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# A randomized controlled trial investigating the use of a predictive nomogram for the selection of the FSH starting dose in IVF/ICSI cycles

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**KEY MESSAGE**

This trial found that the FSH starting dose in IVF/ICSI cycles may be selected according to patient's age and serum AMH and FSH concentrations. This strategy increased the proportion of patients with an optimal response. The possible effects of this approach on pregnancy and live-birth rates needs further investigation.

A B S T R A C T

The number of oocytes retrieved is a relevant intermediate outcome in women undergoing IVF/intracytoplasmic sperm injection (ICSI). This trial compared the efficiency of the selection of the FSH starting dose according to a nomogram based on multiple biomarkers (age, day 3 FSH, anti-Müllerian hormone) versus an age-based strategy. The primary outcome measure was the proportion of women with an optimal number of retrieved oocytes defined as 8–14. At their first IVF/ICSI cycle, 191 patients underwent a long gonadotrophin-releasing hormone agonist protocol and were randomized to receive a starting dose of recombinant (human) FSH, based on their age (150 IU if ≤35 years, 225 IU if >35 years) or based on the nomogram. Optimal response was observed in 58/92 patients (63%) in the nomogram group and in 42/99 (42%) in the control group (+21%, 95% CI = 0.07 to 0.35, $P = 0.0037$). No significant differences were found in the clinical pregnancy rate or the number of embryos cryopreserved per patient. The study showed that the FSH starting dose selected according to ovarian reserve is associated with an increase in the proportion of patients with an optimal response: large trials are recommended to investigate any possible effect on the live-birth rate.



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## Introduction

The number of oocytes retrieved is considered a relevant prognostic marker in women undergoing IVF/ intracytoplasmic sperm injection (ICSI) cycles, and consistent evidence shows that an optimal – rather than a maximal – oocyte yield is the preferred achievement after controlled ovarian stimulation (COS) when fresh embryo transfer is scheduled. In fact, live-birth rates steadily increase when an optimal number of oocytes is collected, whereas low response and hyperresponse are associated with lower implantation rates, increased obstetrical risks and, at least when considering hyper response, increased risk of ovarian hyperstimulation syndrome (OHSS) in the fresh cycle (Baker et al., 2015; Sunkara et al., 2011, 2015). While the use of different drugs to control the spontaneous LH surge may affect the ovarian response to stimulation, with protocols based on gonadotrophin-releasing hormone (GnRH) antagonist usually associated with a reduced duration of ovarian stimulation and the total FSH dose needed, it is universally recognized that choosing different doses of gonadotrophins for different patients is the most important clinical decision in the planning of IVF cycles for infertile couples (Fauser *et al.*, 2008; La Marca and Sunkara, 2014; Moolenaar et al., 2011). However, although exogenous FSH has been used for decades and millions of cycles have been performed worldwide, criteria for selecting the proper starting dose of FSH in daily clinical practice have not yet been clearly identified (Fauser *et al.*, 2008). Clinicians commonly choose the FSH starting dose in accordance with clinical history and criteria, the most important being the ovarian response to stimulation in previous IVF cycles. If no previous cycles have been performed, the choice will be based on such criteria as women's age and markers of ovarian reserve (Fleming et al., 2013; Howles *et al.*, 2006). Currently used markers of ovarian reserve include FSH, anti-Mullerian hormone (AMH) and antral follicle count (AFC), with the last two markers having the best performance in predicting ovarian response to exogenous FSH (Broer *et al.*, 2011, 2013a, 2014; Fleming et al., 2015; Iliodromiti and Nelson, 2015; La Marca et al., 2010; Lan et al., 2013; Nelson et al., 2007). In particular, AMH and AFC are nowadays considered two markers with similar diagnostic performance (Broer et al, 2013b), even if recent evidence seems to suggest some superiority of AMH over AFC, at least when considering their performance at the multicentric level; this is due to the lower variability of AMH when compared with AFC (Anderson et al., 2015). On the use and efficacy of the single value of AMH in tailored treatment, two studies have been published (Nelson et al., 2009; Yates et al., 2011). In both studies, which were not randomized controlled trials (RCT), three different FSH doses were proposed for three different AMH strata levels, i.e. the higher the serum AMH the lower the starting dose of FSH. Both studies indicated that the 'AMH-stratified care' may lead to a reduction of cancelled cycles and increased pregnancy rate.

