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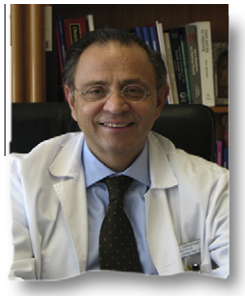
ARTICLE

Comparative incidence of ovarian hyperstimulation syndrome following ovarian stimulation with corifollitropin alfa or recombinant FSH

Basil C Tarlatzis [a,1], Georg Griesinger [b,1], Arthur Leader [c,1], Luk Rombauts [d,1], Pieta C IJzerman-Boon [e,1], Bernadette MJL Mannaerts [e,*,1]

[a] *Chair of the Data Safety Monitoring Board,1St Department of Obstetrics and Gynaecology, Papageorgiou Hospital, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece;* [b] *Department of Obstetrics and Gynaecology, University Clinic of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany;* [c] *The Ottawa Fertility Centre, University of Ottawa, Ontario, Canada;* [d] *Monash IVF, Clayton, Victoria, Australia;* [e] *MSD, Molenstraat 110, PO Box 20, 5340 BH Oss, The Netherlands*

[*] Corresponding author. *E-mail address:* b.mannaerts@merck.com (BMJL Mannaerts). [1]On behalf of all investigators participating in the Engage, Ensure or Trust trials (for list of investigators, see Appendix).



Basil C Tarlatzis, MD, PhD, is professor of obstetrics, gynaecology and reproductive medicine at the Aristotle University of Thessaloniki in Greece and also is dean of the School of Medicine. He is a visiting professor at the Faculty of Medicine and Pharmacy at the Dutch-speaking Brussels Free University, Belgium, and deputy chairman of the National Authority of Medically Assisted Reproduction. He is past chairman of the European Society of Human Reproduction and Embryology, a member of the Ethics and Law Committee of ESHRE and past president of the International Federation of Fertility Societies. He is a member of 22 national and 17 international scientific societies and is on the editorial boards of 21 journals.

Abstract Corifollitropin alfa is a novel recombinant gonadotrophin with sustained follicle-stimulating activity. A single injection can replace seven daily injections of recombinant follicle-stimulating hormone (rFSH) during the first week of ovarian stimulation. All cases of ovarian hyperstimulation syndrome (OHSS) with corifollitropin alfa intervention in a gonadotrophin-releasing hormone antagonist protocol have been assessed in three large trials: Engage, Ensure and Trust. Overall, 1705 patients received corifollitropin alfa and 5.6% experienced mild, moderate or severe OHSS. In the randomized controlled trials, Engage and Ensure, the pooled incidence of OHSS with corifollitropin alfa was 6.9% (71/1023 patients) compared with 6.0% (53/880 patients) in the rFSH group. Adjusted for trial, the odds ratio for OHSS was 1.18 (95% CI 0.81–1.71) indicating that the risk of OHSS for corifollitropin alfa was similar to that for rFSH. The incidence of mild, moderate and severe OHSS was 3.0%, 2.2% and 1.8%, respectively, with corifollitropin alfa, with 1.9% requiring hospitalization, and 3.5%, 1.3% and 1.3%, respectively, in the rFSH arms, with 0.9% requiring hospitalization. Despite a higher ovarian response with corifollitropin alfa compared with rFSH for the first 7 days of ovarian stimulation, the incidence of OHSS was similar.

KEYWORDS: corifollitropin alfa, gonadotrophin-releasing hormone antagonist, OHSS, ovarian stimulation, recombinant FSH, assisted reproductive technology

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially serious complication of ovulation induction and ovarian stimulation for assisted reproductive technology (Delvigne and Rozenberg, 2002, 2003). Two main clinical forms of OHSS, distinguished by time of onset, are described in the literature and appear to be distinct in their aetiology (Mathur et al., 2000). Early OHSS generally occurs within 10 days after human chorionic gonadotrophin (HCG) administration, is an acute effect of exogenous HCG administration and is correlated to the magnitude of the preovulatory ovarian response to stimulation (Lyons et al., 1994; Mathur et al., 2000). Late OHSS generally occurs more than 10 days after HCG administration, is linked to endogenous HCG production by an implanting embryo or HCG administration for luteal-phase support and is poorly correlated to the preovulatory ovarian response to stimulation (Mathur et al., 2000; Papanikolaou et al., 2006). Late OHSS is more likely to be severe than early OHSS (Mathur et al., 2000).

To date, it is difficult to estimate the risk for developing OHSS in the absence of known predisposing factors. However, patient characteristics associated with the ovarian reserve, including age, serum follicle-stimulating hormone (FSH) concentrations, antral follicle count (AFC), inhibin B concentrations and anti-Müllerian hormone concentrations, may be used to estimate the ovarian response prior to ovarian stimulation.

