

PREDICTION MODELS IN MILD STIMULATION

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Introduction: As assisted reproductive science progresses, a shift in the focus of in vitro fertilization (IVF) is occurring from striving for maximizing instant success 'at all costs' to developing safer and more patient friendly protocols in which the risks of treatment are minimized while optimizing the chance of a singleton live birth. Ovarian hyperstimulation is applied in IVF to generate multiple follicle growth in order to obtain an increased quantity of oocytes to compensate for inefficiency of the IVF procedure while maintaining the potential to select the best embryo. Disadvantages of this approach are the high cost, complex stimulation protocols which take several weeks, physical and emotional discomfort, chances for complications and the essentially uncontrollable degree of ovarian response. The current trend of limiting the number of embryos to be transferred reduces the need for large numbers of oocytes. As a consequence, mild ovarian stimulation protocols are being developed to minimise the adverse treatment effects of ovarian hyperstimulation.

A potential drawback of mild stimulation is a decrease in ovarian response compared to conventional stimulation leading to higher cancellation rates. Although low numbers of oocytes appear to be related to good outcomes in mild stimulation cancellations should be prevented to optimise the benefit of mild stimulation. The development of methods to identify women who may benefit from an earlier start of exogenous FSH may reduce the number of cancelled cycles and improve the efficacy of the mild stimulation protocol. Is it therefore possible to identify a subgroup of patients at risk for cancellation due to insufficient ovarian response in mild ovarian stimulation for IVF, starting exogenous FSH on cycle day 5?

Developing a prediction model: In order to address this, women less than 38 years of age, with a regular menstrual cycle (25-35 days) and a body mass index (BMI) between 18-28 kg/m² were asked to participate in a study. Couples who had been previously treated with IVF were excluded.

Patients in the mild stimulation arm were treated with a fixed daily starting dose of 150 IU rFSH (Gonal-F[®]: Serono Benelux B.V., Amsterdam, the Netherlands; or Puregon[®]: N.V. Organon, Oss, the Netherlands) s.c., initiated on the fifth cycle day (CD 5 protocol). The dose of exogenous FSH was not adjusted during the stimulation. GnRH antagonist (ganirelix, Orgalutran[®]: N.V. Organon, 0.25 mg/day; or cetrorelix, Cetrotide[®]: Serono Benelux, 0.25 mg/day) was administered s.c. from the day that at least one follicle attained a diameter ≥ 14 mm (Hohmann et al., 2003). Human chorionic gonadotrophin (hCG) (Profasi[®]: Serono Benelux B.V.; or Pregnyl[®]: N.V. Organon) 10,000 IU s.c. was administered as a single bolus injection to induce final oocyte maturation, when the largest follicle had reached at least 18 mm in diameter and at least one additional follicle ≥ 15 mm was observed. Oocyte retrieval and fertilization "in vitro" was performed according to standard procedures as described previously (Kastrop et al., 1999; Huisman et al., 2000).

Insufficient ovarian response resulting in cancellation of the cycle was defined as the development of less than three follicles > 12 mm. In these patients, exogenous FSH was initiated on cycle day 2 (CD 2 protocol) in a subsequent treatment cycle while the daily dosage remained unchanged. Cycles at risk for ovarian hyperstimulation syndrome (OHSS), defined as more than 20 follicles with a diameter > 10 mm or estradiol concentrations > 15.400 pmol/l were also cancelled before hCG injection.

Of the 174 first cycles started, 39 (22%) ended in a cancellation, 30 (17%) due to an insufficient response and 9 (5%) for other reasons. A significantly shorter menstrual cycle length (the number of days of an average menstrual cycle in the previous year as indicated by the patient) (28.2 vs 27.5 days; $p=0.045$) and longer duration of infertility (4.4 vs 3.6 years; $p=0.022$) were observed in patients with an insufficient response. In multivariate analysis, the variables duration of infertility, menstrual cycle length, primary or secondary infertility and BMI were selected into the prediction model for cancellation during the mild stimulation protocol. A longer duration of infertility, short menstrual cycle length, secondary infertility and higher BMI were found to be associated with an insufficient ovarian response. The predictive ability of the model measured by the area under the ROC curve was 0.69 (95% Confidence Interval 0.58-0.79).

The value of prediction models for mild stimulation: Our prediction model showed that a longer duration of infertility, a shorter menstrual cycle length, secondary infertility and a higher BMI are associated with a higher chance of inadequate response to the mild stimulation protocol. Because the prediction model is based on "a priori" parameters, patients at risk for cancellation can be identified prior to the start of the treatment. The overall cancellation rate for insufficient response is therefore likely to be reduced if these patients are treated with the CD 2 protocol instead of the CD 5 protocol.

In conclusion, midfollicular initiation of rFSH in combination with a GnRH antagonist leads to a mild ovarian stimulation protocol but yields a distinct risk of cancellation due to insufficient response. We developed a model that could predict 33% of the cancellations (sensitivity) with a false positive rate of 8% on our own data and so equalise the cancellation rate for insufficient response to that observed in a standard GnRH antagonist ovarian stimulation protocol for IVF. After external validation, the model might be used to identify patients at risk for insufficient ovarian response previous to the start of the treatment cycle. Treatment with ovarian stimulation initiated in the early follicular phase in these patients may reduce the number of cancelled cycles and therefore improve the efficacy of the mild stimulation protocol. Further prospective randomized trial should evaluate the clinical use of adjusting the starting day of ovarian stimulation based on the current prediction model.