Update on the management of poor ovarian response in IVF: the shift from Bologna criteria to the Poseidon concept

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Abstract: Despite the considerate progress to which assisted reproduction technology (ART) has been subject since 1978, some issues remain unresolved. Notably, the clinical management of patients with a poor ovarian response is still a challenge in everyday practice, frustrating to both the patient and the fertility expert. Poor ovarian responders (PORs) embody 9–24% of patients undergoing ovarian stimulation, meaning that up to one in four patients conceals a poor reproductive prognosis. The last decade has witnessed the attempts of the medical community to standardize diagnosis of POR with the developing of the Bologna Criteria and the subsequent evolution of the low prognosis patient elaborated in the POSEIDON classification. The aim of this article is to summarize all evidence concerning etiology and management of poor ovarian response, including the most recent advances and future prospects in this regard.

Keywords: Bologna criteria, IVF, poor ovarian responder (POR), poor ovarian response, Poseidon classification

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Introduction

The objective of modern assisted reproduction technology (ART) is the live birth of a healthy, singleton baby, achieved with reduced time to pregnancy and costs, and increased patient friendliness and safety. Despite the considerate progress to which this branch of medicine has been subject to in the last 40 years, some issues remain unresolved. Notably, the clinical management of patients with a poor ovarian response is still a challenge in everyday practice, frustrating to both the patient and the fertility expert.

Poor ovarian responders (PORs) embody 9–24% of patients undergoing ovarian stimulation for *in vitro* fertilization (IVF), meaning that up to one in four patients conceals a poor reproductive prognosis.[1,2] Etiopathogenesis is complex and only partly understood; however, some of the recognized etiologies include age-related depletion of ovarian follicles, advanced endometriosis, chromosomal and genetic alterations, prior ovarian surgery and pelvic adhesions, metabolic and enzymatic diseases, as well as toxic, autoimmune and infectious diseases.[3–7] In the last decades, many studies have investigated many different approaches for the management of PORs; however, they have failed to identify strategies that are unequivocally effective.[8,9] The lack of conclusive evidence is mainly due to the huge discrepancy in the definitions of PORs, which makes the comparison of studies and their findings extremely difficult. Indeed in 2011, a systematic review by Polyzos and Devroey[9] reported a shocking number of 41 different definitions of POR in 47 randomized trials that acted as alarm bells for the medical community. Following this publication, the same year, the European Society for Human Reproduction and Embryology (ESHRE) attempted to reduce the vast heterogeneity

underlying the definition of POR by introducing the Bologna Criteria (BC).[10]

Bologna criteria

In the definition of POR by the BC, at least two of the following features must be present: advanced maternal age (⩾40 years), a previous poor ovarian response with ⩽3 oocytes retrieved after conventional stimulation and/or an abnormal ovarian reserve test (ORT) [i.e. antral follicle count (AFC) < 7 or anti-Müllerian hormone (AMH) < 1.1 ng/ml]. In the absence of advanced maternal age or abnormal ORT, a patient can be defined as POR after two episodes of poor ovarian response following maximal stimulation.[10] Initial studies found consistently low fresh live birth rates (LBR) among BC PORs. In particular, La Marca et al.[11] included 210 PORs in a retrospective analysis and showed LBR ranging from 5.5% to 7.4%, while Polyzos et al.[12] and Busnelli et al.[13] also reported low LBR of around 6%.

Nonetheless, BC have been criticized for several reasons, with particular attention drawn to the lack of clarity in defining risk factors and lack of accounting for oocyte quality and other factors that can be associated with diminished ovarian reserve.[14–17] However, the major issue that concerned experts was the persistence of a significant degree of heterogeneity even within the BC population, demonstrated by the several patterns or subgroups of PORs that could emerge by combining risk factors, ORT results, and IVF attempts.[11,16,18] These subpopulations of patients very often present with different baseline characteristics (i.e. age) and therefore, diverse prognoses. Indeed, subsequent investigations confirmed the poor prognosis of BC PORs, with LBR ranging from 2.3% to 8.7% per started IVF cycle, and revealed a lack of homogeneity between the subgroups, with "young proven" PORs having the most favorable reproductive outcomes.[18] Very similarly, Romito et al.[19] found significantly different fresh and cumulative LBR between the four patterns analyzed in their retrospective study, with a better clinical prognosis for the younger subpopulation, confirming the heterogeneity between the various subgroups in BC POR. In the same vein, a 15-year follow-up of 3,391 women with POR by Xu et al.[20] revealed that cumulative LBR decreased from 22% for women <30 years to 18.3% for women aged 31–34 years, 17.2% for 35–37 years, 13.5% for 38–40 years, 10.5% for 41–43 years, and 4.4% among women >43 years, highlighting the importance of age and the heterogeneity among the BC population.