The risk of early-onset OHSS increases in high responders to ovarian stimulation, as measured by the number of ovarian follicles, serum oestradiol concentrations on the day of HCG administration and the number of oocytes retrieved (Mathur et al., 2000; Verwoerd et al., 2008). Patients with more than 18 follicles $\geq$11 mm are at increased risk of developing OHSS (Papanikolaou et al., 2006).

Gonadotrophin-releasing hormone (GnRH) antagonist protocols appear to be effective in reducing the development of OHSS (Kolibianakis et al., 2006). Comparative clinical trials of GnRH antagonist versus long GnRH agonist protocols have shown that long protocols are associated with the recruitment of more follicles and oocytes and eventually a higher incidence of OHSS (Kolibianakis et al., 2006).

Corifollitropin alfa is a novel recombinant gonadotrophin, a single dose of which is capable of initiating and sustaining multifollicular growth during the first 7 days of ovarian stimulation. The pharmacokinetic profile of corifollitropin alfa is characterized by a slow absorption, resulting in peak concentrations 2 days after injection with a steady decline afterwards. Its long elimination half-life accommodates a sufficiently high FSH threshold window to support ovarian stimulation over an entire week (Duijkers et al., 2002; Fauser et al., 2010). This sustained activity may be perceived to be a risk factor for overstimulation. Corifollitropin alfa has equivalent efficacy to recombinant FSH (rFSH) for achieving ongoing pregnancies in a GnRH antagonist protocol but offers a simplified treatment regimen with fewer injections (Corifollitropin Alfa Ensure Study Group, 2010; Devroey et al., 2009). It does promote a slightly higher ovarian response compared with daily rFSH, most likely due to the higher FSH activity during the first few days of stimulation (Corifollitropin Alfa Ensure Study Group, 2010; Devroey et al., 2009).

The current study assessed the incidence of OHSS with corifollitropin alfa intervention in a GnRH antagonist protocol for ovarian stimulation. Cases of OHSS from three phase-3 trials with corifollitropin alfa that were primarily designed, powered and conducted to assess ongoing pregnancy rates (Engage; Devroey et al., 2009), number of oocytes (Ensure; Corifollitropin Alfa Ensure Study Group, 2010) and immunogenicity (Trust; Norman et al., 2011) were captured. Because of the relative rarity of severe OHSS, a pooled analysis of the Engage and Ensure trials (two trials of similar design with rFSH as the comparator) was conducted to provide a reliable estimate of the incidence of OHSS.

Materials and methods

Phase-3 trials

The incidence, severity and time of onset of OHSS were assessed in three trials of corifollitropin alfa (Elonva; N.V. Organon) in a GnRH antagonist protocol in normogonadotrophic women with an indication for ovarian stimulation for IVF/intracytoplasmic sperm injection (ICSI). Details of these trials, Engage (Devroey et al., 2009), Ensure (Corifollitropin Alfa Ensure Study Group, 2010) and Trust (Norman et al., 2011), have been reported previously.

Engage and Ensure were double-blind, double-dummy randomized controlled trials that compared the efficacy of a single injection of corifollitropin alfa during the first 7 days of ovarian stimulation with daily injections of rFSH in a GnRH antagonist (ganirelix) protocol.

Trust was an open, uncontrolled trial that evaluated the safety and tolerability of repeated cycles (up to three per patient) with a single injection of corifollitropin alfa for the first 7 days of ovarian stimulation in a GnRH antagonist protocol. In the current analysis, data from the first cycle only were included.

Study population

In the Engage trial participants aged 18–36 years with a bodyweight of 61–90 kg and body mass index (BMI) 18–32 kg/m^2 received either corifollitropin alfa 150 μg (n = 755) or seven daily injections of rFSH 200 IU (Puregon/Follistim Pen; N.V. Organon) (n = 751). In the Ensure trial, participants aged 18–36 years with a body weight $\leq$60 kg and BMI 18–32 kg/m^2 received either corifollitropin alfa 100 μg (n = 268) or seven daily injections of rFSH 150 IU (n = 129). The different doses of corifollitropin alfa (100 μg for patients $\leq$60 kg and 150 μg for patients $>$60 kg) provide a similar exposure in these two different bodyweight groups (de Greef et al., 2010; Ledger et al., 2011). In the Trust trial, participants aged 18–39 years with a bodyweight of $>$60 kg and BMI of 18–29 kg/m^2 received corifollitropin alfa 150 μg (n = 682).

