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# Treatment modalities for poor ovarian responders

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The term poor ovarian response (POR) was first introduced by the Bologna Criteria (BC), as a condition which includes at least two of the following features: advanced maternal age (⩾40 years), a previous POR with ⩽3 oocytes retrieved after conventional stimulation and/or an abnormal ovarian reserve test [i.e. antral follicle count (AFC) < 7 or anti-Müllerian hormone (AMH) < 1.1 ng/ml]. In the case of non-advanced maternal age and normal ovarian reserve test, POR is defined when a patient reports two episodes of POR following maximal ovarian stimulation.[1] Although the BC represented a milestone in the field of *in vitro* fertilization (IVF),[2] criticism about its substantial heterogeneity of the population may have prevented its widespread use in clinical practice. In this regard, a recent re-evaluation of these criteria has been proposed by the Poseidon Group (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number)[3] in order to overcome limitations of the BC. Some of the weaknesses of the BC are the ambiguity in defining risk factors, its substantial heterogeneity, the lack of accounting for oocyte quality, and other factors that can be associated with a low ovarian reserve.[4–6] In this view, the Poseidon Group classification has been developed to better stratify the 'low-prognosis patient' by considering (1) qualitative and numerical parameters (e.g. expected aneuploidy rate and patient's age); (2) ovarian reserve indicators (AFC and/or AMH); and (3) ovarian response to previous stimulation cycle, including four subgroups of patients: [Group 1: women younger than 35 years with AFC ⩾ 5 and AMH ⩾ 1.2; Group 2: women of age ⩾ 35 with AFC ⩾ 5 and AMH ⩾ 1.2; Group 3: women younger than 35 years old with AFC < 1 and AMH < 1.2 ng/ml; Group 4: ⩾35 with AFC < 1 and AMH < 1.2 ng/ml].

Moreover, the same group has presented a new marker to assess the potential success of assisted reproductive techniques (ARTs) by considering the number of oocytes required to obtain at least one euploid embryo to transfer.[7,8]

PORs consist of up to 20% of patients undergoing ovarian stimulation for IVF,[9] with an expected progressive increase due to the advanced maternal age of women seeking IVF. With regards to the reproductive outcomes, robust evidence has shown low live birth rates (LBRs) and high cancellation rates[10,11] in this specific population that refuses egg donation and prefers to undergo ART with their own genetic material. Thus, the management of PORs represents a real challenge for clinicians involved in ARTs. The last two decades have been marked by efforts focused on methods to improve reproductive outcomes of PORs; however, most studies have failed to identify therapeutic strategies that are unequivocally effective.

## Ovarian stimulation protocol

With regards to ovarian stimulation, among pituitary suppression regimens, it seems that the administration of gonadotropin-releasing hormone (GnRH) agonist or antagonist in PORs results in comparable LBR.[12] A recent meta-analysis replicated these findings and did not show any significant difference in ongoing pregnancy rates between the two groups.[13] However, there is a slight tendency, although statistically non-significant, in obtaining more mature oocytes

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following long GnRH agonist protocol compared to GnRH antagonist protocol.[14] On the contrary, the antagonist protocol seems to be more patient-friendly with a diminished dropout rate compared to regimens with GnRH agonist.[15]

The use of dual stimulation has been recently proposed as a possible therapeutic strategy for patients who have a suboptimal response to ovarian stimulation.[16,17] The rationale of this approach is to increase the total number of oocytes obtained in one menstrual cycle, which in turn might lead to a higher number of embryos and an increased probability to get euploid embryos with improved LBR.[18] The available evidence up to the time of publication is not strong enough to show superiority of dual stimulation compared to conventional stimulation in PORs. In contrast, double stimulation is considered an effective method in the case of patients who urgently need to increase their oocyte yield, such as those with malignant diseases undergoing fertility preservation. Weaknesses of this strategy are considered the mandatory use of 'freeze-all' and the lack of cost-effectiveness data.

## Dosage of gonadotropins

With respect to gonadotropins dosages, traditional approach for PORs consisted in ovarian stimulation regimens with elevated dosages (⩾300 IU gonadotropins/day); however, doubts about the effectiveness of this aggressive strategy have recently emerged, questioning whether milder ovarian stimulation protocols, with lower gonadotropin doses, would be equally effective.[19,20] To date, several studies have been conducted to investigate this topic, with most of them reporting similar clinical pregnancy rates (CPRs) and LBRs between the two regimens.[21]

Given that that the overall oocyte yield expected in PORs is low, the possibility of using a mild stimulation approach has been recommended by the American Society for Reproductive Medicine (ASRM),[22] due to the fact that the similar outcomes in term of CPRs can be achieved with low-dose gonadotropins (<150 IU/day).

