Poor responders in IVF – is there any evidence-based treatment for them?

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Abstract

Despite the vast experience in controlled ovarian hyperstimulation, there are still women who respond poorly to gonadotropins, which results in few oocytes at retrieval, reduced number of embryos for transfer and consequently unsatisfactory pregnancy rates. Although such patients are quite common in IVF practice, the exact prevalence of so-called "poor responders" is difficult to estimate due to the variety of applied definitions. The urgent need for an internationally accepted definition of poor ovarian response (POR) was addressed by an ESHRE Workshop held in Bologna in 2010, where the consensus was reached and criteria were finally established. The application of this uniform definition may allow a correct estimate of POR prevalence and, what is more important, designing proper trials to assess and finally compare the interventions used in POR patients.
The article describes the possible physiology of POR and patient characteristics, mentions risk factors and laboratory tests of decreased ovarian reserve. Finally it reviews the possible management of POR with different stimulation protocols in the light of EBM. Basing on published meta-analyses, various additional alternatives (such as estradiol priming, the addition of rLH, growth hormone, androgens and androgen-modulating agents, aspirin) are also summarized.
Despite the two decades of trying, there is still no consensus on what is best for POR. No single treatment can be recommended over another, as the evidence for all of them is insufficient. It is obvious that interventions used in POR require properly designed large randomized studies, because until now there is no evidence-based treatment for that particular group of patients.

R E V I E W   A R T I C L E

INTRODUCTION

The history of controlled ovarian hyperstimulation (COH) for *in vitro* fertilization (IVF) reaches 40 years. Despite the vast experience in that field, there are still women who respond poorly to gonadotropins, which results in few oocytes at retrieval, reduced number of embryos for transfer and consequently unsatisfactory pregnancy rates. Although such patients are quite common in IVF practice, the exact prevalence is difficult to estimate and it varies between 5.6–35.1%, depending on the definition of poor response used in the studies (Oudendijk *et al.* 2012). The first description of such patient appeared in 1983 (Garcia *et al.* 1983). Nowadays, a simple MEDLINE, EMBASE and

Cochrane library search will reveal hundreds of papers published on poor ovarian response, its possible pathogenesis, suggested treatment options and clinical pregnancy rates. However, the heterogeneity between the trials is so great that the results are difficult to compare and interpret. IVF-Worldwide survey conducted in 45 countries including 196 infertility centers also revealed a huge variation in the definition and treatment used in such patients (IVF Worldwide Survey 2010). The problem was also addressed by Polyzos and Devroey, who aimed at assessing the definitions for "poor ovarian responders" used among randomized trials for the treatment of women with impaired response to stimulation. They found 41 different definitions in 47 randomized trials and, therefore, suggested that meta-analyses of such papers may have ambiguous value (Polyzos & Devroey 2011). The urgent need for an internationally accepted definition of POR was addressed by an ESHRE Campus Workshop held in Bologna in March 2010. The workshop participants first agreed that the term "poor responders" should imply an intrinsic inability of ovaries to react accordingly to the chosen stimulation. Finally, they reached a consensus and suggested the minimal criteria needed to define POR, where at least 2 out of 3 features must be present: (1) advanced maternal age (≥40 years) or any other risk factor for POR; (2) a previous POR (≤3 oocytes retrieved after a conventional stimulation); (3) an abnormal ovarian reserve test (AFC <5–7 follicles or AMH <0.5–1.1 ng/ml) (Ferraretti *et al.* 2011). The application of this uniform definition may allow a correct estimate of POR prevalence and, what is more important, designing proper trials to assess and finally compare the interventions used in POR patients.

PHYSIOLOGY OF POOR OVARIAN RESPONSE AND PATIENT CHARACTERISTICS

It is widely known that there is a physiological decline in the number of ovarian follicles over time, especially from the age of 37–38 onwards (Faddy *et al.* 1992). Poor ovarian response may be treated as a sign of ovarian aging and a reduced ovarian reserve, however, its premature occurrence is not fully understood (Ubaldi *et al.* 2014; Ferraretti *et al.* 2011). Nevertheless, it is worth mentioning that the poor response to controlled ovarian hyperstimulation may be due both to the presence of a reduced number of FSH sensitive follicles (so-called diminished ovarian reserve) and also to the suboptimal exposure to gonadotropins (for example in obese women) or the presence of FSH receptor subtypes rendering follicles less sensitive to exogenous gonadotropins (Oudendijk *et al.* 2012; Maheshwari *et al.* 2007).