Finally, the heterogeneity encountered in BC POR could explain (a) the fact that none of treatment modalities has been shown to be effective[8,21–24] and (b) the reluctance of fertility experts to use the BC in POR studies.[14]

Poseidon criteria

In this context, in yet another attempt to overcome the shortcomings of the BC, a modified definition of impaired ovarian response has been proposed by the Poseidon Group (**P**atient-**O**riented **S**trategies **E**ncompassing **I**ndividualize**D** **O**ocyte **N**umber).[25] This new classification introduces a better stratification of the "low prognosis patient" and suggests four subgroups based on (i) quantitative and qualitative parameters such as age and the expected aneuploidy rate; (ii) ovarian reserve biomarkers (AFC and/or AMH); and (iii) ovarian response—provided a previous stimulation cycle has been performed. In addition, the Poseidon Group has introduced a new marker for measuring the success of ART, namely, the number of oocytes needed for a specific patient to obtain at least one euploid embryo for transfer.[26,27] Along these lines, recently, an online calculator was developed and validated based on predictive modeling to help in estimating the number of metaphase II oocytes required to obtain the Poseidon marker of success.[27,28]

From a clinically practical point of view, the incorporation of age, oocyte yield, and ovarian reserve into the Poseidon classification allows for the distinction of two main categories, namely the "expected" (groups 3 and 4) and the "unexpected" PORs (groups 1 and 2). Overall, Poseidon groups 1 to 4 represent almost half of all patients attending fertility treatment clinics.[29] To summarize the putative advantages and disadvantages of the Poseidon classification we conducted a SWOT analysis (Figure 1), namely an efficient analytical framework useful to summarize strengths, weaknesses, opportunities, and threats of this classification.

Expected POR management

In the Poseidon population, around 55% falls into group 4 (patients ⩾35 years with poor ovarian reserve prestimulation parameters, namely, AFC < 5,

