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ARTICLE

Risk charts to identify low and excessive responders among first-cycle IVF/ICSI standard patients

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Abstract Ovarian stimulation carries a risk of either low or excessive ovarian response. The aim was to develop prognostic models for identification of standard (ovulatory and normal basal FSH) patients' risks of low and excessive response to conventional stimulation for IVF/intracytoplasmic sperm injection. Prospectively collected data on 276 first-cycle patients treated with 150 IU recombinant FSH (rFSH)/day in a long agonist protocol were analysed. Logistic regression analysis was applied to the outcome variables: low (seven or less follicles) and excessive (20 or more follicles) response. Variables were woman's age, menstrual cycle length, weight or body mass index, ovarian volume, antral follicle count (AFC) and basal FSH. The predictive performance of the models was evaluated from the prediction error (Brier score, %) where zero corresponds to a perfect prediction. Model stability was assessed using 1000 bootstrap cross-validation steps. The best prognostic model to predict low response included AFC and age (Brier score 7.94) and the best model to predict excessive response included AFC and cycle length (Brier score 15.82). Charts were developed to identify risks of low and excessive ovarian response. They can be used for evidence-based risk assessment before ovarian stimulation and may assist clinicians in individual dosage of their patients.

KEYWORDS: excessive response, low response, ovarian stimulation, predictive factors, prognostic models, risk charts

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Introduction

In conventional ovarian stimulation for IVF/intracytoplasmic sperm injection (ICSI), it is well known that, even in standard patients, the first treatment cycle exposes patients to a risk of either a low or an excessive ovarian response. Knowing the patient's risk of these responses may assist clinicians in determining an individual dose, which in turn may decrease the rate of cycle cancellations, increase pregnancy rates and reduce side effects of excessive ovarian response, such as ovarian hyperstimulation syndrome (OHSS).

In the early days of IVF, dosing was empirical (van Hooff, 1995). Following the introduction of recombinant preparations, dosage studies were conducted (Asian Puregon Study Group, 2002; Out et al., 2000, 2001; The Latin-American Puregon IVF Study Group, 2001; Yong et al., 2003). The ovarian response was dose-related in standard patients but, irrespective of the doses used (100–250 IU rFSH/day), the response variability was high. Several variables have been investigated as possible predictors of the ovarian response to stimulation (Fauser et al., 2008) and independent predictors such as antral follicle count (AFC), age, FSH and anti-Müllerian hormone (AMH) have been identified (Eldar-Geva et al., 2005; Elgindy et al., 2008; Howles et al., 2006; Popovic-Todorovic et al., 2003a; van Rooij et al., 2002). Few attempts have been made to incorporate these findings into dosing strategies for ovulatory standard patients (Howles et al., 2006; Popovic-Todorovic et al., 2003a), which differ from strategies used for polycystic ovary syndrome (PCOS) patients or expected poor responders (Homburg, 2003; Klinkert et al., 2005; Palomba et al., 2008; The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008). Regarding individual dosing in first-cycle ovulatory standard patients, one randomized controlled trial (RCT) on IVF/ICSI patients (Popovic-Todorovic et al., 2003b) and one RCT on intrauterine insemination patients (Freiesleben et al., 2009) demonstrated an increased proportion of the target number of follicles among individually dosed patients compared with standard dosing. Individual risk assessment of patients is therefore important in daily clinical work and can be used as a basis for individual dosing and counselling of the patients.

The main objective of this analysis was to develop validated prognostic models for identification of first-cycle IVF/ICSI standard patients' risks of low and excessive ovarian responses to 150 IU rFSH/day.

Materials and methods

Patients

The analysis included 276 standard patients treated with 150 IU rFSH/day in their first IVF/ICSI cycle. The data on 145 of the 276 women were derived from a prospective study (study 1; Popovic-Todorovic et al., 2003a). Data on the remaining 131 patients constituted the control group from a randomized study (study 2; Popovic-Todorovic et al., 2003b). These studies were conducted at two public fertility centres in Denmark between September 2000 and January 2003. The regional Ethics Committee of Copenhagen Municipality approved the studies. Inclusion criteria were first IVF/ICSI cycle and standard patient defined as: women $<$40 years of age with two ovaries, spontaneous regular menstrual cycle within the range of 21–35 days (intra-individual variation maximum ±3 days) and basal FSH $\leq$12.5 IU/l. Information on cycle length was obtained from the patients during the initial infertility consultation (most frequent number of days in approximately six cycles before treatment). PCOS patients were not included.

Patients were examined on days 2–5 in the spontaneous cycle preceding gonadotrophin-releasing hormone agonist treatment. Basal characteristics (**Table 1**) were recorded and experienced doctors performed a two-dimensional transvaginal ovarian ultrasonography. The sizes of the follicles were calculated as the mean of two diameters. All follicles of 2–10 mm were included in the AFC. The ovarian volume was calculated from the measurements of the maximum longitudinal (D1), anterior–posterior (D2) and transverse (D3) diameters using the ellipse formula: $D1 \times D2 \times D3 \times 0.523$. Blood samples were drawn from the antecubal vein and serum was stored at −20°C until analysis (Popovic-Todorovic et al., 2003a). Following down-regulation (nafarelin, Synarela; Pharmacia, Denmark), all participants were stimulated with 150 IU rFSH/day (Puregon; Organon, Netherlands) for 7 days. Thereafter, the rFSH dose was increased if the leading follicle was $<$10 mm and in case of asynchrony or decreased if a risk of developing an excessive number ($>$20) of follicles was acknowledged (Popovic-Todorovic et al., 2003a,b). The aim of the stimulation was to achieve 5–14 oocytes. The day of HCG administration (10,000 IU; Profasi, Serono) was defined as the day where a minimum of two follicles were $>$17 mm, but aspiration was offered to women with only one follicle. Standard IVF and ICSI procedures were used and the embryos were transferred on day 2. Vaginal progesterone (Progestan; Organon) 200 mg three times daily was administered from the day of embryo transfer until HCG evaluation 14 days later.

Endpoint

The primary endpoint was the number of follicles $\geq$11 mm on the day of HCG administration. Low response to the standard stimulation was defined as seven or less follicles $\geq$11 mm and excessive response to the standard stimulation was defined as 20 or more follicles $\geq$11 mm.

Statistical analysis

The data on 145 (study 1) and 131 (study 2) patients were pooled. The patient characteristics from studies 1 and 2 were compared by two-sample t-tests.

Advanced statistical procedures were used for developing prognostic models in accordance with the current state of the art (Steyerberg, 2008; Steyerberg et al., 2001). Logistic regression was applied separately to both outcomes: low (seven or less follicles $\geq$11 mm) and excessive (20 or more follicles $\geq$11) response. To create risk charts that are easy to use in clinical practice, this study considered models that included only two out of the following pre-