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Ovarian response to 150 μg corifollitropin alfa in a GnRH-antagonist multiple-dose protocol: a prospective cohort study

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KEY MESSAGE

As a single predictor, AMH can reliably identify patients undergoing ovarian stimulation for IVF who are unlikely to experience hypo- or hyperresponse to corifollitropin alfa 150 μg. Thus, utilization of 150 μg corifollitropin alfa should take the pre-treament serum AMH concentration of patients into account to achieve optimal treatment outcomes.

A B S T R A C T

The incidence of low (<6 oocytes) and high (>18 oocytes) ovarian response to 150 μg corifollitropin alfa in relation to anti-Müllerian hormone (AMH) and other biomarkers was studied in a multi-centre (*n* = 5), multi-national, prospective, investigator-initiated, observational cohort study. Infertile women (*n* = 212), body weight >60 kg, underwent controlled ovarian stimulation in a gonadotrophin-releasing hormone-antagonist multiple-dose protocol. Demographic, sonographic and endocrine parameters were prospectively assessed on cycle day 2 or 3 of a spontaneous menstruation before the administration of 150 μg corifollitropin alfa. Serum AMH showed the best correlation with the number of oocytes obtained among all predictor variables. In receiver-operating characteristic analysis, AMH at a threshold of 0.91 ng/ml showed a sensitivity of 82.4%, specificity of 82.4%, positive predictive value 52.9%

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and negative predictive value 95.1% for predicting low response (area under the curve [AUC], 95% CI; *P*-value: 0.853, 0.769–0.936; <0.0001). For predicting high response, the optimal threshold for AMH was 2.58 ng/ml, relating to a sensitivity of 80.0%, specificity 82.1%, positive predictive value 42.5% and negative predictive value 96.1% (AUC, 95% CI; *P*-value: 0.871, 0.787–0.955; <0.0001). In conclusion, patients with serum AMH concentrations between approximately 0.9 and 2.6 ng/ml were unlikely to show extremes of response.

Introduction

A number of biomarkers are clinically used to predict ovarian response to ovarian stimulation in the context of IVF (Broekmans et al., 2006). The aim of ovarian response prediction is to identify patients who will show an extreme of response. In such patients, management decisions can be taken, such as altering the FSH dose and stimulation protocol (Nelson et al., 2009). Furthermore, the patient can be counselled about the expected response. Anti-Müllerian hormone (AMH) has been reported as a key biomarker for predicting ovarian response (Broer et al., 2013; Nelson et al., 2015a).

Corifollitropin alfa is a hybrid FSH molecule with an increased serum half-life, allowing the initiation and sustainment of multifollicular growth for seven days after a single subcutaneous injection (Fauser et al., 2009). Corifollitropin alfa has been introduced to the market in two dosages, 100 µg and 150 µg. In contrast to ovarian stimulation with daily FSH injections, no dose adaptions are possible for a full week after administration of corifollitropin alfa. Furthermore, corifollitropin alfa 150 µg produces, on average, a slightly stronger ovarian response as compared with daily FSH 200 IU (Devroey et al., 2009). This makes correct response prediction paramount for routine use of corifollitropin alfa. However, in three out of four corifollitropin alfa phase III trials (Corifollitropin alfa Ensure Study Group, 2010; Devroey et al., 2009; Norman *et al.*, 2011), the key biomarker AMH has not been assessed. Furthermore, phase III trial populations are different from routine patients in many aspects such as body weight, age and the expected incidence of extremes of ovarian response.

While there is a wealth of literature to date on ovarian response prediction by AMH, only two studies on predicting ovarian response in the corifollitropin alfa protocol, e.g. cycles utilizing a gonadotrophin-releasing hormone (GnRH)-antagonist multiple-dose protocol and a dose of 150 µg, have been published (Oehninger et al., 2015; Polyzos et al., 2013). While one study (Polyzos et al., 2013) was retrospective and used an AMH immuno-assay, which is no longer available, the other study (Oehninger et al., 2015) employed the widely-used Gen II AMH assay, but the population under study was restricted to women of advanced reproductive age (36–42 years).

This study presents a prospective, clinical cohort study on a broad range of patients undergoing ovarian stimulation with 150 µg corifollitropin alfa with the primary aim of testing the performance of AMH, among other endocrine, demographic and sonographic variables that are available pre-treatment, to predict low and high ovarian response, respectively.

Materials and methods

Study design

The study was a multi-centric (*n* = 5), prospective, investigator-initiated, observational cohort study conducted between 2012 and 2013 (protocol ID: GR 3422/3–1). Four centres were located in Germany (Luebeck, Kiel, Wuerzburg, Muenster), one centre was located in Norway (Haugesund). Institutional review board approval was granted (Ethical Review Board of the University of Luebeck, reference number 10–143) on 26 August 2010 and all patients signed an informed consent sheet. The protocol was prospectively registered (NCT01206803). All eligible patients were prospectively and centrally registered by telephone or fax.

Population

Women with an indication for IVF or intracytoplasmic sperm injection (ICSI), eligible to undergo ovarian stimulation, were prospectively recruited from the routine patient population, age limit 18–45 years. Patients with immediate sex-steroid pre-treatment (e.g. cycle scheduling with an oral contraceptive) were excluded. This exclusion criterion was chosen so that the impact of sex-steroid pre-treatment would not constitute a potential confounding variable of ovarian response.

Protocol

On cycle day 2 or 3 of a spontaneous menstruation (stimulation day 1), patients were scheduled for a monitoring visit at the clinic, a transvaginal scan was performed and a blood sample was drawn for later, centralized analysis. The following parameters were recorded at this visit: woman's age (years), weight (kg), body-mass-index (kg/m^2), average number of cigarettes per day, duration of infertility (months), cycle length (in days, by patient recall), cycle regularity (yes/no; deviation of >5 days from two consecutive cycles is considered an irregular cycle), total number of antral follicles (2–10 mm) in both ovaries, and serum AMH (ng/ml), oestradiol, progesterone, FSH and LH. The patient received corifollitropin alfa 150 µg s.c. (Elonva®; MSD Sharp and Dohme GmbH, Germany) on the same day and initiated GnRH-antagonist 0.25 mg (Orgalutran®; MSD Sharp and Dohme GmbH, Germany) on stimulation day 5 and continued GnRH-antagonist treatment up to and including the day of triggering final oocyte maturation. On stimulation day 7 or 8, the patient was seen for a transvaginal scan, and in case that the triggering criteria had not been met, continued ovarian stimulation with a fixed dose of 200 IU daily recombinant FSH (Purgeon®; MSD Sharp and Dohme GmbH, Germany) until ≥3 follicles ≥17 mm were visualized or one day thereafter. Low response (e.g. growth of one or two follicles) was not a cancellation criterion and in these cases physicians were free to induce final oocyte maturation at a leading follicle size of ≥17 mm. Induction of final oocyte maturation was performed with urinary human chorionic gonadotrophin (HCG) (5000 IU if body weight ≤80 kg, 10,000 IU if body weight >80 kg) (Predalon®; MSD Sharp and Dohme GmbH, Germany). In case of an increased risk of ovarian hyperstimulation syndrome risk (defined as ≥19 follicles ≥11 mm and/or oestradiol >4500 pg/ml), triptorelin 0.2 mg (Decapeptyl®; Ferring GmbH, Germany) was administered instead of HCG for triggering final oocyte maturation, followed by

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