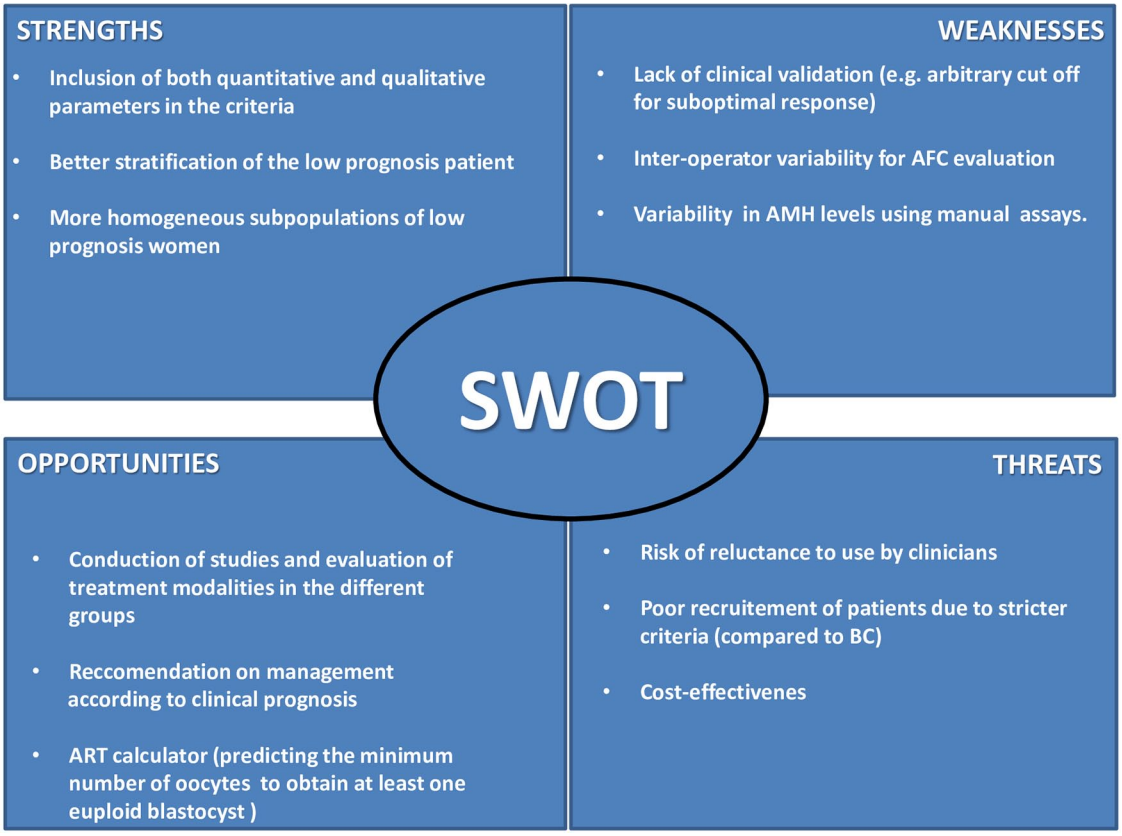

Figure 1. SWOT analysis of the novel POSEIDON criteria.

and/or AMH < 1.2 ng/ml) and 10% into group 3 (patients < 35 years with poor ovarian reserve prestimulation parameters, namely, AFC < 5 and/or AMH < 1.2 ng/ml).[29] However, in today's society, with the increasing age at first maternity wish, the percentage of patients among POR who fall into group 4 can be up to 76%.[30] The following sections encompass the main aspects regarding the management of expected PORs.

1. Pituitary suppression regimens
   A 2011 meta-analysis concluded that the choice of pituitary suppression in non-BC POR is irrelevant to the outcomes, with both gonadotropin-releasing hormone (GnRH) agonist and antagonist resulting in similar LBR.[31] Similarly, a 2017 meta-analysis accounting for ovarian response category also found no evidence of a difference in ongoing pregnancy rates between the antagonist and agonist groups.[32] However, in 2014, a well-designed RCT by Sunkara et al.[33] found that in expected POR, the long GnRH agonist protocol, albeit non-significantly, increased the number of mature oocytes by one oocyte as compared with the GnRH antagonist protocol. A plausible explanation of this finding may be the follicular synchronization following luteal follicle-stimulating hormone (FSH) suppression and inhibition of early follicular recruitment obtained with downregulation using an agonist protocol. Thus, hypothetically similar results would be obtained in GnRH antagonist cycles, using short-term daily estradiol for 5 days prior to menses, short GnRH antagonist pre-treatment at the beginning of the cycle, or oral contraceptives/progestins for 12–14 days as pretreatment.[34–36] Furthermore, the antagonist regimen is more patient-friendly and could eventually reduce the high dropout rates encountered in this difficult population.[37]
2. Type and dose of gonadotropins
   According to ESHRE 2019 guidelines on controlled ovarian stimulation, there is insufficient valid scientific evidence to favor the use of one type of gonadotropin rather than another in POR, making this

decision subject to availability, convenience, and costs.[38] Moreover, increasing the dose of the recombinant FSH (r-FSH) above 300 IU does not benefit the patient in terms of LBR,[39] while it may be even detrimental. In fact, a large retrospective study that analyzed more than 600,000 cycles reported that daily dosing above 300 IU of (including both) urinary (uFSH) and recombinant FSH (rFSH) significantly decreased the odds of a live birth.[40] There is, however, some evidence that the addition of recombinant human LH (rhLH) to rFSH during ART may have beneficial effects on outcomes in women with POR since it leads to increased FSH receptor expression and growth, improved follicular recruitment, and a reduced rate of granulosa cell apoptosis.[41–44] However, a large RCT enrolling ESHRE BC PORs in a long GnRH agonist downregulation protocol failed to find a significant difference in the number of oocytes retrieved through the addition of rhLH, while a benefit was reported for moderate and severe POR.[44] Ultimately, in 2018, a systematic review concluded that the benefit of rLH supplementation was more pronounced in unexpected PORs and women 36–39 years of age, while its use in the general POR population remains controversial.[45]

