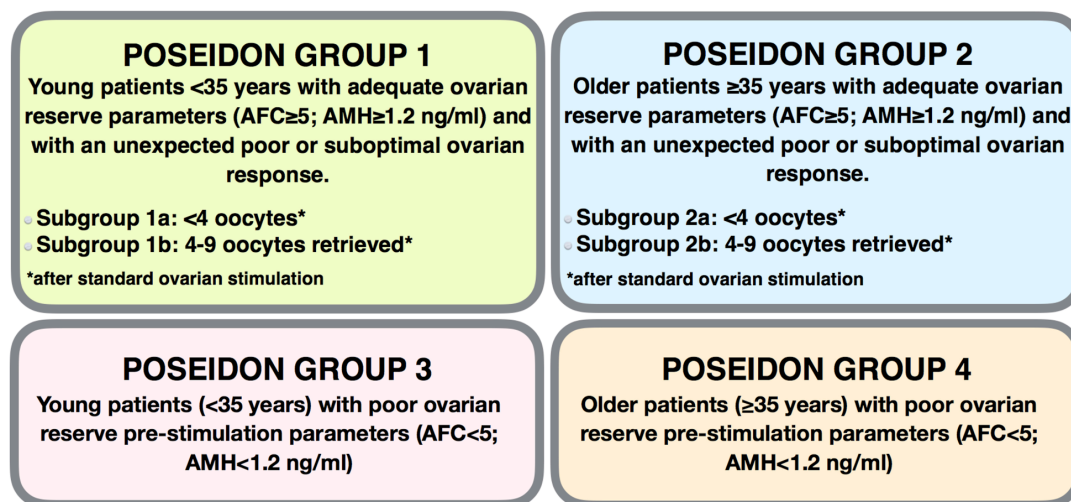


Figure 1. Four groups of ‘low prognosis patients’ in assisted reproductive technology according to the POSEIDON’s stratification based on oocyte quantity and quality. AFC: antral follicle count; AMH: anti-Müllerian hormone. Adapted with permission from Elsevier; Poseidon Group (Patient-Oriented Strategies 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.

Grant information

This work is supported by institutional funding of Androfert Center to the Poseidon group.

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Open Peer Review

Current Referee Status:   

Version 1

Referee Report 08 February 2017

doi:[10.5256/f1000research.11186.r18761](https://doi.org/10.5256/f1000research.11186.r18761)



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

doi:[10.5256/f1000research.11186.r19119](https://doi.org/10.5256/f1000research.11186.r19119)



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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.

Referee Report 23 January 2017

doi:10.5256/f1000research.11186.r19116



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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.

Competing Interests: No competing interests were disclosed.
