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ARTICLE

No association between endogenous LH and pregnancy in a GnRH antagonist protocol: part II, recombinant FSH

George Griesinger [a,*], Daniel B Shapiro [b], Efstratios M Kolibianakis [c], Han Witjes [d], Bernadette M Mannaerts [e]

[a] *Department of Obstetrics and Gynaecology, University Clinic of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany;* [b] *Reproductive Biology Associates, Atlanta, GA, USA;* [c] *Unit for Human Reproduction, Medical School, Aristotle University of Thessaloniki, Papagerogiou General Hospital, Thessaloniki, Greece;* [d] *Biostatistics and Research Decision Sciences, Women's Health and Endocrine, MSD, Oss, The Netherlands;* [e] *Global Clinical Research, Women's Health and Endocrine, Merck Research Laboratories, MSD, The Netherlands*

[*] Corresponding author. *E-mail address:* georg.griesinger@frauenklinik.uni-luebeck.de (G Griesinger).

Georg Griesinger is a professor for reproductive medicine at the Department of Obstetrics and Gynecology, University Clinic of Schleswig–Holstein, Luebeck, Germany. He was trained at the University of Vienna, where he worked in trophoblast research for his MD thesis at the Department of Obstetrics, and then did postdoctoral studies at University College London, where he obtained an MSc in prenatal genetics and fetal medicine. His PhD was on ovarian stimulation for IVF using gonadotrophin-releasing hormone antagonists. His research interests include the endocrinology of ovarian stimulation, evidence-based medicine in reproductive health care and epidemiological studies in IVF.

Abstract The association between endogenous LH concentrations during ovarian stimulation in a gonadotrophin-releasing hormone (GnRH) antagonist protocol and pregnancy likelihood was examined in a large combined analysis of individualized patient data obtained after treatment with recombinant FSH and a GnRH antagonist prior to IVF/intracytoplasmic sperm injection. Data from 1764 patients from six randomized controlled trials were pooled for retrospective analysis. Ongoing pregnancy and miscarriage rates for patients stratified by LH percentiles were assessed. Patients in the lowest LH quartile (<P25) were younger with a higher predicted ovarian reserve and response compared with patients in the highest quartile (>P75). With adjustment for identified predictive factors of pregnancy, estimated odds ratios (95% confidence interval) for ongoing pregnancy for LH categories <P25 versus ≥P25, >P75 versus ≤P75 and <P25 versus >P75 were 0.96 (0.75–1.22), 1.13 (0.88–1.45) and 0.89 (0.66–1.21) on stimulation day 8, and 0.96 (0.76–1.21), 1.03 (0.82–1.30) and 0.95 (0.72–1.26) on the day of human chorionic gonadotrophin, respectively. No significant differences in pregnancy or miscarriage rates between the LH categories were observed. Endogenous LH concentrations have no association with the likelihood of ongoing pregnancy in women undergoing ovarian stimulation using a recombinant FSH/GnRH antagonist protocol.

KEYWORDS: combined analysis, endogenous LH, GnRH antagonist, pregnancy rates

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Introduction

The association between endogenous LH concentrations and clinical outcome in a recombinant FSH (rFSH) gonadotrophin-releasing hormone (GnRH) antagonist protocol has not been studied extensively but should be understood before advocating clinical management decisions based on endogenous LH concentrations.

The first studies on the relationship between low endogenous LH concentrations and clinical outcome in GnRH antagonist protocols were published in 2004, by Merviel et al. (2004), who found no impact of low endogenous LH (≤0.5 IU/l) on clinical pregnancies in 270 patients following ovarian stimulation for IVF, and by Kolibianakis et al. (2004), who reported that profound LH suppression (≤0.5 IU/l) on stimulation day 8 in a study of 116 women was associated with a higher chance of achieving an ongoing pregnancy.

Previous dose-finding studies have indicated that high doses of GnRH antagonists may induce very profound LH suppression and reduce the probability of clinical pregnancy (Huirne et al., 2005; The Ganirelix Dose-finding Study Group, 1998). However, low serum LH concentrations, defined by percentile analysis in 110 patients treated with 0.25 mg GnRH antagonist, were not shown to be associated with the probability of pregnancy (Bosch et al., 2005).