A significant reduction in oocyte quality comes together with age-dependent declining ovarian reserve. Therefore, it seems clear that older poor responders have poorer chances of implantation and higher risk of early pregnancy loss. Nevertheless, we do not know for sure what the link between the quantity of antral follicles and the quality of oocytes held within them is. We can assume that not all POR patients are similar in quality and pregnancy prognosis, but they might be quite difficult to identify.

Certain patient characteristics are definitely important in terms of prognosis. According to Oudendijk *et al.* age remains the most important when pregnancy rates are discussed. Their pooled data showed a decreased pregnancy rate in older poor responders (from 1.5% to 12.7% in patients >36 years of age) and significantly higher in younger POR patients (13% to 35% up to the age of 36). However, the heterogeneity of the meta-analyzed studies was the weakness of their paper regarding this particular matter (Oudendijk *et al.* 2012).

There is a substantial lack of studies regarding the influence of BMI on pregnancy rates in poor responders. Orvieto *et al.* showed that, regardless of age, obese poor responders (BMI >30 kg/m²) had significantly lower pregnancy rates in comparison to non-obese poor responders (4.5% vs. 23%) (Orvieto *et al.* 2009). Therefore, the initial BMI seems to be a very important prognostic factor in that difficult group of patients.

The number of retrieved oocytes (the degree of poor response) is also a very important prognostic factor for pregnancy rate in POR patients. Few studies investigated pregnancy rates in women with one to four oocytes retrieved. The pregnancy rate was very low with one oocyte (0–2.3%), higher with two retrieved oocytes (4.3–15.2%) and still slightly better with 3–4 oocytes obtained at pick-up (11.5–15.9%) (Ulug *et al.* 2003, Baka *et al.* 2006, Timeva *et al.* 2006).

RISK FACTORS OF DECREASED OVARIAN RESERVE

Controlled ovarian hyperstimulation may be perceived as a dynamic test for the resting ovarian follicular pool. It is obvious that the mentioned pool diminishes with advancing age, but at the same time it is known that younger age does not completely protect against POR – therefore POR patients are not a homogenous group. There are some genetic and acquired conditions that can be described as poor responder risk factors. Primary ovarian insufficiency is an ovarian dysfunction, often caused by an unknown mechanism, which leads to the premature exhaustion of the resting pool of primordial follicles. It may be due to an underlying genetic condition (numerical and structural chromosomal aberrations, various mutations or genetic variability – Turner syndrome or FMRI premutations being the most typical examples). Primary ovarian insufficiency is also caused by chronic smoking, autoimmune disorders, radiotherapy, chemotherapy – especially with alkylating agents or ovarian surgery, especially for endometriomas (Zou *et al.* 2008, De Vos *et al.* 2010,Ubaldi *et al.* 2014). Some authors suggest that new risk factors of POR emerged – among them diabetes mellitus type I, transfusion-

dependent B-thalassemia and uterine artery embolization for uterine myomas (Ubaldi *et al.* 2010). It is obvious that such patients require a stimulation protocol that could fully exploit their depleted reserve in order to achieve the best possible pregnancy rate.

TESTS FOR OVARIAN RESERVE

The ideal ovarian reserve test (ORT) should reflect the extent of the primordial follicle pool and reproductive competence of the oocytes within. However, the tests used nowadays only provide an indirect measure of the cohort of antral follicles present in the FSH window at the beginning of the menstrual cycle. ORT used worldwide include basal FSH, inhibin B, antral follicle count (AFC), ovarian volume, some dynamic tests and anti-Mullerian hormone (AMH) (Broekmans *et al.* 2006, La Marca *et al.* 2010).

Basal FSH may be considered a good predictor only at high threshold levels, representing deeply compromised ovarian reserve. A suggested cut-off level of FSH is >12mIU/mL, which is still fairly good after correcting for age (Galey-Fontaine *et al.* 2005, Broekmans *et al.* 2006).

