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ARTICLE

No association between endogenous LH and pregnancy in a GnRH antagonist protocol: part I, corifollitropin alfa

Kevin J Doody [a,*], Paul Devroey [b], Arthur Leader [c], Han Witjes [d], Bernadette M Mannaerts [e]

[a] *Center for Assisted Reproduction, Bedford, TX, USA;* [b] *Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Belgium;* [c] *The Ottawa Fertility Centre, Division of Reproductive Medicine, University of Ottawa, Ontario, Canada;* [d] *Biostatistics and Research Decision Sciences, Women's Health and Endocrine, MSD, Oss, The Netherlands;* [e] *Global Clinical Research, Women's Health and Endocrine, MSD, Oss, The Netherlands*

[*] Corresponding author. *E-mail address:* kevind@embryo.net (KJ Doody).

Kevin Doody, MD, received his medical degree and served a residency in obstetrics and gynaecology at Baylor College of Medicine in Houston. After completing his residency, Dr Doody received subspecialty training at UT Southwestern Medical Center. He completed his fellowship in reproductive endocrinology/infertility in 1989. He is board certified in obstetrics and gynaecology and subspecialty board certified in reproductive endocrinology/infertility. Dr Doody has been repeatedly honoured as one of Fort Worth's Top Docs, one of Texas's Super Doctors and one of the Best Doctors in America. Dr Doody was also recognized as Microsoft Physician of the Year 2004.

Abstract The relationship between endogenous LH concentrations and ongoing pregnancy rates among normogonadotrophic patients undergoing ovarian stimulation in a gonadotrophin-releasing hormone antagonist protocol were examined. In the Engage trial, 1506 patients received corifollitropin alfa (150 μg) or daily recombinant FSH (rFSH) (200 IU) for the first 7 days of stimulation with 0.25 mg ganirelix from stimulation day 5. Patients were retrospectively stratified by serum LH percentiles (<25th, 25th–75th and >75th) on stimulation day 8 and day of human chorionic gonadotrophin administration. Odds ratios (OR) with and without adjustment for predictive factors for ongoing pregnancy were estimated. LH concentration was not associated with pregnancy rates in either treatment arm, in contrast to ovarian response and serum progesterone. With adjustment for these predictors and age, OR (95% confidence interval) for ongoing pregnancy on stimulation day 8 for LH categories <P25 versus ≥P25, >P75 versus ≤P75 and <P25 versus >P75 were 0.75 (0.53–1.06), 1.26 (0.87–1.83) and 0.70 (0.46–1.09) in the corifollitropin alfa arm and 0.80 (0.54–1.17), 1.28 (0.87–1.87) and 0.73 (0.46–1.16) in the rFSH arm respectively. There was also no significant difference in pregnancy rates between LH categories on day of human chorionic gonadotrophin administration with either treatment.

KEYWORDS: endogenous LH, Engage trial, GnRH antagonist, pregnancy rates

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Introduction

The role of LH during ovarian stimulation in women less than 37 years old is not completely understood and contradictory evidence exists as to whether or not profound suppression of endogenous LH affects IVF/intracytoplasmic sperm injection (ICSI) outcomes (Balasch et al., 2001; Esposito et al., 2001; Humaidan et al., 2002; Merviel et al., 2004; Westergaard et al., 2000). Patients with hypogonadotrophic hypogonadism (World Health Organization group I) require the administration of a daily low amount (75 IU) of exogenous LH activity, as recombinant LH, human chorionic gonadotrophin (HCG) or human menopausal gonadotrophin, for adequate follicular and endometrial development (Burgués, 2001; Filicori et al., 1999; The European Recombinant Human LH Study Group, 1998).