3. Natural cycle IVF/mild stimulation
   In a scenario where the overall oocyte yield is low (e.g. expected POR), the possibility of using mild stimulation regimens in PORs has been recommended by the American Society for Reproductive Medicine (ASRM),[46] underlying the fact that clinical pregnancy rates after conventional IVF gonadotropin protocols are similar to those obtained after mild ovarian stimulation protocols using low-dose gonadotropins (<150 IU/day).[46] In this setting, the stimulation is often preceded by use of adjuvant agents such as clomiphene citrate or letrozole; however, a recent network meta-analysis found that cotreatment with clomiphene, even though the most economical, had the lowest probability of resulting in pregnancy.[47] Mild ovarian stimulation approach in POR offers some advantages such as patient friendliness, reduced duration and dose of gonadotropins, as well as reduced overall cost per ovarian stimulation cycle. Indeed, a managed natural cycle might be a patient-friendly alternative in BC PORs of more than 40 years.[48] However, its potential is very limited irrespective of patient's age, as the live birth rate per cycle was estimated to be 2.6%.[49]
4. Dual stimulation
   To maximize the exploitation of the ovarian reserve in a limited timeframe, double stimulation in the same ovarian cycle (DuoStim) has been proposed. It combines follicular phase stimulation (FPS) with luteal phase stimulation (LPS) and can be considered a valuable option in patients with poor ovarian reserve.[50] This strategy led to reports of ongoing pregnancy rate per DuoStim cycle that reach 20.7% in POSEIDON group 4 patients.[50] Moreover, according to a recent publication, the oocytes derived by LPS appear to increase the cumulative LBR in a single ovarian cycle in patients fulfilling BC, making this approach a promising option in this difficult setting of patients.[51]
5. Additional supplements

a. Androgens
   Over the years of ART development, several therapeutic approaches have been proposed to increase the overall number of oocytes available in PORs. In particular, pretreatment with androgens such as dehydroepiandrosterone (DHEA) and/or testosterone has been investigated in a few small trials with conflicting results.[52–54] The rationale derived from primate studies is that androgens may augment FSH receptor expression in granulosa cells and, therefore, promote follicular growth and oestrogen biosynthesis by amplifying the effects of FSH, which in turn increases the recruitability and growth of pre-antral and antral follicles, through the IGF-1 system.[55] Nonetheless, the dosage, exact molecule, and the timing of pretreatment need to be further elucidated. The results of the T-TRANSPORT TRIAL (Clinicaltrial.gov identifier NCT02418572) evaluating a 60-day pretreatment using a daily dose of 5.5 mg transdermal testosterone in a large population of BC POR patients are expected to clarify these concerns.

b. Growth hormone
Another widely investigated therapeutic approach in ART has explored the efficacy of growth hormone (GH) in PORs. The biological rationale, deducted through animal models, relies on the observation that GH itself increases follicular insulin-like growth factor 1 (IGF-1), improving the response to gonadotropins, increasing oocyte competence and possibly increasing the DNA repair capacity in oocytes.[56–58] Evidence up to now used to suggest that adjuvant treatment with GH for POR patients could lead to a higher number of retrieved oocytes. This appeared to be particularly relevant in patients with very low or deficient levels of GH as identified by a clonidine challenge test.[3] However, a recently published double-blind, placebo-controlled randomized trial that enrolled 130 PORs found no statistical differences between the group subject to GH supplementation and the control group in terms of mean number of oocytes retrieved (5 *versus* 4, rate ratio 1.25, 95% CI 0.95–1.66).[59] Therefore, more studies are warranted before administration of GH in expected POR, and evidence regarding the optimal dose and duration of administration is still missing.

c. Antioxidants
Antioxidants are another class of medication with promising prospective in the POR population, especially as they manifest minimal to no adverse reactions and side effects. Recently, Zhang et al. reported the results of an RCT in 169 POSEIDON group 3 patients, showing a significantly higher number of retrieved oocytes and significantly less consumed FSH in the group pretreated for 60 days prior to ovarian stimulation with CoQ10 supplement as compared with controls. Hypothetically, CoQ10 would reduce mitochondrial oxidative stress resulting in improved oocyte competence.[60] Further prospective RCTs should be conducted to validate these findings.

