A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept

The management of patients with impaired or poor ovarian response (POR) remains a controversial and complex clinical issue. A systematic review of 47 randomized controlled trials revealed 41 different definitions of POR (1). Notably, the number of oocytes retrieved was adopted as a criterion of POR in 40% of the trials, although the threshold number differed considerably among studies (1). To standardize the definition of POR, Ferraretti et al. (2) proposed new criteria, known as the "Bologna criteria," based on three conditions: 1) advanced maternal age (≥40 years) or any other POR risk factor; 2) a previous incident of POR; and 3) a low ovarian reserve test in terms of antimüllerian hormone (AMH) and antral follicle count (AFC). Two of these three criteria are required for a POR diagnosis. In addition, two cycles with POR after maximal stimulation are sufficient to classify a patient as a poor responder even in the absence of the other criteria mentioned. Although the Bologna criteria were found to be useful in predicting the outcome of IVF and for counseling purposes, their use in clinical trials has been questioned because they entail the risk of grouping together women who differ significantly in biologic characteristics (3). For example, according to the Bologna criteria, young women with a low ovarian reserve associated with a previous episode of POR, young women with a normal ovarian reserve and two POR episodes, and older women (≥40 years) with a normal ovarian reserve and a previous episode of POR would be included in the same category even though the clinical management of these patients requires different strategies.

In clinical terms, apart from the number of oocytes retrieved, various features that may affect treatment outcomes must be considered in the management of patients, namely: 1) the age-related embryo/blastocyst aneuploidy rate, which could dramatically change the prognosis in women that have the same oocyte yield; and 2) ovarian "sensitivity" to exogenous gonadotropins, which could be related to a specific genetic profile.

To introduce a more nuanced picture of POR, we here propose clinically relevant criteria that can help to guide the physician in the management of patients. In detail, we suggest a more specific new definition of "low prognosis" patients that:

1) Introduces two new categories of impaired response:
   a. A "suboptimal response," defined as the retrieval of four to nine oocytes, which is associated, at any given age, with a significantly lower live birth rate compared with normal responders i.e., those with 10–15 oocytes (4).
   b. A "hyporesponse," in which a higher dose of gonadotropins and more prolonged stimulation are required to obtain an adequate number of oocytes (more than three) (5).
2) Combines "qualitative" and "quantitative" parameters, namely:
   a. The age of the patient and the expected aneuploidy rate.
   b. Biomarkers and functional markers (i.e., AMH and AFC).

In essence, to improve the outcome of treatment, we propose a change from the definition of POR based on a combination of heterogeneous criteria to a concept of low prognosis. Specifically, we suggest the following groups of patients with different degrees of low prognosis, each of which requires specific evidence-based clinical algorithms that include all possible strategies "before, during, and after" stimulation.

Group 1: Patients < 35 years with sufficient prestimulation ovarian reserve parameters (AFC ≥5, AMH ≥1.2 ng/mL) and with an unexpected poor or suboptimal ovarian response. This group could be further divided into: subgroup 1a, constituted by patients with fewer than four oocytes; and subgroup 1b, constituted by patients with four to nine oocytes retrieved after standard ovarian stimulation, who, at any age, have a lower live birth rate than age-matched normal responders (4).

Group 2: Patients ≥ 35 years with sufficient prestimulation ovarian reserve parameters (AFC ≥5, AMH ≥1.2 ng/mL) and with an unexpected poor or suboptimal ovarian response. This group could be further divided into: subgroup 2a, constituted by patients with fewer than four oocytes; and subgroup 2b, constituted by patients with four to nine oocytes retrieved after standard ovarian stimulation, who, at any age, have a lower live birth rate than age-matched normal responders.

Group 3: Patients < 35 years with poor ovarian reserve prestimulation parameters (AFC <5, AMH <1.2 ng/mL).

Group 4: Patients ≥ 35 years with poor ovarian reserve prestimulation parameters (AFC <5, AMH <1.2 ng/mL).

The proposed stratification will serve as a guide to personalize treatment protocols by, for example,

a. Using different GnRH analogue regimens.
b. Detecting polymorphisms of gonadotropins and their receptors.
c. Tailoring the FSH starting dose.
d. Personalizing gonadotropin doses (i.e., FSH monotherapy or LH-containing drugs).
e. Evaluating special regimens, including oocyte/embryo accumulation to maximize outcomes.

In this context, we wish to introduce a new measure for successful treatment, namely, the ability to retrieve the

number of oocytes necessary to obtain at least one euploid embryo for transfer in each patient.

In conclusion, it is suggested that the new concept of low prognosis helps to improve the management of patients undergoing assisted reproductive technologies, promotes a tailored approach to patient handling, and identifies more homogeneous populations for clinical trials, thereby providing better tools with which to maximize IVF success rates.

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