Patients with a history of ovarian hyper-response to ovarian stimulation (more than 30 follicles $\geq$11 mm), of OHSS or polycystic ovarian syndrome or with more than 20 basal antral follicles on ultrasound ($<$11 mm, both ovaries combined), i.e. all predisposing factors that confer an increased

risk of developing OHSS during ovarian stimulation (Delvigne and Rozenberg, 2002; Lee et al., 2008), were excluded. Patients with a history of low or no ovarian response or more than three unsuccessful ovarian stimulation cycles since the last established pregnancy were also excluded.

Study design

In these trials, corifollitropin alfa treatment (or daily rFSH for Engage and Ensure) started on menstrual cycle day 2 or 3 (stimulation day 1). From stimulation day 8 onwards, treatment was continued as needed with a daily subcutaneous dose of ≤200 IU of rFSH (Engage and Ensure) or ≤225 IU FSH/human menopausal gonadotrophin (Trust) up to and including (optional in Trust) the day of HCG administration. To prevent premature luteinizing hormone surges, the GnRH antagonist ganirelix (0.25 mg, Orgalutran/ganirelix acetate injection; N.V. Organon) was administered once daily subcutaneously, starting on stimulation day 5, up to and including the day of HCG injection. Urinary HCG 10,000 IU (or 5000 IU in the case of a high ovarian response; Engage, Ensure and Trust) or recombinant HCG 250 μg (Trust) was administered to induce final oocyte maturation as soon as 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 (Corifollitropin Alfa Ensure Study Group, 2010; Devroey et al., 2009; Norman et al., 2011).

The dose of rFSH could be reduced from day 6 onwards in case of too high an ovarian response in the Engage and Ensure trials and from day 8 as appropriate in the Trust trial. The investigator could reduce the dose of rFSH (dose tapering) or withhold rFSH administration for a maximum of 3 days (coasting) up to and including the day of HCG administration. In the case of too high an ovarian response, the cycle could be cancelled at any time. However, if there was a risk of OHSS, defined as >30 follicles ≥11 mm on ultrasound scan, HCG was withheld and the treatment cycle was cancelled. The maximum total duration of stimulation was 19 days.

Patients who were cancelled from the treatment cycle because of hyper-response were included in the analysis with 0 oocytes if they did not reach oocyte retrieval.

Assessments

Cases of OHSS were categorized as mild, moderate or severe according to World Health Organization guidelines (WHO, 1973), with a slight modification to the classification of mild OHSS to require the presence of abdominal discomfort, including abdominal pain: (i) mild OHSS (grade I): excessive steroid secretion and ovarian enlargement (5–7 cm), accompanied by abdominal discomfort, including abdominal pain; (ii) moderate OHSS (grade II): distinct ovarian cysts (ovary size 8–10 cm), accompanied by abdominal pain and tension, nausea, vomiting and diarrhoea; and (iii) severe OHSS (grade III): enlarged cystic ovaries (ovary size >10 cm), accompanied by ascites and occasionally hydrothorax; abdominal tension and pain may be severe; pronounced hydrothorax together with an abdominal cavity filled with cysts and fluid elevating the diaphragm may cause severe breathing difficulties; large quantities of fluid inside the cysts and in the peritoneal and pleural cavities cause haemoconcentration and increased blood viscosity; in rare cases, the syndrome may be further complicated by the occurrence of thromboembolic phenomena.

OHSS that occurred less than 10 days after oocyte retrieval was termed early-onset OHSS and OHSS that occurred 10 or more days after oocyte retrieval was termed late-onset OHSS.

Statistical analysis

Demographics and infertility characteristics were summarized per trial. Data were pooled for the two comparative randomized controlled trials (Engage and Ensure) and presented separately for the Trust trial, as there was no comparator rFSH arm in the latter and there were differences from the other two trials in the patient population.

The most important baseline and treatment characteristics were summarized for patients with OHSS versus without OHSS per treatment group for the randomized, controlled trials, pooled.

To examine whether the incidence of OHSS was possibly related to differences in serum FSH activity at day 8 of stimulation, the incidence of OHSS in the Engage and Ensure trials was evaluated both in the corifollitropin alfa and the rFSH arms for patients with relatively low, average or high serum FSH concentrations on day 8 (<P25, P25–75 and >P75).

From the two randomized trials, an odds ratio (OR) for OHSS (corifollitropin alfa versus rFSH) was derived and stratified by trial. Additionally, a logistic regression model was fitted, with covariate treatment group incorporated into the model and other covariates selected in a stepwise fashion. Covariates started within the stepwise selection were study, age, bodyweight, BMI, AFC, FSH at stimulation day 1 and 8, duration of stimulation, HCG received, number of follicles and serum oestradiol concentration (log transformed with base 10) at day of HCG and number of oocytes retrieved. Forward selection ($P \leq 0.05$ for entry) and backward elimination ($P > 0.05$ for removal) led to the same set of covariates.