6. Other considerations
In the last couple of years, emerging treatments are being investigated in an infertile population setting. In particular, *in vitro* activation (IVA) of follicles and drug-free IVA have attracted much interest and have been studied in PORs.[61,62] In 2013, Kawamura et al.[63] demonstrated that fragmenting ovarian cortexes, in order to disrupt the Hippo signaling pathway, and incubating them for 2 days with follicle activating (Akt-stimulating) agents promoted ovarian follicle growth after implantation. Drug-free IVA is a more recent experimental technique that may be possibly effective in promoting ovarian follicle growth without detrimental effects.[64] Preliminary results are encouraging: increased AFC, increased metaphase II oocytes, and six patients with clinical pregnancies.[64] Nonetheless, the small number of patients analyzed in these publications warrants cautious interpretation of the results.[3,64] In addition, very few studies have investigated perinatal and neonatal outcomes in patients with poor ovarian response, and although preliminary data are reassuring,[65] the issue cannot be considered settled. Therefore, large-scale randomized trials are needed to validate experimental techniques and their conclusions and clarify unsettled issues.

Unexpected POR management

Unexpected POR comprises groups 1 (<35 years old) and 2 (⩾35 years old) according to the Poseidon classification. Patients belonging to the aforementioned groups have normal ovarian reserve markers (AFC ⩾ 5 and/or AMH ⩾ 1.2 ng/ml), but for several reasons respond poorly (<4 oocytes retrieved) or suboptimally (4–9 oocytes retrieved) following conventional ovarian stimulation (COS).[25] Although numerous explanations have been given for the nature of unexpected poor/suboptimal ovarian response, the most dominant theory is that these patients may have polymorphisms [single nucleotide polymorphisms (SNPs)] in the receptor or genes of gonadotropins. The most well-studied SNP is found in the position 680 of the FSH receptor, and several studies have shown that patients homozygous for Serine may require more gonadotropins and have a longer stimulation compared with heterozygous or homozygous for asparagine counterparts.[45,66] In the same context, patient with a variant of the beta subunit of the LH gene (V LH–β) may also need a higher dose of stimulation and show hyposensitivity to COS,[67,68] while recent evidence suggests that even the combination of

different SNPs may affect pregnancy chances in women undergoing IVF.[69] Other causes of the unexpected anomalous response to COS include low gonadotropin starting dose,[70] asynchronous follicular development, and technical issues related to final oocyte maturation trigger and oocyte retrieval (e.g., obesity).[71]

FORT (follicular output rate) and FOI (follicle to oocyte index) are excellent qualitative markers of ovarian response that measure the consistency between AFC – number of pre-ovulatory follicles and AFC – number of oocytes retrieved, respectively.[72,73] Therefore, patients with low FORT/FOI (<50%) are typically those who produce a lower than expected (based on AMH/AFC) number of pre-ovulatory follicles/oocytes following gonadotropin stimulation.

Although the exact prevalence of hyporesponse to COS is difficult to estimate, it is supposed to range between 40% and 45%, thus highlighting that a remarkable number of women with normal ovarian reserve tests attending an IVF center might end up exhibiting an abnormal ovarian response after COS.[74,75] Furthermore, identification of suboptimal responders cannot be made *a priori*, given the lack of association between the presence of SNPs and AMH/AFC.[76] Whether FSH or LH receptor SNPs screening should be offered to all women with adequate ovarian reserve prior to their first IVF treatment is currently under debate as it depends on the prevalence of such SNPs in this particular IVF population and their clinical impact. Therefore, further studies evaluating the real role of SNPs and their association with reproductive outcomes are expected, and specific polygenetic traits may tailor IVF treatment in the future.

