The promised land of individualized ovarian stimulation: Are we there yet?

Over the past decade, the merits of individualized ovarian stimulation protocols for in vitro fertilization (IVF) using validated dosing algorithms have become increasingly evident. A 2016 American Society for Reproductive Medicine Practice Committee guideline identified factors such as polycystic ovarian syndrome, elevated antimüllerian hormone levels, and peak estradiol levels, which would place patients at increased risk for ovarian hyperstimulation syndrome (OHSS). This guideline also recognized the need for adjustment of ovarian stimulation protocols to mitigate these risks (1). Currently, stimulation protocols for IVF, including starting doses of gonadotropins and dose adjustments during the cycle, are selected for patients based on the practitioners' predilections, which develop from their subjective experience using presumed predictive factors such as age, measures of ovarian reserve, body mass index, and diagnosis. Individualized ovarian stimulation dosing protocols on the basis of standardized algorithms would offer a powerful advantage—substituting objective data for a clinician's subjective decision-making. Although there have been significant advances in predicting which patients will be at the extremes of ovarian response, the optimal dosing regimen for a given patient is still difficult to predict because of significant heterogeneity in an individual's response to gonadotropins. A systematic review published in 2006 found that patient characteristics such as antral follicle count, basal estradiol, and follicle-stimulating hormone (FSH) have limited utility in predicting the ovarian response to controlled stimulation with the gonadotropins that were available at that time (2).

The development of a new recombinant gonadotropin, follitropin delta, has led to renewed attempts at developing dosing algorithms for optimal ovarian response. Follitropin delta is a novel recombinant FSH. Because of differences in glycosylation profile, follitropin delta has a lower serum clearance than currently available recombinant follitropin preparations (3). When administered at equal doses of biologic activity in international units or same microgram weight dose, follitropin delta induces a higher ovarian response than follitropin alfa (4). In the Evidence-based Stimulation Trial with Human recombinant FSH in Europe and Rest of World (ESTHER-1) study published in 2017 (3), the investigators compared individualized dosing of follitropin delta to conventional dosing of follitropin alfa in 1,329 women. In the ESTHER-1 trial, an individualized dose of follitropin delta was selected on the basis of the subject's serum antimüllerian hormone and body weight. No dose adjustments of follitropin delta were permitted during the stimulation. In contrast, in the conventional dosing group with follitropin alfa, 36.8% of women received dose adjustments during their cycle (3). The investigators found that when comparing the individually-dosed follitropin delta to conventional follitropin alfa dosing, there were similar rates of implantation and ongoing pregnancy (3). Additionally, oocyte yields were similar in the 2 groups despite lower amounts of gonadotropin used in the follitropin delta group. The investigators also reported improved safety, with fewer women requiring hospitalization or preventive measures such as cycle cancelation, gonadotropin-releasing hormone agonist trigger, or dopamine agonist for OHSS (3).

Although the findings of the ESTHER-1 trial were encouraging, it was unclear how this new drug would be adopted in broader clinical practice. In human ovarian physiology, the dominant follicle develops in response to stimulation by LH along with FSH. For IVF, many clinicians prefer mixed protocols, which use LH activity along with FSH. The IVF outcomes of women treated with FSH alone or FSH combined with other gonadotropins such as LH or human chorionic gonadotropin were investigated in a 2017 meta-analysis, which included 70 studies (5). No differences in metaphase II oocyte number were found; however, in this meta-analysis, pregnancy rates were higher in the FSH+LH group (5). Currently, it is unknown whether the addition of LH activity to follitropin delta would have the same result.

In the current issue of *Fertility and Sterility*, Bissonnette et al. (4) investigate the use of a mixed protocol for IVF in their study, Menopur and Rekovelle Combined Study (MARCS). They present a multicenter, open label, exploratory study of participants undergoing controlled ovarian stimulation for IVF. They compared 110 participants who underwent a mixed protocol with follitropin delta coadministered with highly purified human menopausal gonadotropin (HP-hMG) to a historical control group, the follitropin delta monotherapy group from the ESTHER-1 study. As with the ESTHER-1 trial, the dose of follitropin delta was individualized, and no dose adjustments of follitropin were permitted during the stimulation. In the MARCS trial, however, dose adjustments of HP-hMG were permitted. They found that a mixed protocol of follitropin delta and HP-hMG resulted in a significantly higher number of metaphase II oocytes (11.28 $\pm$ 5.76 vs. 7.4 $\pm$ 4.3) and good quality blastocysts (4.91 $\pm$ 3.9 vs. 2.0 $\pm$ 2.2) compared with follitropin delta monotherapy in ESTHER-1.

Despite the use of preventive measures for OHSS in the MARCS trial, an increased incidence of OHSS (9.3% vs. 2.6% in ESTHER-1) was seen along with the increased yield of oocytes and good quality blastocysts (4). In the MARCS trial, 43% of patients were triggered with gonadotropin-releasing hormone agonist compared with 2.3% reported in the ESTHER-1 follitropin delta cohort. Additionally, freeze-all strategy was used in 63.6% of women in the MARCS trial (4). The investigators noted that all cases of OHSS were mild, and no case of moderate or severe OHSS was noted in women who received the HP-hMG along with follitropin delta (4). The incidence of OHSS, however, may have been under-estimated because adverse events in the MARCS trial were recorded only until day 6 blastocyst formation.

Despite the promise that individualized dosing of follitropin delta offers, there still is significant ambiguity and heterogeneity in an individual's response to gonadotropins.

Although the findings of the ESTHER-1 trial were encouraging and suggested that use of the novel gonadotropin follitropin delta would permit the development of individualized dosing algorithms, this exploratory study by Bissonnette et al. (4) suggests that the optimal gonadotropin combination and starting doses are yet to be determined. In their study, despite the use of a dosing protocol for follitropin delta that appeared efficacious in a prior study, 39.1% of women had dose adjustments of HP-HMG during their IVF cycle (4). Compared with monotherapy with follitropin delta, the addition of HP-HMG resulted in better quality blastocysts but at the expense of safety, with an increased incidence of OHSS. Before the promised land of individualized ovarian stimulation is reached, further research is required to refine gonadotropin dosing algorithms for a better balance of efficacy and safety.

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https://doi.org/10.1016/j.fertnstert.2021.02.023

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