In order to retain all 1903 subjects in the final model, missing covariate values for FSH (109 subjects) and log serum oestradiol (128 subjects) were replaced by their population medians. The number of oocytes was set to 0 for subjects who did not reach oocyte retrieval, thus there were no missing values for the number of oocytes. Note that for subjects who discontinued due to hyper-response the chance of developing OHSS is substantially reduced by withholding HCG and therefore it is also justified to include these patients with 0 oocytes in the model. The receiver operating characteristic (ROC) curve for the final model was plotted and the associated area under the curve (AUC) was calculated.

Results

Patient demographics in the three trials

Overall, 2585 patients were treated with either corifollitropin alfa ($n = 1705$) or rFSH ($n = 880$) in the three trials. The patient demographics and fertility characteristics per trial are summarized in **Table 1**.

Table 1 Overall patient demographics and fertility characteristics.

Variable	*Engage* (n = *1506*)	*Ensure* (n = *397*)	*Trust* (n = *682*)
Age (years)	31.5 ± 3.3	31.0 ± 3.1	32.9 ± 3.6
Bodyweight (kg)	68.6 ± 7.5	54.2 ± 4.2	67.0 ± 6.5
Body mass index (kg/m^2)	24.8 ± 2.7	20.6 ± 1.5	24.2 ± 2.4
Race			
Asian	42 (2.8)	177 (44.6)	9 (1.3)
Black	61 (4.1)	1 (0.3)	20 (2.9)
Caucasian	1293 (85.9)	219 (55.2)	640 (93.8)
Other	110 (7.3)	0	13 (1.9)
Fertility characteristics			
Primary infertility	796 (52.9)	246 (62.0)	392 (57.5)
Duration of infertility (years)	3.3 ± 2.3	3.2 ± 2.2	3.8 ± 3.0
Cause of infertility[a]			
Male factor	735 (48.8)	196 (49.4)	405 (59.4)
Tubal factor	389 (25.8)	101 (25.4)	165 (24.2)
Endometriosis	224 (14.9)	43 (10.8)	80 (11.7)
Cervical mucous problems	11 (0.7)	4 (1.0)	7 (1.0)
Unexplained infertility	413 (27.4)	108 (27.2)	131 (19.2)
Other	115 (7.6)	9 (2.3)	5 (0.7)
Stimulation day 1			
FSH (IU/l)	6.4 (4.2, 10.0)	6.5 (4.1, 9.8)	6.8 (4.4, 11.3)
Antral follicle count <11 mm	12.4 ± 4.5	11.2 ± 4.4	11.0 ± 4.9

All values are means ± SD, *n* (%) or median (5th and 95th percentiles). All patients treated.
[a]Subjects can have more than one cause of infertility, so percentages do not necessarily add up to 100%.

The study populations in the two randomized controlled trials (Engage and Ensure) were broadly comparable to those in the uncontrolled trial (Trust). However, participants in the Trust trial were slightly older (mean 32.9 years) than in the Engage (31.5 years) and Ensure trials (31.0 years), as the upper limit for inclusion in Trust was 39 years, compared with 36 years in the Engage and Ensure trials. In line with this age difference, the basal AFC was also slightly lower in the Trust trial (11.0 versus 12.4 for Engage and versus 11.2 for Ensure). The median FSH concentration at stimulation day 1 was also slightly higher in the Trust population.

In the randomized controlled trials, cycle cancellations due to too high an ovarian response or risk of OHSS occurred before HCG and oocyte retrieval for 12 subjects (0.6%; eight subjects [0.8%] in the corifollitropin alfa arm and four subjects [0.5%] in the rFSH arm) and for 12 subjects after oocyte retrieval (0.6%, 12 [1.2%] in the corifollitropin alfa arm and none [0.0%] in the rFSH arm). In the Trust trial, 12 subjects [1.8%] discontinued before HCG for this reason and four subjects (0.6%) after oocyte retrieval.

Characteristics of patients with and without OHSS (pooled data from Engage and Ensure)

The demographic and fertility characteristics of patients with OHSS (any grade) treated with either corifollitropin alfa or rFSH are compared with those without OHSS in **Table 2**, which shows the pooled data for the two randomized controlled trials. Patients with OHSS were younger ($P < 0.01$) and had a higher AFC ($P < 0.01$) and lower FSH concentrations ($P < 0.01$) at stimulation day 1 than patients without OHSS. On the day of HCG administration, patients with OHSS had more follicles ≥11 mm ($P < 0.01$) and higher serum oestradiol concentrations ($P < 0.01$) than those with no OHSS. The number of oocytes retrieved per started cycle was higher in patients with OHSS than in those without OHSS ($P < 0.01$). This holds regardless of whether subjects were treated with a single dose of corifollitropin alfa or daily rFSH for the first 7 days of ovarian stimulation.