AFC and AMH have the best sensitivity and specificity for predicting ovarian response among all available tests. Nevertheless, their best cut-off values are still associated with a false positive rate of 10 to 20% (Broekmans *et al.* 2006, La Marca *et al.* 2010, Broer *et al.* 2009). Moreover, a meta-analysis performed by Verhagen *et al.* showed that the use of combined tests has no advantage over a single test (Verhagen *et al.* 2008). According to Bologna criteria the suggested cut-off values for AFC are less than 5–7 follicles and for AMH the range 0.5–1.1 ng/mL. It was suggested that extreme cut-off values are preferred, as they are associated with high specificity (Ferraretti *et al.* 2011). From the clinical point of view AFC is the most widely used marker of ovarian reserve due to its simplicity and omnipresence of ultrasound. Nevertheless, there is no better test than response of the ovaries to ovarian stimulation itself.

THE MANAGEMENT OF POOR RESPONDERS

Stimulation protocols

Poor ovarian response to controlled ovarian hyperstimulation remains a major problem in assisted reproduction, as for the past 20 years many different stimulation protocols have been suggested for POR patients and none of them is significantly better than the other.

Increasing doses of gonadotropins in stimulation protocols is the common management used by all clinicians in poor responders. To what extent should it be performed? In one of the papers regarding that subject, the authors confirmed that there was no difference in the number of oocytes retrieved, number of embryos obtained and pregnancy rates, between the starting dose of 300UI, 450UI and 600UI of gonadotropins daily (Berkkanoglu & Ozgur 2010). It seems clear that the administered gonadotropins can only support the cohort of follicles receptive to stimulation, with no ability to produce new ones.

It was also suggested that long agonist protocols could have a detrimental effect in POR patients due to excessive suppression. Various authors tried to decrease the length of suppression or to lower / stop the dose of GnRH agonists initiated in the luteal phase. Short and ultrashort flare up regimens have been widely used in poor responders, but none of the studies could clearly demonstrate any beneficial effect of the applied management on the clinical outcome. Kyrou *et al.* published a meta-analysis, in which the authors compared the variety of stimulation regimens used in poor responders. They showed that there was no statistically significant difference in the clinical pregnancy rate per randomized patient, in the duration of stimulation, or in the dose of gonadotropins used when different types of stimulation regimens were compared (Kyrou *et al.* 2009).

Some clinicians suggest that there is a rationale for the use of GnRH antagonists in poor responders, as they might benefit from the lack of suppression of endogenous gonadotropins during follicular recruitment. However, two meta-analyses regarding this subject demonstrated that although the duration of stimulation was shorter with antagonists, there were no differences in the number of retrieved oocytes, cycle cancellation rates and clinical pregnancy rates between agonist and antagonist regimens (Griesinger at al. 2006, Pu *et al.* 2011).

The introduction of a new hybrid molecule with a prolonged half-life (corifollitropin alfa) was thought to bring some hope for poor responders – due to its pharmacokinetics it could exploit the reduced ovarian reserve better than standard gonadotropins (rapid increase in serum FSH concentration during the early follicular phase). The pilot study assessing the use of corifollitropin alfa in poor responders utilized Bologna criteria, which makes it more eligible for practice. However, it showed that the treatment of poor ovarian responders with the new gonadotropin in a GnRH antagonist protocol resulted in low pregnancy rates, similarly to conventional stimulation with a short agonist protocol (Polyzos *et al.* 2013).

Additional alternatives for poor responders

Over the years several alternative approaches have been suggested for poor responders, aiming at strengthening the effect of exogenous gonadotropins. So far, all the management alternatives are inconclusive. Below the main meta-analyses are shortly described.

Estradiol priming: the addition of estradiol in the luteal phase preceding GnRH antagonist protocols could improve the synchronization of the pool of follicles for COH. Reynolds *et al.* selected 8 studies referring

to estradiol priming in POR and suggested that such management decreases the risk of cycle cancellation and increases the risk of clinical pregnancy (Reynolds *et al.* 2013). However, their meta-analysis was strongly criticized a year later due to important methodological pitfall (Polyzos & Tournaye 2014). Therefore, there is insufficient evidence regarding that particular treatment option in poor responders.