## Modified natural cycle

The use of modified natural cycle (MNC-IVF) with minimal stimulation has been proposed as a therapeutic strategy in PORs,[20,23,24] with the aim to retrieve a single oocyte, showing better characteristics, which may result in a single top-quality embryo.[25] However, so far, the scientific community had mainly focused on the efficiency of IVF-MNC compared to conventional ovarian stimulation in women with predicted POR, without investigating whether the choice of type and dose of gonadotropin could have an impact on the clinical outcome of MNC-IVF cycles. Boudry *et al.*[26] recently commented on different dosages (75 IU/daily and 150 IU/daily) and type of treatment strategy (rFSH and hpHMG) used in PORs during MNC-IVF cycles.[27,28] Conclusions showed that dosage of gonadotropins should be individualized.[26]

## Gonadotropins type

The ESHRE 2019 guidelines on controlled ovarian stimulation suggest that there is no robust scientific evidence supporting the use of one type of gonadotropin rather than another,[29] with similar results described between the use of recombinant (r-FSH) and urinary (uFSH) FSH.[30,31] Several randomized clinical trials (RCTs) and meta-analyses have shown that the use of rFSH results in significantly more oocytes compared with urinary preparations, especially for Poseidon groups 1 and 2.[32,33] Nevertheless, this may not be translated into better reproductive outcomes.[26] The addition of recombinant human LH (rhLH) to rFSH during ART in PORs has been investigated, showing conflicting results; in particular, some studies encouraged the addition of rhLH to rFSH during ovarian stimulation, given that it may increase FSH receptor expression and growth as well as improve follicular recruitment and reduce the apoptotic rate of granulosa cell,[34–37] but other studies have failed to replicate these findings.[37] A recent systematic review concluded that the administration of rLH supplementation in the general POR population is not recommended, while unexpected PORs and women of 36–39 years of age, may benefit from its addition.[38]

Regarding modified FSH preparations, the new long-acting FSH (corifollitropin alfa) represents an interesting option for patients who prefer to minimize the discomfort of daily injections of exogenous gonadotropins, as one injection sustains follicular development for 7 days. In 2015, an RCT, focused on the use of long-acting FSH

in poor responders showed no significant difference in terms of cumulus-oocyte complexes (COCs) retrieved when compared to daily injections of gonadotropins.[39] On the contrary, although an increase in ongoing pregnancy rate was reported in a small pilot study conducted in young poor responders, investigating the use of long-acting corifollitropin alfa followed by daily injections of hMG,[40] a large RCT in 2017 did not show any significant difference in the number of oocytes or ongoing pregnancy rate.[41]

## Adjuvant treatments

The use of human growth hormone (GH) has been investigated, as a safe and active agent that may increase ovarian activity.[42] GH, as shown in animal models, may increase follicular insulin-like growth factor 1 (IGF-1), improving the response to gonadotropins; moreover, it seems that it also acts ameliorating oocyte competence and DNA repair mechanisms in oocytes.[43,44]

Although, to date, scientific evidence has suggested that the additional therapy with GH may be of benefit for PORs, potentially leading to a higher number of retrieved oocytes, a recent RCT conducted in this category of women did not report any statistically significant difference in the number of occytes retrieved between the group who underwent GH supplementation and the control group (5 versus 4, rate ratio 1.25, 95% CI: 0.95–1.66).[45] In current clinical practice, GH is administered as a potential adjuvant therapy for human reproduction, however should be used cautiously due to the lack of firm evidence supporting its role during ART.[46] Among adjuvant treatments aiming to enhance PORs outcomes, androgens pretreatment with dehydroepiandrosterone (DHEA) and/or testosterone have been investigated in a few small trials with controversial results.[47–49] The biological rationale for this strategy relies on the fact that androgens may increase the expression of FSH receptors in granulosa cells, promoting the growth of follicles and FSH effects, leading to enhanced recruitment and growth of pre-antral and antral follicles, through the IGF-1 system.[50]

With regards to antioxidants, it seems that their use might improve oocyte competence in PORs due to the fact that they may reduce mitochondrial oxidative stress. In fact, a recent RCT conducted in 169 Poseidon group 3 women showed that patient belonging to the group pretreated with CoQ10 for 60 days prior to ovarian stimulation had a higher number of oocytes and significantly less consumed gonadotropins compared to the group not receiving CoQ10 pretreatment.[51] However, larger prospective RCTs are warranted to validate these findings.

## Oocyte rejuvenation

Cytoplasmic replacement strategy has been proposed as a strategy to improve oocyte quality, considering the pivotal role of mitochondria and other cellular components in achieving oocyte competence. Indeed, this interesting therapeutic approach relies on the fact that several important components such as proteins, energy-producing components, RNAs, and mitochondria are located in the cytoplasm of young and healthy oocytes and contribute to the correct function of gametes;[52] thus it could be hypothesized that transferring these factors may lead to oocyte rejuvenation by improving the processes of maturation, fertilization, and embryo development. In this context, mitochondrial enrichment techniques, consisting in cytoplasm transfer from heterologous cells, or from autologous ovarian stem cells, adipose-derived stem cells and granulosa cells, have been recently proposed as a method to improve the oocyte quality of PORs.[53] Although promising, this strategy is still experimental, with few clinical trials conducted in humans.

In conclusion, several therapeutic proposals aiming to enhance fertility of PORs have been introduced in the last decades; however, most of them did not show any significant effect, while they were limited by small sample size and heterogeneous populations. Well designed, RCTs performed in homogeneous subgroups of low-prognosis women are warranted. We hope that future trials will be of sufficient quality to give clear and conclusive answers on how to best manage this challenging group of patients.

## Declarations

*Ethics approval and consent to participate*

Not applicable.

*Consent for publication*

Not applicable.

### *Author contributions*

**Federica Di Guardo:** Conceptualization;Writing – original draft;Writing – review & editing.

**Nicola Pluchino:** Writing – review & editing.

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### *Availability of data and materials*

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