Incidence of OHSS

In total, over the three trials, 5.6% (95/1705) of the patients treated with corifollitropin alfa experienced signs or symptoms of OHSS (mild, moderate or severe).

In the two randomized controlled trials (Engage and Ensure), the pooled overall incidence of OHSS in the corifollitropin alfa group was 6.9% (71/1023), compared with 6.0% (53/880) in the rFSH group. The (unadjusted) corifollitropin alfa to rFSH OR for OHSS was 1.16. Adjusted for trial, the OR was 1.18 (95% CI 0.81−1.71), indicating that the risk of OHSS for corifollitropin alfa was similar to that for rFSH. Considering the severity of OHSS encountered, the incidence of mild, moderate and severe OHSS in the corifollitropin alfa-treated patients was 3.0%, 2.2% and 1.8%, respectively, with 1.9% requiring hospitalization, and in the rFSH-treated patients 3.5%, 1.3% and 1.3%, respectively, with 0.9% requiring hospitalization (**Figure 1A**). The pooled data from the two randomized controlled trials on OHSS of all grades of severity showed that early onset OHSS developed in 4.6% of patients (47/1023) in the corifollitropin alfa group and 3.6% (32/880) in the rFSH group whilst late-onset OHSS developed in 2.3% of patients (24/1023) in the corifollitropin alfa group and 2.4% (21/880) in the rFSH group (**Figure 1A**).

Table 2 Characteristics of patients with mild, moderate or severe ovarian hyperstimulation syndrome (OHSS) and patients with no OHSS (pooled data from two randomized controlled trials, Engage and Ensure).

	OHSS		*Without OHSS*		*P-value OHSS versus without OHSS*
	Corifollitropin alfa (n = 71)	*rFSH (n = 53)*	*Corifollitropin alfa (n = 952)*	*rFSH (n = 827)*	
Age (years)	30.6 ± 3.1	30.3 ± 3.3	31.4 ± 3.3	31.5 ± 3.2	<0.01[a]
Bodyweight (kg)	64.0 ± 9.7	66.4 ± 6.8	65.0 ± 9.4	66.3 ± 8.7	NS
Body mass index (kg/m^2)	23.5 ± 3.1	24.2 ± 2.5	23.7 ± 3.1	24.2 ± 3.0	NS
AFC <11 mm at stimulation day 1	13.9 ± 4.5	13.9 ± 3.1	11.8 ± 4.5	12.1 ± 4.5	<0.01[a]
FSH at stimulation day 1 (IU/l)	5.8 (4.0, 8.5)	5.9 (4.4, 7.7)	6.5 (4.3, 10.3)	6.5 (4.1, 10.1)	<0.01[a]
FSH at stimulation day 8 (IU/l)	10.9 (6.6, 16.1)	10.7 (7.4, 14.3)	11.1 (7.3, 16.1)	11.3 (7.9, 15.9)	0.03[a]
Duration of stimulation (days)	9.4 ± 1.2	9.1 ± 1.3	9.4 ± 1.7	9.2 ± 1.3	NS
HCG administered	71 (100.0)	52 (98.1)	927 (97.4)	818 (98.9)	NS
Dose of HCG[c]					
10,000 IU	47 (66.2)	46 (88.5)	749 (80.8)	711 (86.9)	
5000 IU	23 (32.4)	6 (11.5)	177 (19.1)	106 (13.0)	
Other	1 (1.4)	0 (0.0)	1 (0.1)	1 (0.1)	
Follicles ≥11 mm on day of HCG	21.5 ± 8.5	17.6 ± 6.1	15.2 ± 6.6	13.5 ± 6.0	<0.01[a]
Serum oestradiol concentration on day of HCG (pmol/l)	7193 (2767, 17,212)	6606 (2463, 12,001)	4367 (1534, 11,083)	4404 (1677, 10,349)	<0.01[b]
Oocytes retrieved	21.4 ± 9.8	17.0 ± 6.9	13.0 ± 7.5	11.9 ± 6.5	<0.01[c]

All values are means ± SD, *n* (%) or median (5th and 95th percentiles).
AFC = antral follicle count; HCG = human chorionic gonadotrophin; rFSH = recombinant FSH.
[a]*P*-value adjusted for treatment group and trial.
[b]*P*-value per treatment group (*P*-values for corifollitropin alfa and rFSH groups were both <0.01).
[c]Restricted to subjects with HCG.

In the uncontrolled Trust trial including 682 slightly older patients undergoing their first corifollitropin alfa treatment cycle, the overall incidence of OHSS (mild, moderate and severe) was 3.5% (24/682). The incidence of mild, moderate and severe OHSS was 1.8%, 0.9% and 0.9%, respectively, with 1.2% hospitalizations. The incidence of early-onset OHSS was 2.6% (18/682), and that for late-onset OHSS was 0.9% (6/682; **Figure 1B**).