The addition of recombinant LH to recombinant FSH during stimulation: There are two recently published meta-analyses regarding that topic, revealing conflicting results. Fan *et al.* showed that the addition of LH did not increase the number of retrieved oocytes, the total dose of FSH, cycle cancellation and pregnancy rates (Fan *et al.* 2013). One year later another meta-analysis of 40 randomized trials supported the use of recombinant LH, showing the 30% increase in clinical pregnancy rates in poor responders (Lehert *et al.* 2014).

Addition of androgens: Basing on animal studies it was proved that androgens are crucial for an adequate follicular steroidogenesis – they increase FSH receptor expression in granulosa cells, thus promoting the initiation of primordial follicle growth, resulting in the improved number of growing preantral and antral follicles. Therefore, pretreatment with androgens (dehydroepiandrosterone or testosterone prior to stimulation) and androgen-modulating agents (aromatase inhibitors at the beginning of stimulation) has been very popular. A meta-analysis of Luo *et al.* demonstrated that transdermal testosterone effectively improved clinical outcomes of poor responders. The main problem of their study was the small sample size (3 papers included) and the heterogeneity of the treated group (Luo *et al.* 2014). Sunkara *et al.* analyzed testosterone and DHEA supplementation in poor responders, also showing improvement, but again the included studies were small and methodologically heterogenous (Sunkara *et al.* 2011). The addition of DHEA was also strongly criticized in one of the recently published papers pointing out to the retrospective character of the DHEA studies and again to the great heterogeneity of included subjects (Urman & Yakin 2012).

Growth hormone (GH) in poor responders: through its upregulating effect on the local production of insulin-like growth factor I, GH might modulate the FSH action on granulosa cells. It was suggested that the addition of GH increases the probability of live birth in POR population. The two available meta-analyses included a small number of patients, therefore their results definitely require reevaluation in properly designed larger RCTs (Kyrou *et al.* 2009, Kolibianakis *et al.* 2009)

Aspirin for POR: increased intraovarian vascularity might improve the delivery of hormones required for folliculogenesis. The evidence regarding aspirin is the poorest of all – the majority of papers failed to confirm any beneficial effect of such management (Ubaldi *et al.* 2014). The conclusion from the meta-analysis and a systematic review was that no improvement in clinical pregnancy rate was found with aspirin administration, thus it should not be routinely recommended for IVF treatment (Gelbaya *et al.* 2007).

Some authors suggest natural cycles IVF for poor responders, as an easy and relatively cheaper alternative. However, in such cycles only 50% proceed to embryo transfer (Ubaldi *et al.* 2014). Nevertheless, the introduction of Bologna criteria allowed the proper analysis of the efficiency of natural cycles IVF in poor responders – the cumulative birth rate per patient was extremely low and did not exceed 8%, thus they do not benefit from such management (Polyzos *et al.* 2012). The only available Cochrane review on interventions in poor responders was published prior to the introduction of Bologna criteria. It also proved that there was insufficient evidence to support the routine use of any particular intervention in POR patients (Pandian *et al.* 2010).

It is known that the number of retrieved oocytes increases the chances for pregnancy. In a recent analysis by Polyzos *et al.* using Bologna criteria for POR, the number of oocytes was the only variable significantly associated with live births (OR 1.92, 95% CI 1.03–3.55 for >3 versus 1–3 oocytes). Such patients demonstrated very low live birth rates, irrespective of age and treatment protocol used (Polyzos *et al.* 2014). However, as stated most recently, they still can achieve reasonable treatment outcomes and IVF treatment should not be precluded (Chai *et al.* 2015).

Despite the two decades of trying, there is still no consensus on what is best for poor responders. One cannot recommend any suggested treatment over another, as the evidence for all of them is insufficient. One must remember that evidence-based medicine means the application of science to the clinical practice – it is the only way leading to the reproducibility and transparency of the studies' results. It is obvious that interventions used in poor responders require properly designed large randomized studies, because until now there is no evidence-based treatment for that particular group of patients. On the other hand, some of those POR women might never live to see EBM treatment for them. Therefore, they are willing to try anything that could at least improve their chances for pregnancy (Urman & Yakin 2012). It makes us all susceptible to alternative therapies and marketing efforts of pharmaceutical companies.

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