Recently, an easy to use nomogram has been proposed in order to calculate the most appropriate FSH starting dose in IVF cycles when the long GnRH agonist protocol is used (La Marca et al., 2012a). The nomogram is based on a patient's age, serum day 3 FSH and AMH, and may be the basis for the individualization of the FSH dose for patients entering the IVF programme. In this model, AMH is the leading predictor, explaining the large part of the model variability followed by serum FSH and female age that can improve just by a little, even if significantly, the accuracy of the model (**Figure 1**). Such a nomogram, however, needs to be externally validated. In fact, before clinicians can adopt any treatment model in routine clinical practice, the accuracy of the model should be independently evaluated in a population different from the one on which the model was elaborated. External validation of the model is therefore crucial to assess the generalizability to other populations.

The objective of this RCT was to investigate the performance of the nomogram in selecting the most appropriate FSH starting dose in IVF/ICSI cycles. In particular, women undergoing IVF/ICSI were randomized to receive a starting dose of recombinant (human) FSH (rFSH) selected merely on the basis of their age (150 IU if younger than 35 years, 225 IU if older than 35 years) or on the basis of their ovarian reserve, by using the nomogram including age, day 3 serum FSH and AMH.

## Materials and methods

### *Participants*

This two-arm, single-centre, prospective, randomized, interventional trial involved 194 couples attending their first IVF/ICSI cycle at the Andros Day Surgery Clinic, Palermo, Italy. All the women had been trying to conceive for at least 12 months and had undergone a fertility workup.

The couples were only included if all the following inclusion criteria were satisfied: first IVF/ICSI cycle, female age between 18 and 40 years, body mass index (BMI) between 18 and 25 kg/m$^2$, serum AMH concentrations between 1.0 and 4.0 ng/ml, basal serum day 3 FSH ≤15 IU/l, normal regular menstrual cycles, ranging from 25 to 33 days in length, normal thyroid-stimulating hormone (TSH) and prolactin concentrations, normal uterine cavity as assessed by hysteroscopy or sonohysterography or three-dimensional ultrasound and presence of both ovaries. Clinical exclusion criteria were: irregular menstrual cycles, polycystic ovary syndrome, severe endometriosis (stage III-IV of the American Society for Reproductive Medicine revised classification, American Society for Reproductive Medicine, 1997), previous ovarian surgery, presence of ovarian cysts, use of hormonal contraception in the previous three months, any known metabolic or endocrinological disease.

### *Interventions*

COS was performed after pituitary down-regulation with a GnRH agonist (buserelin acetate, Sanofi, Italy; 0.1 ml subcutaneously twice per day), beginning from day 21 of the previous cycle until the day of recombinant human chorionic gonadotrophin administration. Multifollicular development was achieved by daily injections of rFSH (Gonal F; Merck Serono, Italy), commencing after at least 12 days of pituitary down-regulation. Ovarian suppression was demonstrated by thin endometrium and low oestradiol concentrations.

Three couples were excluded because they dropped out (one for a spontaneous pregnancy, this being between the recruitment and the starting of the ovarian stimulation, two for personal reasons), thus 191 couples constituted the population included in the statistical analysis.

In the control group ($n$ = 99), the starting dose of rFSH was fixed and established on the basis of the female age: 150 IU of rFSH if female age was ≤35 years or 225 IU of rFSH if female age was >35 years. In the study group ($n$ = 92), an individualized starting dose of rFSH was decided on the basis of the nomogram based on female age, AMH and basal FSH.

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