Research regarding the need for LH add-back in normogonadotrophic patients should distinguish between long gonadotrophin-releasing hormone (GnRH) agonist protocols, which induce profound pituitary suppression prior to stimulation, and GnRH antagonist protocols, in which normal to partially suppressed endogenous LH concentrations are observed during stimulation. Most published studies on LH requirement are based on retrospective analyses of low endogenous LH concentrations during stimulation using a long GnRH agonist protocol (Balasch et al., 2001; Fleming et al., 1998; Westergaard et al., 2000). In both GnRH agonist and antagonist cycles, supplementation with LH activity enhances androgen and oestrogen biosynthesis. Patients receiving LH/HCG supplementation have higher oestradiol concentrations per growing follicle than patients stimulated with FSH only (Bosch et al., 2008; Smitz et al., 2007; Tarlatzis et al., 2006). In addition, it has been shown that the use of exogenous HCG may reduce or even replace the requirements for FSH administration during the last days of stimulation (Blockeel et al., 2009; Filicori et al., 2005).

Previous studies using GnRH antagonist protocols showed that low endogenous LH concentrations during recombinant FSH (rFSH) stimulation (Bosch et al., 2005; Kolibianakis et al., 2004; Merviel et al., 2004) or supplementation with recombinant LH (Baruffi et al., 2007; Griesinger et al., 2005) or human menopausal gonadotrophin (Bosch et al., 2008) do not affect pregnancy rates. One prospective study and LH analysis of patients treated with an rFSH/GnRH antagonist protocol suggested that those patients with the lowest endogenous LH concentrations on stimulation day 8 had the highest pregnancy rate (Kolibianakis et al., 2004). A recent univariate analysis indicated that low endogenous LH concentrations as measured on stimulation days 1, 5 and 8 in 750 patients treated with daily rFSH in a GnRH antagonist protocol did not adversely affect ongoing pregnancy rates (Doody et al., 2010).

The present retrospective analysis of a large, randomized controlled trial (Devroey et al., 2009) examines the association between endogenous LH concentrations and ongoing pregnancy rates in corifollitropin alfa and rFSH treatment groups.

Materials and methods

Ongoing pregnancy rates relative to endogenous serum LH concentrations during ovarian stimulation were retrospectively analysed from the Engage trial, the details of which have been reported previously (Devroey et al., 2009). Briefly, women aged 18–36 years with bodyweight from >60 kg to ≤90 kg and a regular menstrual cycle received a single dose of 150 μg corifollitropin alfa (Elonva; N.V. Organon, The Netherlands) or daily 200 IU rFSH (Puregon/Follistim pen; N.V. Organon) for the first 7 days of ovarian stimulation. From stimulation day 8 onwards, treatment in both groups was continued as needed with a daily s.c. dose of ≤200 IU rFSH up to and including the day of HCG administration. GnRH antagonist ganirelix (0.25 mg, Orgalutran/Ganirelix Acetate Injection; N.V. Organon) was administered once daily s.c. starting on stimulation day 5 up to and including the day of HCG injection. Urinary HCG (10,000 IU or 5000 IU) was administered to induce final oocyte maturation when three follicles ≥17 mm were observed by ultrasound scan or the next day. Oocyte retrieval was performed 34–36 h later, followed by either IVF or ICSI (Devroey et al., 2009).

Blood samples were drawn in the morning just prior to GnRH antagonist and gonadotrophin injections and the serum was immediately stored at −20°C until analysis of FSH, LH, oestradiol and progesterone concentrations.

Validated immunoassays were performed to measure serum concentrations of FSH, LH, oestradiol and progesterone at stimulation days 1, 5, 8 and day of HCG administration. All hormone measurements were determined at one central laboratory (Waltrop, Germany) using a time-resolved fluoroimmunoassay (AutoDelfia immunofluorometric assay; PerkinElmer Life and Analytical Sciences, Brussels, Belgium). Detection limits for serum FSH, LH, oestradiol and progesterone were 0.25 IU/l, 0.6 IU/l, 50 pmol/l and 1.3 nmol/l (0.4 ng/ml) respectively. The intra- and inter-assay variabilities of these assays were <5% and <10%, respectively.

Statistical analysis

All analyses were performed for the intention-to-treat (ITT) population. The ITT population includes all randomized subjects who received one or more dose(s) of corifollitropin alfa or rFSH. Subjects were grouped according to the treatment they were randomized to. Ongoing pregnancy rates were analysed per started cycle: subjects in the ITT group whose IVF cycles were cancelled were included and considered not pregnant in the statistical analyses.