There was no difference in the incidence of OHSS for patients starting on cycle day 2 or 3 with corifollitropin alfa treatment. Combining the three phase-3 trials, patients treated with corifollitropin alfa starting on day 2 had an incidence of 3.1% (25/812) moderate/severe OHSS and patients starting on day 3 had an incidence of 3.2% (27/836) moderate and severe OHSS. The overall incidence of OHSS was 5.3% versus 6.0%. This analysis is based on the all-subjects-treated-group, restricted to subjects treated with HCG.

Incidence of OHSS by FSH concentration on day 8

The FSH percentile concentrations P25, P50 and P75 on stimulation day 8 in the corifollitropin alfa and rFSH arms were, respectively, 9.7, 11.6, 13.5 IU/l and 9.8, 11.4, 13.2 IU/l in the Engage trial, and 9.0, 10.1, 11.6 IU/l and 9.1, 10.3, 11.6 IU/l in the Ensure trial (**Table 3**).

The incidence of OHSS in the corifollitropin alfa and rFSH treatment groups according to serum FSH concentrations (percentiles <P25, P25—P75 and >P75) on stimulation day 8 in the Engage and Ensure trial are shown in **Table 3**. Patients with higher FSH concentrations on day 8 did not have a higher risk of OHSS.

Logistic regression model for OHSS

Results for the logistic regression model for OHSS are given in **Table 4** and the associated ROC curve is given in **Figure 2**. The AUC for the final model was 0.753. It appeared that higher FSH concentrations on day 1 were associated with a lower probability of OHSS, whereas higher serum oestradiol concentrations on the day of HCG and a higher number of oocytes retrieved were associated with a higher probability of OHSS. It should be noted that the OR for these continuous covariates should be interpreted per unit increase. For the number of oocytes, for example, the OHSS OR increases by a factor of 1.08 for every additional oocyte. The adjusted

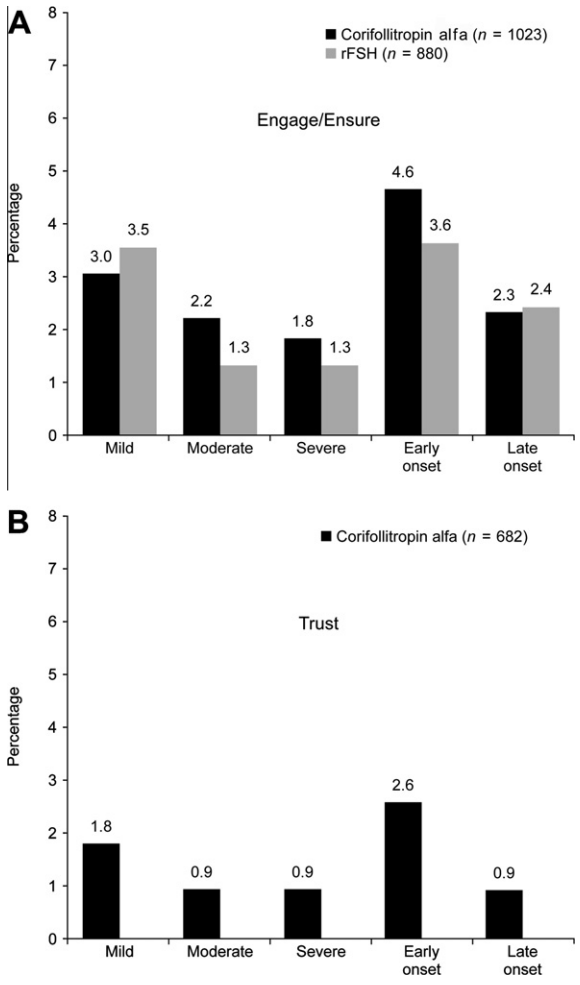

Figure 1 Ovarian hyperstimulation syndrome in patients treated with corifollitropin alfa or recombinant FSH (rFSH). Data from (A) Engage and Ensure (pooled) and (B) Trust.

corifollitropin alfa to rFSH OR was 0.99 (95% CI 0.67—1.45), again indicating that the OHSS risks for corifollitropin alfa and rFSH were similar. Other covariates, including age and AFC (which also had a univariate association with OHSS) did not contribute statistically to the multivariate model.

Another application of the logistic regression model is that the (absolute) risk of OHSS can be calculated for any given patient. For example, for a patient with median values for FSH on day 1 of 6.4 IU/l, serum oestradiol on the day of HCG of 4514 pmol/l and with 12 oocytes retrieved, the OHSS risk would be 4.5% if this patient were to be treated with corifollitropin alfa, versus 4.6% if they were to be treated with rFSH.

