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 considerable 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 considerable 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 Devroey8 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 POR 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.

Finally, the heterogeneity encountered in BC POR could explain (a) the fact that none of treatment modalities has been shown to be effective8,21–24 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 (Patient-Oriented Strategies Encompassing Individualize DOocyte Number).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, 2.9% among women ≥43 years, highlighting the importance of age and the heterogeneity among the BC population.
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). 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%. 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. 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. However, in 2014, a well-designed RCT by Sunkara et al. 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. Furthermore, the antagonist regimen is more patient-friendly and could eventually reduce the high dropout rates encountered in this difficult population.

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.\textsuperscript{38} Moreover, increasing the dose of the recombinant FSH (r-FSH) above 300 IU does not benefit the patient in terms of LBR,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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),\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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%.\textsuperscript{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.\textsuperscript{50} This strategy led to reports of ongoing pregnancy rate per DuoStim cycle that reach 20.7% in POSEIDON group 4 patients.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 recruitable and growth of pre-antral and antral follicles, through the IGF-1 system.\textsuperscript{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, deduced 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, \textit{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.

\textbf{ 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. Other causes of the unexpected anomalous response to COS include low gonadotropin starting dose, asynchronous follicular development, and technical issues related to final oocyte maturation trigger and oocyte retrieval (e.g., obesity).

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. 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. Furthermore, identification of suboptimal responders cannot be made a priori, given the lack of association between the presence of SNPs and AMH/AFC. 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.

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, 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. Furthermore, they seem to perform better compared with the short flare-up protocol. 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. 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. 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. 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 cycle. 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.

5. Dual stimulation
Dual stimulation could also be considered for patients showing a suboptimal response, 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, 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. Nonetheless, the small sample size and the absence of sample size calculation preclude from drawing firm conclusions.

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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References
1. Ubaldi FM, Rienzi L, Ferrero S, et al. Management of poor responders in IVF. Reprod Biomed Online 2005; 10: 235–246.
2. Vaiarelli A, Cimadomo D, Ubaldi N, et al. What is new in the management of poor ovarian response in IVF. Curr Opin Obstet Gynecol 2018; 30: 155–162.
3. Blumenfeld Z. What is the best regimen for ovarian stimulation of poor responders in ART/IVF. Front Endocrinol (Lausanne) 2020; 11: 192.
4. Blumenfeld Z. Premature ovarian failure: etiology and possible prevention. Expert Rev Endocrinol Metab 2009; 4: 173–181.
5. Goswami D and Conway GS. Premature ovarian failure. Hum Reprod Update 2005; 11: 391–410.
6. Lee HC, Lyndon A, Blumenfeld YJ, et al. Antenatal steroid administration for premature neonates in California. Obstet Gynecol 2011; 117: 603–609.
7. Skillern A and Rajkovic A. Recent developments in identifying genetic determinants of premature ovarian failure. Sex Dev 2008; 2: 228–243.
8. Drakopoulos P, Vuong TNL, Ho NAV, et al. Corifollitropin alfa followed by highly purified HMG versus recombinant FSH in young poor ovarian responders: a multicentre randomized controlled clinical trial. *Hum Reprod* 2017; 32: 2225–2233.

9. Polyzos NP and Devroye P. A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the end of the tunnel. *Fertil Steril* 2011; 96: 1058–1061.

10. Ferraretti AP, La Marca A, Fauser BC, et al. ESHRE consensus on the definition of “poor response” to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Hum Reprod* 2011; 26: 1616–1624.

11. La Marca A, Grisendi V, Giuliani S, et al. Live birth rates in the different combinations of the Bologna criteria poor ovarian responders: a validation study. *J Assist Reprod Genet* 2015; 32: 931–937.

12. Polyzos NP, Nwoye M, Corona R, et al. Live birth rates in Bologna poor responders treated with ovarian stimulation for IVF/ICSI. *Reprod Biomed Online* 2014; 28: 469–474.

13. Busnelli A, Papaleo E, Del Prato D, et al. A retrospective evaluation of prognosis and cost-effectiveness of IVF in poor responders according to the Bologna criteria. *Hum Reprod* 2015; 30: 315–322.

14. Boza A, Oguz SY, Misirlioglu S, et al. Utilization of the Bologna criteria: a promise unfulfilled? A review of published and unpublished/ongoing trials. *Fertil Steril* 2018; 109: 104–109.