Patients were stratified by LH percentiles to examine the LH effect on ongoing pregnancy rates. They were divided into three groups: below the 25th LH percentile (<P25), between the 25th and 75th LH percentiles (P25–P75) and above the 75th LH percentile (>P75). LH concentration was analysed as a three-level class variable and not as a continuous variable because almost a quarter of the LH measurements on stimulation day 8 and day of HCG were below the lower limit of quantification. Patients without LH measurements were excluded from the analyses.

Overall differences in baseline characteristics, stimulation characteristics and ovarian response between the <P25, P25–P75 and >P75 groups of patients were tested using either analysis of variance (ANOVA; for comparing means) or the Kruskal–Wallis test (for comparing medians).

The effect of treatment (corifollitropin alfa, rFSH) on the LH concentrations on stimulation days 5 and 8 and day of HCG was tested using the Mann–Whitney *U*-test.

Differences in ongoing pregnancy rates between the <P25, P25–P75 and >P75 groups of patients were analysed using PROC GENMOD in SAS version 9.1 (SAS Institute, Cary, NC, USA). A logistic regression model between ongoing pregnancy rate and LH concentration (<P25, P25–P75, >P75) was fitted for each combination of treatment group (corifollitropin alfa, rFSH) and day (stimulation day 8 and day of HCG). Separate models for the treatment groups were applied because the results for the rFSH group will be included in the combined analysis described in part II of this article (Griesinger et al., 2011). *P*-values of the LH effect on ongoing pregnancy rate were derived using the likelihood ratio test. Maximum likelihood estimates of odds ratios (OR) and associated two-sided 95% confidence intervals (CI) were computed for <P25 versus ≥P25 (low versus not-low LH), >P75 versus ≤P75 (high versus not-high LH) and <P25 versus >P75 (low versus high LH). The *P*-values and estimated OR and CI were computed with and without adjustment for predictive factors of ongoing pregnancy.

Age was selected as one of the predictive factors of ongoing pregnancy as it is well known that the chance of pregnancy is age related. Stepwise logistic regression analysis was applied to identify the other predictive factors per treatment group and stimulation day. Candidate predictive factors entered in the model were age, serum FSH concentration on stimulation day 1, antral follicle count (AFC) on stimulation day 1 and number of oocytes retrieved. Progesterone concentration and number of follicles ≥11 mm on stimulation day 8 were added to the above factors to identify the predictive factors for ongoing pregnancy for OR adjustment at stimulation day 8, while progesterone concentration and number of follicles ≥11 mm on day of HCG were added to identify the predictive factors for OR adjustment on day of HCG. The significance level of the candidate predictive factors to enter the model was set to 0.15 and to stay in the model was set to 0.10. The final model selects the predictive factors with statistical significance, i.e. $P \leq 0.05$. The predictive factors were added as independent covariates to the model to find the adjusted estimates of LH effect. Only additive models were considered to identify predictive factors.

Results

Baseline characteristics by LH category

Table 1 presents the baseline characteristics of patients treated with either corifollitropin alfa or rFSH for the first 7 days of ovarian stimulation, divided into three groups: low (<P25), medium (P25–P75) and high (>P75) serum LH concentrations on stimulation day 8. Patients with higher serum LH concentrations were more likely to demonstrate markers of diminished ovarian reserve (AFC, FSH). These

Table 1 Demographic and other baseline characteristics by treatment group and LH on stimulation day 8.