Discussion

The overall incidence of OHSS (5.6%), and the incidence per severity and per time of onset in all three phase-3 trials with corifollitropin alfa treatment for the first 7 days of ovarian stimulation to date (Engage, Ensure and Trust), are in line with those anticipated with daily rFSH treatment in this relatively young IVF population. Accordingly, the incidence of mild, moderate and severe OHSS (3.0%, 2.2% and 1.8%, respectively) in the current evaluation of patients (mean age 31 years) treated with corifollitropin alfa for ovarian stimulation in two large randomized controlled trials is lower than or within the range of previously reported incidences of OHSS for patients undergoing ovarian stimulation for IVF/ICSI (mild OHSS 8—33%, moderate 3—6% and severe OHSS 0.1—2%) (Delvigne and Rozenberg, 2002; Alper et al., 2009). The current analysis of incidence of OHSS with the same grading criteria in two large comparative randomized controlled trials is important, because the variety of grading systems for OHSS severity and the inclusion of different patient populations and treatment regimens has made it difficult to compare incidences of OHSS reported in the literature, and the wide incidence range for OHSS severity grades reported most likely reflects this (Brinsden et al., 1995; Golan and Weissman, 2009; Papanikolaou et al., 2006; WHO, 1973).

The current pooled analysis of data from two large randomized controlled trials indicates that the risk of OHSS following corifollitropin alfa treatment for ovarian stimulation tends to be higher than with rFSH treatment, with a difference of 1.4% in the incidence of moderate and/or severe OHSS and of 0.5% for severe OHSS. These differences, which are not statistically significant, are considered to be small and acceptable in view of the significant estimated difference of 2% (95% CI, 3% to 0%) in the incidence of severe OHSS reported in over 3000 patients from 15 randomized controlled trials treated with either the long GnRH agonist

Table 3 Incidence of OHSS according to FSH concentration percentiles on stimulation day 8: individual data from Engage and Ensure.

	Corifollitropin alfa			*rFSH*		
	<P25	*P25—P75*	*>P75*	*<P25*	*P25—P75*	*>P75*
Engage, *N*	174	357	175	170	347	163
FSH (IU/l)	P25 = 9.68	P50 = 11.60	P75 = 13.50	P25 = 9.83	P50 = 11.40	P75 = 13.20
Any OHSS (*n*, %)	16 (9.2)	20 (5.6)	12 (6.9)	13 (7.6)	23 (6.6)	4 (2.5)
Ensure, *N*	64	131	62	30	61	30
FSH (IU/l)	P25 = 9.02	P50 = 10.10	P75 = 11.60	P25 = 9.10	P50 = 10.30	P75 = 11.60
Any OHSS (*n*, %)	5 (7.8)	8 (6.1)	5 (8.1)	1 (3.3)	4 (6.6)	0 (0.0)
Randomized controlled trials combined, *N*	238	488	237	200	408	193
Any OHSS (*n*, %)	21 (8.8)	28 (5.7)	17 (7.2)	14 (7.0)	27 (6.6)	4 (2.1)

OHSS = ovarian hyperstimulation syndrome; rFSH = recombinant FSH.

Table 4 Logistic regression model for ovarian hyperstimulation syndrome (any grade).

Factor	*DF*	*Estimate*	*SE*	*OR*	*95% CI*	*P-value*
Intercept	1	−6.986	1.693			<0.0001
Corifollitropin alfa[a]	1	−0.013	0.197	0.99	0.67−1.45	0.9486
FSH day 1[b]	1	−0.182	0.071	0.83	0.73−0.96	0.0100
^{10}log oestradiol[c]	1	1.152	0.456	3.16	1.29−7.74	0.0115
No. of oocytes[d]	1	0.075	0.013	1.08	1.05−1.11	<0.0001

DF = degrees of freedom; OR = odds ratio; SE = standard error.
[a]Versus rFSH.[b]Per IU/l increase.[c]Per log unit increase.
[d]Per unit increase.

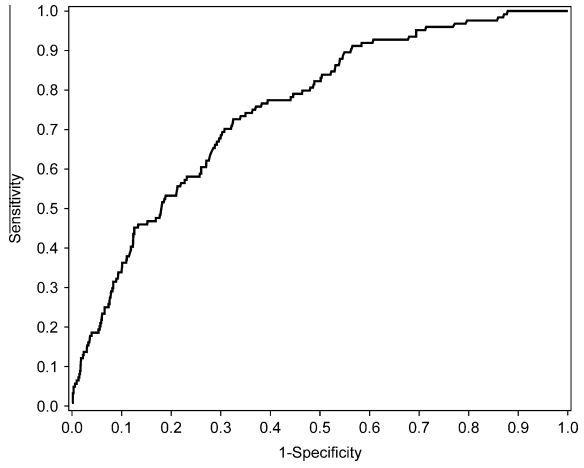

Figure 2 Receiver operating characteristic curve for logistic regression model. The area under the curve is 0.753, showing the sensitivity of the final logistic regression model.