15. Frydman R. Poor responders: still a problem. *Fertil Steril* 2011; 96: 1057.

16. Papathanasiou A. Implementing the ESHRE “poor responder” criteria in research studies: methodological implications. *Hum Reprod* 2014; 29: 1835–1838.

17. Younis JS. The Bologna criteria for poor ovarian response; has the job been accomplished? *Hum Reprod* 2012; 27: 1874–1875; author reply 1875–1876.

18. Bozdag G, Polat M, Yarali I, et al. Live birth rates in various subgroups of poor ovarian responders fulfilling the Bologna criteria. *Reprod Biomed Online* 2017; 34: 639–644.

19. Romito A, Bardhi E, Errazuriz J, et al. Heterogeneity among poor ovarian responders according to Bologna criteria results in diverging cumulative live birth rates. *Front Endocrinol (Lausanne)* 2020; 11: 208.

20. Xu B, Chen Y, Geerts D, et al. Cumulative live birth rates in more than 3,000 patients with poor ovarian response: a 15-year survey of final in vitro fertilization outcome. *Fertil Steril* 2018; 109: 1051–1059.

21. Polyzos NP, Corona R, Van De Vijver A, et al. Corifollitropin alfa followed by hMG in GnRH agonist protocols. Two prospective feasibility studies in poor ovarian responders. *Gynecol Endocrinol* 2015; 31: 885–890.

22. Polyzos NP, Drakopoulos P and Tournaye H. Modified natural cycle IVF for poor ovarian responders: rethink before concluding. *Hum Reprod* 2016; 31: 221–222.

23. Errázuriz J, Romito A, Drakopoulos P, et al. Cumulative live birth rates following stimulation with corifollitropin alfa compared with h-pHMG in a GnRH antagonist protocol in poor ovarian responders. *Front Endocrinol (Lausanne)* 2019; 10: 175.

24. Errázuriz J, Drakopoulos P, Pening D, et al. Pituitary suppression protocol among Bologna poor responders undergoing ovarian stimulation using corifollitropin alfa: does it play any role. *Reprod Biomed Online* 2019; 38: 1010–1017.

25. Poseidon Group (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number), Alviggi C, Andersen CY, et al. A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept. *Fertil Steril* 2016; 105: 1452–1453.

26. Humaidan P, Alviggi C, Fischer R, et al. The novel POSEIDON stratification of “Low prognosis patients in Assisted Reproductive Technology” and its proposed marker of successful outcome. *F1000Res* 2016; 5: 2911.

27. Esteves SC, Carvalho JF, Bento FC, et al. A novel predictive model to estimate the number of mature oocytes required for obtaining at least one euploid blastocyst for transfer in couples undergoing in vitro fertilization/intracytoplasmic sperm injection: the ART calculator. *Front Endocrinol (Lausanne)* 2019; 10: 99.

28. Esteves SC, Yarali H, Ubaldi FM, et al. Validation of ART calculator for predicting the number of metaphase II oocytes required for obtaining at least one euploid blastocyst for transfer in couples undergoing in vitro fertilization/intracytoplasmic sperm injection. *Front Endocrinol (Lausanne)* 2019; 10: 917.
29. Haahr T, Dosouto C, Alviggi C, et al. Management strategies for POSEIDON groups 3 and 4. Front Endocrinol (Lausanne) 2019; 10: 614.

30. Alsbjerg B, Haahr T, Elbaek HO, et al. Dual stimulation using corifollitropin alfa in 54 Bologna criteria poor ovarian responders—a case series. Reprod Biomed Online 2019; 38: 677–682.

31. Pu D, Wu J and Liu J. Comparisons of GnRH antagonist versus GnRH agonist protocol in poor ovarian responders undergoing IVF. Hum Reprod 2011; 26: 2742–2749.

32. Lambalk CB, Banga FR, Huirne JA, et al. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. Hum Reprod Update 2017; 23: 560–579.

33. Sunkara SK, Coomarasamy A, Faris R, et al. Long gonadotropin-releasing hormone agonist versus short agonist versus antagonist regimens in poor responders undergoing in vitro fertilization: a randomized controlled trial. Fertil Steril 2014; 101: 147–23.

34. Humaidan P, La Marca A, Alviggi C, et al. Future perspectives of POSEIDON stratification for clinical practice and research. Front Endocrinol (Lausanne) 2019; 10: 439.