Characteristic	*LH percentile category*			*P-value*
	<P25	*P25–P75*	*>P75*	
Corifollitropin alfa (*n*)	216[a]	316	176	–
Age (years)	31.3 ± 3.3	31.4 ± 3.4	31.9 ± 3.3	NS
Body mass index (kg/m^2)	24.5 ± 2.6	24.9 ± 2.9	25.1 ± 2.7	≤0.05
Bodyweight (kg)	68.2 ± 7.0	68.9 ± 7.9	69.3 ± 7.6	NS
Serum LH on day 1 (IU/l; median (P5, P95))	4.0 (2.1, 7.0)	4.5 (2.4, 7.9)	4.9 (2.5, 9.8)	≤0.05
Serum FSH on day 1 (IU/l; median (P5, P95))	6.1 (3.9, 8.9)	6.3 (4.5, 9.6)	6.9 (4.5, 13.1)	≤0.05
Antral follicles <11 mm	12.8 ± 5.0	12.7 ± 4.3	11.4 ± 4.2	≤0.05
Duration of infertility (years)	3.1 ± 2.3	3.5 ± 2.5	3.4 ± 2.6	NS
Primary infertility	55.6	51.9	55.1	NS
Secondary infertility	44.4	48.1	44.9	NS
Recombinant FSH (*n*)	169	340	169	–
Age (years)	30.9 ± 3.4	31.6 ± 3.1	32.0 ± 3.4	≤0.05
Body mass index (kg/m^2)	24.6 ± 2.7	24.9 ± 2.8	25.1 ± 2.5	NS
Bodyweight (kg)	68.1 ± 7.3	68.5 ± 7.4	68.8 ± 7.0	NS
Serum LH on day 1 (IU/l; median (P5, P95))	4.2 (2.1, 7.0)	4.4 (2.3, 8.0)	4.8 (2.7, 8.6)	≤0.05
Serum FSH on day 1 (IU/l; median (P5, P95))	6.4 (3.9, 9.5)	6.4 (4.4, 9.9)	6.5 (4.9, 10.9)	≤0.05
Antral follicles <11 mm	12.4 ± 4.4	12.6 ± 4.6	12.1 ± 4.4	NS
Duration of infertility (years)	3.1 ± 2.2	3.3 ± 2.3	3.2 ± 2.0	NS
Primary infertility	52.7	53.5	50.9	NS
Secondary infertility	47.3	46.5	49.1	NS

Values are mean ± standard deviation or %, unless otherwise stated.
≤0.05 indicates unequal means or medians among the three LH categories.
NS = not statistically significant; <P25 = patients below the 25th LH percentile; P25–P75 = patients between the 25th and 75th LH percentiles; >P75 = patients above the 75th LH percentile.
[a]On stimulation day 8, >25% of patients treated with corifollitropin alfa had a value below the lower limit of quantification and were all included in the <P25 category.

Table 2 LH concentrations in LH percentile categories per treatment group and stimulation day.

Stimulation day	*LH percentiles*				
	P5	*P25*	*P50*	*P75*	*P95*
Corifollitropin alfa					
Day 1	2.28	3.39	4.48	5.82	8.11
Day 5	<0.6	1.18	2.04	4.19	12.5
Day 8	<0.6	<0.6	0.96	1.58	3.07
Day of HCG	<0.6	<0.6	1.00	1.77	3.53
Recombinant FSH					
Day 1	2.30	3.38	4.41	5.64	7.95
Day 5	<0.6	0.93	1.46	2.31	6.60
Day 8	<0.6	0.91	1.57	2.66	5.27
Day of HCG	<0.6	0.75	1.39	2.57	4.92

Values are IU/l.
HCG = human chorionic gonadotrophin.
Median LH concentrations differed ($P \leq 0.05$) between the two treatment groups on stimulation day 5, stimulation day 8 and day of HCG.

patients were older and had lower AFC and higher FSH (stimulation day 1) than patients with medium or low serum LH concentrations. There was no difference between the three groups with respect to the cause of infertility (data not shown), the duration of infertility or the incidence of primary infertility (**Table 1**).

Serum LH concentrations during treatment with corifollitropin alfa or daily rFSH

Table 2 presents the serum LH percentiles (P5, P25, P50, P75 and P95) in each treatment group at stimulation days 1, 5 and 8 and day of HCG administration. Serum LH concentrations were higher at stimulation day 5 in the corifollitropin alfa group than in the rFSH group, whereas the reverse was observed at stimulation day 8 and day of HCG administration

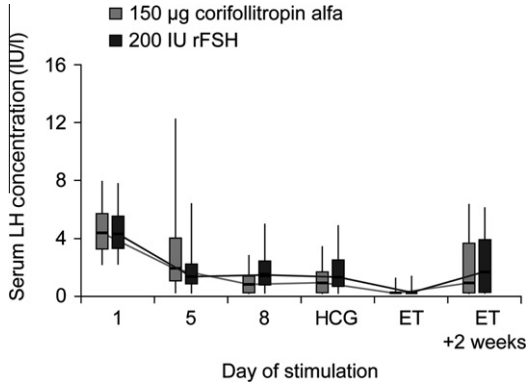

Figure 1 Box plot of serum LH concentrations during and after stimulation with corifollitropin alfa and rFSH. Treatment with the gonadotrophin-releasing hormone antagonist was started for all patients at stimulation day 5. Solid lines = median; boxes = P25–P75; whiskers = P5–P95; ET = embryo transfer; HCG = human chorionic gonadotrophin; rFSH = recombinant FSH.

