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Short commentary

Ovarian Stimulation: Will we be able Once and for all to reach a Consensus?

Gorka Barrenetxea MD PhD*

Gynaecology and Obstetrics UPV/EHU, Reproducción Bilbao, Bizkaia, Spain

A recently published article on controversies about ovarian stimulation [1] deserves some reflections. Ovarian stimulation constitutes a key step, an inherent part of a full Assisted Reproduction (ART) process. The availability of a number of mature oocytes suitable for IVF improves the likelihood of achieving fertilization, and, thus, of generating good quality embryos and attaining a successful pregnancy. Nevertheless, the process faces different challenges. There are controversial points regarding ovarian stimulation. First, the fact that a significant number of women show a Poor Ovarian Response (POR) to stimulation. Furthermore, the number of oocytes necessary to obtain at least one live birth increases exponentially with age [2].

Second, the search of a marker to predict ovarian response is controversial and there is still debate as to what marker (or combination of them) is the most suitable [3]. Evaluation of ovarian reserve has been the focus of clinical research during last years since there is an increasing demand for assisted reproduction due in part to maternity postponement. As a result, a myriad of markers of ovarian reserve, including age, menstrual cycle length, basal FSH and Antral Follicle Count (AFC), Anti-Mullerian Hormone (AMH) levels have evolved to become part of the routine diagnostic testing performed prior to IVF [4].

For the purposes of knowing the usual practice in the field of ovarian stimulation with such a level of controversy, a Delphi study was carried out in Spain in 2021. This Delphi consensus provides a real-life clinical perspective on gonadotropin usage in IVF [1].

The Delhi study is practical in problematic areas where either statistical model-based evidence is not available or controversial, or the problem is not suited for precise analytical techniques. Furthermore, it can take advantage of subjective judgments on a collective basis. In its literal sense, Delphi method is a structured communication technique developed as a method of systematic and interactive forecasting based on a panel of experts. Although the method was initially developed for business forecasting using an expert panel's interactive discussion, assuming collective judgments are more valuable than individuals [5]. The principles of the method are that more minds are better than a single mind and the aim is to elicit and refine group judgments [6].

Unlike conventional surveys, the Delphi method consists of an iterative and interactive consultation. The method allows an iterative consultation of experts and/or stakeholders, in the written form, with the aim of obtaining an increasingly consensual response. Consensus can mean a group opinion or an alignment of the opinion of experts. Although a meta-analysis to evaluate quality of published Delphi studies found that only a 73% of the studies reported a consensus method, it is mandatory to define the process to reach the consensus and its definition. The consensus definition used commonly is the percentage of agreement based on a predefined cut-off, central tendency, or a combination of both [5,6].

Regarding patients with poor ovarian response, initially there are different parameters available to stratify the patients, such as age, baseline Follicle-Stimulating Hormone (FSH) concentration, Anti-Mullerian Hormone (AMH) concentration, and the Antral Follicle Count (AFC), used alone or in combination via algorithms or clinical nomograms. Although other authors have described baseline FSH, body mass index and older age as predictors of ovarian response, the experts considered antral follicle count and the AMH value to be predictors of response, which are also indicators that are preferentially recommended by the guidelines of the European Society of Human Reproduction and Embryology [7] compared to other markers.

The participants agreed on recommending antral follicle counts for all patients before stimulation and in each cycle. The experts also consider that when a previous cycle is not available, an antral follicle count or a determination of AMH should be carried out, but that it is unnecessary to measure the basal FSH [1]. The goal of ovarian stimulation is to achieve an adequate number of oocytes. The term adequate may have different meanings depending on the ovarian reserve of the patient being treated. For normal-responding patients, the panel of experts reached a consensus greater than 80% that the mentioned goal could be set at obtaining 10-15 oocytes. This figure is according with the most recently published data of the National Registry of activity of Spanish Fertility Society (SEF). The estimated number of oocytes necessary for achieving a pregnancy were 14,3 and 13,9 in 2019 and 2020 respectively [8,9].

From a quantitative point of view, the objective of ovarian stimulation among women with low ovarian reserve is to achieve as many oocytes as possible. Although there are a myriad of published studies assessing different protocols used among POR women, the results are controversial and there is no general consensus. The panel of experts agreed that the use of rFSH is recommended in 35-years-old women and younger and that combination gonadotropin treatment (i-e. combination of FSH and LH or LH effect) may be limited to women over 35 years of age [1].

***Corresponding author:** Gorka Barrenetxea MD PhD, Gynaecology and Obstetrics UPV/EHU, Reproducción Bilbao, Bizkaia, Spain, E-mail: gbarrenetxea@reproduccionbilbao.es

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Summing up, the recently published Delphi study gives relevant data regarding the clinical reality of ovarian stimulation for POR patients undergoing IVF in Spain with some conclusions:

- The different gonadotropins cannot alter the quality of the oocytes obtained. Ovarian stimulation can only support the growth of the follicles available during each ovarian cycle, but it cannot generate follicles ex-novo;
- The goal of ovarian stimulation is to obtain an adequate number of oocytes (in poor responders this is the maximum number possible, and in normal or hyper-responders it is between 10 and 15);
- The starting dose is determined well by response prediction factors;
- The most valid prediction factor is the response in a previous cycle;
- If there is no previous cycle, the antral follicle count and AMH value are the most reliable indicators of response [1].

All of our work should be based on three mainstays. First, the scientific evidence; second, our clinical experience and third, we always should take into account our patient´s preferences. This practical perspective output from the Delphi study based on the judgment and experience of panel of experts, is of great value in a field with numerous clinical questions raised and a high variability in clinical practice due to the scarcity of conclusive scientific evidence.

Thus, consensus may be closer.

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