35. Blockeel C, Riva A, De Vos M, et al. Administration of a gonadotropin-releasing hormone agonist during the 3 days before the initiation of the in vitro fertilization/ intracytoplasmic sperm injection treatment cycle: impact on ovarian stimulation. Fertil Steril 2011; 95: 1714–1719.

36. Fischer R, Nakano FY, Roque M, et al. A quality management approach to controlled ovarian stimulation in assisted reproductive technology: the “Fischer protocol.” Panminerva Med 2019; 61: 11–23.

37. Ubaldi F, Vaiarelli A, D’Anna R, et al. Management of poor responders in IVF: is there anything new. Biomed Res Int 2014; 2014: 352098.

38. Group EREG. Guideline on ovarian stimulation for IVF/ICSI. Grimbergen: European Society of Human Reproduction and Embryology, 2019.

39. Berkkanoglu M and Ozgur K. What is the optimum maximal gonadotropin dosage used in microdose flare-up cycles in poor responders. Fertil Steril 2010; 94: 662–665.

40. Baker VL, Brown MB, Luke B, et al. Gonadotropin dose is negatively correlated with live birth rate: analysis of more than 650,000 assisted reproductive technology cycles. Fertil Steril 2015; 104: 1145–1152.e5.

41. Bosch E, Labarta E, Crespo J, et al. Impact of luteinizing hormone administration on gonadotropin-releasing hormone agonist cycles: an age-adjusted analysis. Fertil Steril 2011; 95: 1031–1036.

42. Hill MJ, Levens ED, Levy G, et al. The use of recombinant luteinizing hormone in patients undergoing assisted reproductive techniques with advanced reproductive age: a systematic review and meta-analysis. Fertil Steril 2012; 97: 1108–1114.e1.

43. Lehert P, Kolibianakis EM, Venetis CA, et al. Recombinant human follicle-stimulating hormone (r-hFSH) plus recombinant luteinizing hormone versus r-hFSH alone for ovarian stimulation during assisted reproductive technology: systematic review and meta-analysis. Reprod Biol Endocrinol 2014; 12: 17.

44. Humaidan P, Chin W, Rogoff D, et al. Efficacy and safety of follitropin alfa/lutropin alfa in ART: a randomized controlled trial in poor ovarian responders. Hum Reprod 2017; 32: 544–555.

45. Alviggi C, Conforti A, Esteves SC, et al. Recombinant luteinizing hormone supplementation in assisted reproductive technology: a systematic review. Fertil Steril 2018; 109: 644–664.

46. Practice Committee of the American Society for Reproductive Medicine. Comparison of pregnancy rates for poor responders using IVF with mild ovarian stimulation versus conventional IVF: a guideline. Fertil Steril 2018; 109: 993–999.

47. Zhang Y, Zhang C, Shu J, et al. Adjuvant treatment strategies in ovarian stimulation for poor responders undergoing IVF: a systematic review and network meta-analysis. Hum Reprod Update 2020; 26: 247–263.

48. Drakopoulos P, Romito A, Errázuriz J, et al. Modified natural cycle IVF versus conventional stimulation in advanced-age Bologna poor responders. Reprod Biomed Online 2019; 39: 698–703.

49. Polyzos NP, Blockeel C, Verpoest W, et al. Live birth rates following natural cycle IVF in women with poor ovarian response according to the Bologna criteria. Hum Reprod 2012; 27: 3481–3486.

50. Vaiarelli A, Cimadomo D, Trabucco E, et al. Double stimulation in the same ovarian cycle (DuoStim) to maximize the number of oocytes retrieved from poor prognosis patients: a multicenter experience and SWOT analysis. Front Endocrinol (Lausanne) 2018; 9: 317.
51. Vaiarelli A, Cimadomo D, Conforti A, et al. Luteal phase after conventional stimulation in the same ovarian cycle might improve the management of poor responder patients fulfilling the Bologna criteria: a case series. Fertil Steril 2020; 113: 121–130.

52. Yeung T, Chai J, Li R, et al. A double-blind randomised controlled trial on the effect of dehydroepiandrosterone on ovarian reserve markers, ovarian response and number of oocytes in anticipated normal ovarian responders. BJOG 2016; 123: 1097–1105.

53. Zhang M, Niu W, Wang Y, et al. Dehydroepiandrosterone treatment in women with poor ovarian response undergoing IVF or ICSI: a systematic review and meta-analysis. J Assist Reprod Genet 2016; 33: 981–991.