(**Figure 1**). The difference in median LH concentration between the corifollitropin alfa group and the rFSH group was significant ($P \leq 0.05$) on stimulation day 5, stimulation day 8 and day of HCG, respectively (**Table 2**). At stimulation day 8, the P50 (median) value was 0.96 IU/l in the corifollitropin alfa group and 1.57 IU/l in the rFSH group. The P25 values were <0.6 IU/l and 0.91 IU/l and the P75 values were 1.58 IU/l and 2.66 IU/l, respectively.

Stimulation characteristics and ovarian response per LH category

The main stimulation characteristics in the trial per LH category at stimulation day 8 for both the corifollitropin alfa and rFSH arms are shown in **Table 3**. In both treatment groups, patients with lower LH required a slightly longer duration of stimulation and slightly more daily rFSH (50–80 IU) from stimulation day 8 onwards to reach the same HCG criteria. In both treatment groups, fewer follicles ≥11 mm were observed at stimulation day 8 and day of HCG in patients with higher LH concentrations (**Table 4**). Despite this, serum oestradiol and progesterone concentrations of patients in the higher percentile of endogenous LH were higher than in patients with lower LH concentrations. Fewer oocytes were retrieved in patients with higher LH concentrations.

There was no difference in the total number of embryos or the number of good-quality embryos obtained among the low, medium and high LH concentration groups of patients in each treatment group. The number and quality of embryos transferred were very similar among all the different subsets (data not shown).

Identification of predictive factors

Predictive factors of ongoing pregnancy in addition to age were identified using stepwise logistic regression to adjust the estimated OR at stimulation day 8 and day of HCG, respectively. The identified predictive factors to adjust the estimated OR at stimulation day 8 were: (i) serum progesterone on stimulation day 8 (corifollitropin alfa group: OR 0.80, 95% CI 0.68–0.95, $P = 0.01$; rFSH group: OR 0.87, 95% CI 0.75–1.00, $P = 0.05$): a higher progesterone concentration on stimulation day 8 was associated with a lower pregnancy rate in both treatment groups; (ii) number of follicles ≥11 mm on stimulation day 8 (corifollitropin alfa group only: OR 1.03, 95% CI 1.00–1.05, $P = 0.03$): a higher number of follicles was associated with a higher pregnancy rate; and (iii) number of oocytes retrieved (rFSH group only: OR 1.03, 95% CI 1.01–1.06, $P = 0.02$): a higher number of oocytes was associated with a higher pregnancy rate.

On the day of HCG trigger, none of the candidate predictive factors were statistically significant. Age was borderline significant in the rFSH group on day of HCG administration (OR 0.96, 95% CI 0.91–1.00).

Ongoing pregnancy rates according to LH percentiles

In both the corifollitropin alfa and rFSH groups, the ongoing pregnancy rates were similar for patients with low (<P25), medium (P25–75) or high (>P75) endogenous LH

Table 3 Stimulation characteristics by treatment group and LH on stimulation day 8.