Treatment strategies

Management of patients belonging to the POSEIDON groups 1 and 2 requires a distinct diagnostic and therapeutic approach, taking primarily into account the fact that these women have an adequate ovarian reserve. Although evidence regarding the optimal treatment management of these patients is sparse and is mainly derived from retrospective studies, an increase in the oocyte yield represents a logical endpoint, given that the higher the number of oocytes retrieved, the higher the probability to obtain an euploid embryo and therefore increase the chances of success.[74,77–79]

1. Type of gonadotropins
   The main problem behind unexpected suboptimal/poor response is that the oocyte yield is not consistent with ovarian reserve. In this scenario and with the aim to retrieve more oocytes, a more "potent" gonadotropin formulation should be applied. Several RCTs and meta-analyses have shown that rFSH results in significantly more oocytes compared with urinary preparations,[80,81] suggesting that rFSH may be the gonadotropin of choice for Poseidon groups 1 and 2.
2. Type of downregulation protocol
   Both GnRH long agonist and antagonist protocols may be used in Poseidon groups 1 and 2, as extrapolated evidence from POR studies has shown comparable efficacy between the two regimens.[32] Furthermore, they seem to perform better compared with the short flare-up protocol.[33] Nonetheless, it would be relevant in the near future to make a direct comparison of the different protocols and assess their efficacy, specifically in unexpected POR.
3. Increase of initial dose of stimulation
   The adjustment of the gonadotropins' dose in the following cycle of unexpected POR represents one of the most common treatment modalities used in clinical practice. A pharmacogenetic study demonstrated that higher rFSH starting dose (225IU) in women homozygous for Ser680 (SS) resulted in significantly higher serum estradiol (E2) levels compared with SS women treated with a lower (150IU) dose and similar serum E2 levels with women homozygous for Asn680 (AA)/heterozygous (AS) treated with 150IU of rFSH.[82] In the same vein, a recent retrospective study evaluated the second cycle of 150 suboptimal responders and found that an increase in the stimulation dose of the second IVF cycle was associated with a significantly higher oocyte yield.[83] In particular, it seems that an increase by 50 units in the initial dose may result in one more oocyte. This finding should not be overlooked, especially if we consider that each additional oocyte may increase the LBR by 5%.[84]

4. Addition of rLH
   Administration of rLH supplementation in COS cycles of unexpected poor/suboptimal response has been evaluated by several studies, showing a benefit in terms of oocyte yield and pregnancy rates.[45,85–87] A 2:1 ratio of rFSH:LH could be suggested, with rLH starting at the mid-follicular phase in an attempt to rescue the ongoing cycle or from day 1 of the following IVF cyle.[88]
   The mechanism by which rLH acts is not fully understood, but its administration mainly benefits patients who are carriers of LH–β and present ovarian resistance to exogenous gonadotropins administration.[68]
5. Dual stimulation
   Dual stimulation could also be considered for patients showing a suboptimal response,[89] especially the older ones (group 2), given that oocyte and embryo aneuploidy rates are higher in this group compared with women <35 years, and a higher oocyte yield is required to obtain an euploid embryo. If we further take into account that oocytes/embryos derived from luteal phase stimulation show similar competence as follicular phase stimulation-ones,[90] it is evident that maximizing the total number of oocytes in one menstrual cycle would result in a higher probability to get a genetically normal embryo and as a consequence, the cumulative LBR would be increased. Nonetheless, these findings come from patients not explicitly fulfilling Poseidon groups 1 and 2 criteria, and thus caution is needed. Moreover, a "freeze only" strategy is mandatory which may not be convenient to all patients.
6. Androgens supplementation
   DHEA has been evaluated in a small RCT, including 109 women belonging to Poseidon group 2. Patients assigned to DHEA supplementation for 8 weeks before COS were found to have significantly higher LBR and lower miscarriage rate.[91] Nonetheless, the small sample size and the absence of sample size calculation preclude from drawing firm conclusions.

Conclusion

Poor ovarian response is a particularly unpleasant event in ART and represents a challenge both to the fertility expert and the patient itself. This difficult setting of patients has long been investigated, but only recently, clinicians are coming around to elaborating standard diagnostic criteria leading to comparable management strategies.

While there has been considerable progress, further randomized prospective studies are necessary to elucidate on remaining issues.

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