54. Nagels HE, Rishworth JR, Siristatidis CS, et al. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database Syst Rev 2015: CD009749.

55. Polyzos NP, Davis SR, Drakopoulos P, et al. Testosterone for poor ovarian responders: lessons from ovarian physiology. Reprod Sci 2018; 25: 980–982.

56. Drakopoulos P, Pluchino N, Bischof P, et al. Effect of growth hormone on endometrial thickness and fertility outcome in the treatment of women with panhypopituitarism: a case report. J Reprod Med 2016; 61: 78–82.

57. Mason HD, Martikainen H, Beard RW, et al. Direct gonadotrophic effect of growth hormone on oestradiol production by human granulosa cells in vitro. J Endocrinol 1990; 126: R1–R4.

58. Bachelot A, Monget P, Imbert-Bolloré P, et al. Growth hormone is required for ovarian follicular growth. Endocrinology 2002; 143: 4104–4112.

59. Norman RJ, Alvino H, Hull LM, et al. Human growth hormone for poor responders: a randomized placebo-controlled trial provides no evidence for improved live birth rate. Reprod Biomed Online 2019; 38: 908–915.

60. Xu Y, Nisenblat V, Lu C, et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reprod Biol Endocrinol 2018; 16: 29.

61. Sfakianoudis K, Simopoulou M, Nitos N, et al. A case series on platelet-rich plasma revolutionary management of poor responder patients. Gynecol Obstet Invest 2019; 84: 99–106.

62. Stojkovska S, Dimitrov G, Stamenkovska N, et al. Live birth rates in poor responders’ group after previous treatment with autologous platelet-rich plasma and low dose ovarian stimulation compared with poor responders used only low dose ovarian stimulation before in vitro fertilization. Open Access Maced J Med Sci 2019; 7: 3184–3188.

63. Kawamura K, Cheng Y, Suzuki N, et al. Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment. Proc Natl Acad Sci U S A 2013; 110: 17474–17479.

64. Kawamura K, Ishizuka B and Hsueh AJW. Drug-free in vitro activation of follicles for infertility treatment in poor ovarian response patients with decreased ovarian reserve. Reprod Biomed Online 2020; 40: 245–253.

65. Bardhi E, Blockeel C, Cools W, et al. Is ovarian response associated with adverse perinatal outcomes in GnRH antagonist IVF/ICSI cycles? Reprod Biomed Online. Epub ahead of print 11 April 2020. DOI: 10.1016/j.rbmo.2020.03.010.

66. Perez Mayorga M, Gromoll J, Behre HM, et al. Ovarian response to follicle-stimulating hormone (FSH) stimulation depends on the FSH receptor genotype. J Clin Endocrinol Metab 2000; 85: 3365–3369.

67. Alviggi C, Humaidan P, Howles CM, et al. Biological versus chronological ovarian age: implications for assisted reproductive technology. Reprod Biol Endocrinol 2009; 7: 101.

68. Alviggi C, Pettersson K, Longobardi S, et al. A common polymorphic allele of the LH beta-subunit gene is associated with higher exogenous FSH consumption during controlled ovarian stimulation for assisted reproductive technology. Reprod Biol Endocrinol 2013; 11: 51.

69. Lindgren I, BAYAY M, Uvebrant K, et al. Combined assessment of polymorphisms in the LHCGR and FSHR genes predict chance of pregnancy after in vitro fertilization. Hum Reprod 2016; 31: 672–683.

70. Sunkara SK and Polyzos NP. OPTIMIST trial: optimistic evidence? Hum Reprod 2018; 33: 983–984.

71. Romanski PA, Farland LV, Tsen LC, et al. Effect of class III and class IV obesity on oocyte retrieval complications and outcomes. Fertil Steril 2019; 111: 294–301.

72. Gallot V, Berwanger da Silva AL, Genro V, et al. Antral follicle responsiveness to follicle-stimulating hormone administration assessed by the Follicular Output RaTe (FORT) may predict in vitro fertilization-embryo transfer outcome. Hum Reprod 2012; 27: 1066–1072.
73. Alviggi C, Conforti A, Esteves SC, et al. Understanding ovarian hypo-response to exogenous gonadotropin in ovarian stimulation and its new proposed marker—the follicle-to-oocyte (FOI) index. *Front Endocrinol (Lausanne)* 2018; 9: 589.