Characteristic	*LH percentile category*			*P-value*
	<P25	*P25–P75*	*>P75*	
Corifollitropin alfa (*n*)	216	316	176	–
Total dose of rFSH (IU)	443.6 ± 316.0	407.3 ± 298.9	395.3 ± 317.8	NS
Total dose of rFSH from day 8 onwards (IU)	442.7 ± 315.2	407.3 ± 298.9	376.0 ± 281.4	≤0.05
Duration of stimulation (days)	9.8 ± 1.6	9.6 ± 1.4	9.3 ± 1.8	≤0.05
Recombinant FSH (*n*)	169	340	169	–
Total dose of rFSH (IU)	1811.8 ± 292.5	1742.9 ± 252.3	1728.6 ± 249.5	≤0.05
Total dose of rFSH from day 8 onwards (IU)	424.3 ± 277.1	353.9 ± 244.0	337.5 ± 238.4	≤0.05
Duration of stimulation (days)	9.6 ± 1.3	9.3 ± 1.1	9.2 ± 1.1	≤0.05

All values are mean ± standard deviation.
$P \leq 0.05$ indicates unequal means among the three LH categories.
NS = not statistically significant; rFSH = recombinant FSH; <P25 = patients below the 25th LH percentile; P25–P75 = patients between the 25th and 75th LH percentiles; >P75 = patients above the 75th LH percentile.

Table 4 Ovarian response by treatment group and LH on stimulation day 8.

Ovarian response	*LH percentile category*			*P-value*
	<P25	*P25–P75*	*>P75*	
Corifollitropin alfa (*n*)	216	316	176	–
Follicles on day 8				
≥11 mm	13.8 ± 6.9	13.1 ± 6.6	10.9 ± 6.0	≤0.05
≥15 mm	5.1 ± 5.2	5.2 ± 4.5	4.5 ± 3.9	NS
≥17 mm	2.2 ± 3.6	2.1 ± 2.6	2.0 ± 2.5	NS
Hormones on day 8				
Oestradiol (pmol/l)	2466 (598, 7046)	3068 (1013, 8368)	3397 (818, 10,570)	≤0.05
Progesterone (nmol/l)	1.7 (1.3, 3.2)	1.8 (1.3, 3.5)	2.1 (1.3, 3.9)	≤0.05
Follicles on day of HCG				
≥11 mm	16.6 ± 7.5	16.2 ± 7.0	13.6 ± 7.2	≤0.05
≥15 mm	10.3 ± 5.5	9.6 ± 4.7	8.1 ± 4.4	≤0.05
≥17 mm	6.1 ± 4.1	5.7 ± 3.0	4.8 ± 2.8	≤0.05
Hormones on day of HCG				
Oestradiol (pmol/l)	3743 (1380, 9212)	4881 (1875, 12,111)	6129 (2000, 13,689)	≤0.05
Progesterone (nmol/l)	2.6 (1.3, 7.4)	2.8 (1.3, 5.4)	3.0 (1.4, 5.5)	≤0.05
Oocytes	14.9 ± 8.1	14.1 ± 7.6	12.3 ± 9.2	≤0.05
Recombinant FSH (*n*)	169	340	169	–
Follicles on day 8				
≥11 mm	11.8 ± 6.5	11.8 ± 6.0	10.8 ± 5.0	NS
≥15 mm	4.9 ± 4.4	5.3 ± 4.0	5.0 ± 3.8	NS
≥17 mm	2.0 ± 2.5	2.6 ± 2.8	2.7 ± 2.8	≤0.05
Hormones on day 8				
Oestradiol (pmol/l)	2096 (690, 7524)	3162 (1158, 8936)	3854 (1453, 9982)	≤0.05
Progesterone (nmol/l)	2.1 (1.3, 4.6)	2.4 (1.4, 4.6)	2.7 (1.5, 5.1)	≤0.05
Follicles on day of HCG				
≥11 mm	14.9 ± 6.7	13.7 ± 6.1	12.6 ± 5.5	≤0.05
≥15 mm	9.3 ± 4.5	8.7 ± 4.0	7.8 ± 3.8	≤0.05
≥17 mm	5.9 ± 3.6	5.5 ± 2.7	5.5 ± 2.9	NS
Hormones on day of HCG				
Oestradiol (pmol/l)	3354 (1171, 8588)	4588 (1967, 10,093)	6092 (2567, 11,010)	≤0.05
Progesterone (nmol/l)	2.7 (1.4, 6.0)	3.0 (1.5, 5.4)	3.2 (1.5, 5.4)	≤0.05
Oocytes	13.2 ± 6.9	12.9 ± 7.0	11.5 ± 6.0	≤0.05

Values are mean ± standard deviation or median (P5, P95).
$P \leq 0.05$ indicates unequal means or medians among the three LH categories.
HCG = human chorionic gonadotrophin; NS = not statistically significant; <P25 = patients below the 25th LH percentile; P25–P75 = patients between the 25th and 75th LH percentiles; >P75 = patients above the 75th LH percentile.