A recent publication (Doody et al., 2010) reported no association between endogenous LH concentrations measured on stimulation days 1, 5 or 8 and ongoing pregnancy rates in 750 patients treated with daily rFSH and 0.25 mg ganirelix in the Engage trial (Devroey et al., 2009). The analysis of this trial was then extended with a study of endogenous LH concentrations measured on stimulation day 8 and on the day of human chorionic gonadotrophin (HCG) administration, and the probability of pregnancy in both the rFSH and corifollitropin alfa treatment arms of the study (approximately 750 patients in each treatment arm) (Doody et al., 2011, part I of this study). In this study, endogenous LH concentrations ranging between <0.6 IU/l and 5 IU/l were not associated with the chance of ongoing pregnancy, whereas serum progesterone concentration on stimulation day 8 and ovarian response (follicles on stimulation day 8/oocytes) appeared to be significant predictors of ongoing pregnancy. Moreover, this analysis demonstrated that patients with lower serum LH concentrations tend to be younger, with a higher ovarian reserve and a higher ovarian response than patients with higher LH concentrations. In the study by Kolibianakis et al. (2004), patients with lower serum LH concentrations during stimulation had a higher chance of pregnancy but were also slightly younger and had statistically significantly lower endogenous FSH concentrations on stimulation day 1.

The present study examined the association of endogenous LH concentrations during the follicular phase with ongoing pregnancy rates in large data sets derived from six randomized trials with a total of 1764 patients treated with rFSH in a GnRH antagonist (ganirelix) protocol prior to IVF or intracytoplasmic sperm injection (ICSI). Identified predictors from the rFSH arm of the Engage trial (Doody et al., 2011, part I) were included as covariates in a combined analysis of the six trials using individual patient data stratified by LH concentrations determined within each trial by a central laboratory.

Materials and methods

Ongoing pregnancy rates and miscarriage rates relative to endogenous serum LH concentrations during ovarian stimulation were assessed from the following six trials, all of which included a GnRH antagonist (ganirelix) treatment arm with a daily dosage of 0.25 mg: (i) Engage (Devroey et al., 2009); (ii) Ensure (Corifollitropin alfa Ensure Study Group, 2010); (iii) Xpect (NCT identifier NCT00778999, Nyboe Andersen et al., in press); (iv) Ganirelix EU (The European Orgalutran Study Group, 2000); (v) Ganirelix ME (The European and Middle East Orgalutran Study Group, 2001); and (vi) Ganirelix NA (The North American Ganirelix Study Group, 2001). Patients were normogonadotrophic women with an indication for ovarian stimulation prior to IVF or ICSI. In all six trials, only data from the rFSH/ganirelix arms were used for the current analyses.

Engage trial (rFSH arm only)

Women aged 18–36 years with bodyweight from >60 kg to ≤90 kg received daily 200 IU rFSH (Puregon/Follistim pen; Organon, The Netherlands) up to and including the day of HCG administration. From stimulation day 8, the dose of rFSH was adjusted if necessary, according to the ovarian response. The GnRH antagonist ganirelix (0.25 mg, Orgalutran/ganirelix acetate injection, Organon) was administered once daily s.c. starting on stimulation day 5 upto and including the day of HCG injection. Urinary HCG (10,000 IU or 5000 IU) was administered i.m. to induce final oocyte maturation (Devroey et al., 2009).

Ensure trial (rFSH arm only)

Women aged 18–36 years with bodyweight ≤60 kg received daily 150 IU rFSH (Puregon/Follistim pen) upto and including the day of HCG administration. From stimulation day 8, the dose of rFSH was adjusted if necessary, according to the ovarian response. The GnRH antagonist ganirelix (0.25 mg) was administered once daily s.c. starting on stimulation day 5 upto and including the day of HCG injection. Urinary HCG (10,000 IU) was administered i.m. to induce final oocyte maturation (Corifollitropin alfa Ensure Study Group, 2010).

Xpect trial (excluding the oral contraception pretreatment arm)

Women aged 18–39 years with body mass index (BMI) ≤32 kg/m^2 received daily 200 IU rFSH (Puregon/Follistim pen) upto and including the day of HCG administration, with dose adjustment as necessary after stimulation day 6. On stimulation day 5, the GnRH antagonist ganirelix (0.25 mg) was administered daily s.c. upto and including the day of HCG administration. To induce final oocyte maturation, 5000–10,000 IU HCG was administered (NCT identifier NCT00778999; Nyboe Andersen et al., in press).