74. Drakopoulos P, Blockeel C, Stoop D, et al. Conventional ovarian stimulation and single embryo transfer for IVF/ICSI. How many oocytes do we need to maximize cumulative live birth rates after utilization of all fresh and frozen embryos? *Hum Reprod* 2016; 31: 370–376.

75. Conforti A, Esteves SC, Picarelli S, et al. Novel approaches for diagnosis and management of low prognosis patients in assisted reproductive technology: the POSEIDON concept. *Panminerva Med* 2019; 61: 24–29.

76. Mohiyiddeen L, Newman WG, McBurney H, et al. Follicle-stimulating hormone receptor gene polymorphisms are not associated with ovarian reserve markers. *Fertil Steril* 2012; 97: 677–681.

77. Polyzos NP, Drakopoulos P, Parra J, et al. Cumulative live birth rates according to the number of oocytes retrieved after the first ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection: a multicenter multinational analysis including approximately 15,000 women. *Fertil Steril* 2018; 110: 661–670.e1.

78. Ata B, Kaplan B, Danzer H, et al. Array CGH analysis shows that aneuploidy is not related to the number of embryos generated. *Reprod Biomed Online* 2012; 24: 614–620.

79. Drakopoulos P, Errazuriz J, Santos-Ribeiro S, et al. Cumulative live birth rates in in-vitro fertilization. *Minerva Ginecol* 2019; 71: 207–210.

80. Devroey P, Pellicer A, Nyboe Andersen A, et al. A randomized assessor-blind trial comparing highly purified hMG and recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer. *Fertil Steril* 2012; 97: 561–571.

81. Santi D, Casarini L, Alviggi C, et al. Efficacy of follicle-stimulating hormone (FSH) alone, FSH + luteinizing hormone, human menopausal gonadotropin or FSH + human chorionic gonadotropin on assisted reproductive technology outcomes in the “personalized” medicine era: a meta-analysis. *Front Endocrinol (Lausanne)* 2017; 8: 114.

82. Behre HM, Greb RR, Mempel A, et al. Significance of a common single nucleotide polymorphism in exon 10 of the follicle-stimulating hormone (FSH) receptor gene for the ovarian response to FSH: a pharmacogenetic approach to controlled ovarian hyperstimulation. *Pharmacogenet Genomics* 2005; 15: 451–456.

83. Drakopoulos P, Santos-Ribeiro S, Bosch E, et al. The effect of dose adjustments in a subsequent cycle of women with suboptimal response following conventional ovarian stimulation. *Front Endocrinol (Lausanne)* 2018; 9: 361.

84. Martin JR, Bromer JG, Sakkas D, et al. Live babies born per oocyte retrieved in a subpopulation of oocyte donors with repetitive reproductive success. *Fertil Steril* 2010; 94: 2064–2068.

85. De Placido G, Alviggi C, Perino A, et al. Recombinant human LH supplementation versus recombinant human FSH (rFSH) step-up protocol during controlled ovarian stimulation in normogonadotrophic women with initial inadequate ovarian response to rFSH. A multicentre, prospective, randomized controlled trial. *Hum Reprod* 2005; 20: 390–396.

86. Papaleo E, Vanni VS, Viganò P, et al. Recombinant LH administration in subsequent cycle after “unexpected” poor response to recombinant FSH monotherapy. *Gynecol Endocrinol* 2014; 30: 813–816.

87. Conforti A, Esteves SC, Di Rella F, et al. The role of recombinant LH in women with hypo-response to controlled ovarian stimulation: a systematic review and meta-analysis. *Reprod Biol Endocrinol* 2019; 17: 18.

88. Conforti A, Esteves SC, Cimadomo D, et al. Management of women with an unexpected low ovarian response to gonadotropin. *Front Endocrinol (Lausanne)* 2019; 10: 387.

89. Vaiarelli A, Cimadomo D, Argento C, et al. Double stimulation in the same ovarian cycle. *Hum Reprod* 2005; 20: 390–396.

90. Cimadomo D, Vaiarelli A, Colamaria S, et al. Luteal phase anovulatory follicles result in the production of competent oocytes: intra-patient paired case-control study comparing follicular versus luteal phase stimulations in the same ovarian cycle. *Hum Reprod* 2018; 33: 1442–1448.

91. Tartagni M, Cicinelli MV, Baldini D, et al. Dehydroepiandrosterone decreases the age-related decline of the in vitro fertilization outcome in women younger than 40 years old. *Reprod Biol Endocrinol* 2015; 13: 18.