Table 5 Ongoing pregnancy rate per started cycle, treatment group, stimulation day and LH.

Stimulation day	*LH percentile category*	*Ongoing pregnancy rate*	
		n/total	*% (95% CI)*
Corifollitropin alfa			
Day 8	<P25	77/216	35.6 (29.3–42.4)
	P25–P75	125/316	39.6 (34.1–45.2)
	>P75	68/176	38.6 (31.4–46.3)
Day of HCG	<P25	75/208	36.1 (29.5–43.0)
	P25–P75	126/307	41.0 (35.5–46.8)
	>P75	73/170	42.9 (35.4–50.7)
Recombinant FSH			
Day 8	<P25	60/169	35.5 (28.3–43.2)
	P25–P75	125/340	36.8 (31.6–42.1)
	>P75	65/169	38.5 (31.1–46.2)
Day of HCG	<P25	63/175	36.0 (28.9–43.6)
	P25–P75	132/352	37.5 (32.4–42.8)
	>P75	74/174	42.5 (35.1–50.2)

CI = confidence interval; HCG = human chorionic gonadotrophin; <P25 = patients below the 25th LH percentile; P25–P75 = patients between the 25th and 75th LH percentiles; >P75 = patients above the 75th LH percentile.

Table 6 Logistic regression model for ongoing pregnancy in LH percentile categories per treatment group and day.

Treatment group	*<P25 versus ≥P25*	*>P75 versus ≤P75*	*<P25 versus >P75*
Stimulation day 8			
Corifollitropin alfa	0.86 (0.62–1.21)	1.05 (0.74–1.49)	0.88 (0.58–1.33)
	0.75 (0.53–1.06)[a]	1.26 (0.87–1.83)[a]	0.70 (0.46–1.09)[a]
rFSH	0.91 (0.63–1.32)	1.10 (0.77–1.59)	0.88 (0.57–1.37)
	0.80 (0.54–1.17)[b]	1.28 (0.87–1.87)[b]	0.73 (0.46–1.16)[b]
Day of HCG			
Corifollitropin alfa	0.78 (0.55–1.10)	1.20 (0.84–1.71)	0.75 (0.49–1.13)
	0.77 (0.55–1.08)[c]	1.22 (0.85–1.74)[c]	0.74 (0.49–1.12)[c]
Recombinant FSH	0.84 (0.59–1.21)	1.27 (0.89–1.82)	0.76 (0.49–1.17)
	0.79 (0.55–1.14)[c]	1.35 (0.94–1.93)[c]	0.70 (0.45–1.09)[c]

Values are estimated odds ratios (95% confidence interval).
The LH effect was not statistically significantly different ($P > 0.05$) for any of the stimulation days or treatment arms, unadjusted or adjusted for predictive factors.
HCG = human chorionic gonadotrophin.
[a]Adjusted for age and progesterone and number of follicles ≥11 mm on stimulation day 8.
[b]Adjusted for age, progesterone on stimulation day 8 and oocytes.
[c]Adjusted for age.

concentrations on stimulation day 8 and day of HCG administration (Table 5). The effect of LH concentration on stimulation day 8 and day of HCG was not statistically significant in these treatment groups (Table 6). The estimated OR for <P25 versus ≥P25, >P75 versus ≤P75 and <P25 versus >P75 groups were not statistically significantly different from 1.0 for any of the stimulation days or treatment arms (Table 6), regardless of whether the estimated OR was unadjusted or adjusted for predictive factors.

Discussion

In the 1506 normogonadotrophic women who received either corifollitropin alfa or rFSH during the Engage study, there was no relationship between endogenous LH concentrations and ongoing pregnancy rates. The LH analyses showed that, with a GnRH antagonist protocol to prevent premature LH surges during ovarian stimulation, the

ongoing pregnancy rate was not influenced by either lower or higher endogenous LH concentrations on stimulation day 8 or day of HCG administration. This observation suggests that neither implantation rate nor early miscarriage rates are affected by the amount of circulating LH activity.

On stimulation day 8, the P25 value was <0.6 IU/l in the corifollitropin alfa group and 0.91 IU/l in the rFSH group. These values are below 1.2 IU/l, the cut-off value below which recombinant LH is indicated for ovulation induction in anovulatory women with profound LH deficiency (The European Recombinant Human LH Study Group, 1998). These findings are in agreement with other studies that used GnRH antagonist protocols (Bosch et al., 2005; Merviel et al., 2004), which also showed that low LH values were not associated with decreased pregnancy rates. Although it is known that high concentrations of GnRH antagonist may reduce clinical pregnancy rates (Huirne et al., 2005; The Ganirelix Dose-finding Study Group, 1998), this reduction of fertility does not appear to be mediated through LH deficiency.

In the current trial of young women aged 18–36 years, serum LH concentrations on stimulation day 8 varied from undetectable concentrations (<0.6 IU/l) to 3 IU/l in the corifollitropin alfa group and 5 IU/l in the daily rFSH group. This variability was partly related to the woman's age and the ovarian reserve as women with lower serum LH concentrations had a higher ovarian response. In contrast to GnRH-agonist protocols, GnRH antagonist needs to be administered only during the period of stimulation when a LH rise becomes imminent. In the current study, GnRH antagonist was started for all patients on stimulation day 5 and the observed difference in endogenous LH concentrations at the end of the follicular phase may be related to the larger recruited cohort of follicles in the corifollitropin alfa group compared with the rFSH group. This observation is in line with the lower endogenous LH on day of HCG in patients treated with a fixed daily dose of 200 IU rFSH as compared with a fixed daily dose of 150 IU rFSH (Out et al., 2004).

Endogenous LH concentrations on stimulation day 8 showed a negative association with the number of follicles. This relationship is due to the difference in ovarian reserve in the three LH categories, but it is noted that both serum oestradiol and progesterone showed a positive association, which confirms that steroidogenesis is to a certain extent driven by endogenous LH concentrations regardless of the number of antral follicles or oocytes recovered (The Ganirelix Dose-finding Study Group, 1998).

The stepwise logistic regression analyses indicated that higher progesterone concentrations on stimulation day 8 reduce the ongoing pregnancy rate, while an increased number of follicles on stimulation day 8 (corifollitropin alfa group) or oocytes (rFSH group) increase the ongoing pregnancy rate. Thus, a higher oocyte yield and lower progesterone concentrations are associated with a higher chance of pregnancy. However, serum progesterone concentrations increase during the late follicular phase with the number of growing follicles. This finding supports the concept of an optimal range of oocytes, below and above which outcomes are compromised (van der Gaast et al., 2006). This would imply that pregnancy rates may be improved as long as the number of oocytes is still below the optimal range, whereas overstimulation may increase serum progesterone concentrations during the late follicular phase, which is known to compromise the chance of implantation (Bosch et al., 2010). Further data analysis is required to explore the impact of high progesterone concentrations during stimulation on pregnancy outcome in a GnRH antagonist protocol, which has significantly lower progesterone concentrations than a GnRH agonist protocol.

On the day of HCG administration, the stepwise regression analysis indicated that only age was a significant factor – this may be due to the large variability in the number of follicles and progesterone concentrations at this time. In the current investigation, as neither low nor high endogenous LH concentrations impacted ongoing pregnancy rates in either direction, the data suggest that the amount of endogenous LH was sufficient to support follicular function and implantation in both treatment groups during ovarian stimulation prior to IVF or ICSI. Also, the estimated OR for ongoing pregnancy of low LH (<P25) versus not low LH (≥P25), high LH (>P75) versus not high LH (≤P75) and low LH ($P < 25$) versus high LH (>P75) were not statistically significant for any of the treatment groups and treatment days investigated.

In conclusion, LH analysis of the Engage trial showed that ongoing pregnancy rates were not affected by the extent of LH suppression as measured at stimulation day 8 and day of HCG administration. These findings support previous GnRH antagonist studies that indicated that clinical outcome is not compromised in the absence of exogenous LH supplementation.

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