protocol (average incidence 4.3% for severe OHSS) or with the GnRH antagonist protocol (average incidence 2.6%). By analogy to the difference between corifollitropin alfa and rFSH, the higher incidence of OHSS with the GnRH agonist may be related to the higher ovarian response compared with GnRH antagonist protocols (Kolibianakis et al., 2006). The difference with daily FSH is that following corifollitropin alfa administration, exposure largely reduces from stimulation day 3 to day 8 as in a step-down protocol which may be helpful in preventing overstimulation (Ledger et al., 2011).

There are several adaptations that can be made to individualize ovarian stimulation treatment protocols in order to reduce the likelihood of OHSS if the ovarian response during stimulation treatment cycles is too high (Humaidan et al., 2010b). Treatment with daily rFSH can be withheld for a maximum of 3 days (coasting), administration of HCG to trigger final oocyte maturation can be delayed, the dose of HCG can be reduced, all embryos may be frozen to prevent pregnancy, or worst case the cycle is cancelled as HCG is withheld. All these preventive measures were allowed in the current protocol and, whereas the cancellation prior to HCG was similar between the two treatment groups, it should be noted that fresh embryo transfer was more often omitted in the corifollitropin alfa group. Another effective measure which was not allowed in the current trial, but which prevents cycle cancellation, is the utilization of GnRH agonist (instead of HCG) to trigger final oocyte maturation (Devroey et al., 2011; Engmann et al., 2008; Griesinger et al., 2011). Subsequent cryopreservation of embryos would circumvent the luteal-phase insufficiency following triggering with GnRH agonists whereas additional luteal-phase support would allow transfer in the same treatment cycle with good clinical outcome (Humaidan et al., 2010a,2010b). The corifollitropin alfa treatment regimen has the flexibility to incorporate these modifications according to the patient's ovarian response.

In the current randomized controlled trials, the incidence of OHSS (mild, moderate and severe combined) was 6.9% and 6.0% in the corifollitropin alfa and rFSH treatment arms, respectively. The incidence of late-onset OHSS was similar in both treatment groups (2.3% and 2.4%) but there was a trend for a higher incidence of early-onset OHSS in the corifollitropin alfa group (4.6% compared with 3.6% in the rFSH group). Because early OHSS is related to the ovarian response (Lyons et al., 1994; Mathur et al., 2000), this may reflect the higher ovarian response observed with corifollitropin alfa treatment compared with rFSH (13.7 oocytes retrieved versus 12.5, respectively, in the Engage study and 13.3 versus 10.6, respectively, in the Ensure study) (Corifollitropin Alfa Ensure Study Group, 2010; Devroey et al., 2009). In the Trust trial too, early-onset OHSS was more prevalent (2.6%) than late-onset OHSS (0.9%), although both incidences were lower than in the Engage and Ensure trials.

The more frequent observation of early rather than late OHSS is in accordance with a prospective cohort study of 1801 patients undergoing ovarian stimulation with rFSH in a GnRH antagonist protocol for IVF/ICSI, which reported that moderate and severe early OHSS were more frequently observed (1.2% of patients) than late OHSS (0.9%; Papanikolaou et al., 2006).

In the Trust trial, the observed incidence of OHSS in patients receiving corifollitropin alfa was lower (moderate OHSS 0.9%, severe OHSS 0.9%) than in the corifollitropin alfa arms of the randomized controlled trials. It should be noted that the Trust trial was conducted more closely in line with current medical practice; only 33.6% of the patients received FSH/human menopausal gonadotrophin on the day of HCG for triggering final oocyte maturation (compared with approximately 65% in the randomized trials) and 23.3% of patients received 250 μg recombinant HCG (~6500 IU) instead of 10,000 IU urinary HCG. Furthermore, in patients

who required additional FSH injections from day 8 onwards, a lower dose than 200 IU was more frequently given than in Engage to complete ovarian stimulation (Norman et al., 2011). The patients enrolled in the Trust trial were also older (mean age 33 years) than in the Engage and Ensure trials (mean age 31 years) and had a lower mean basal AFC, both factors related to ovarian reserve, which impacts on the likelihood of OHSS development.

The lack of association between OHSS incidence and higher FSH concentrations on stimulation day 8 in the Engage and Ensure trials supports the premise that the risk of OHSS (for both corifollitropin alfa and rFSH treatment regimens) is more likely to be related to the ovarian reserve and subsequent ovarian response than to a higher FSH activity during the first week of corifollitropin alfa treatment.

In the current pooled analysis of data from the Engage and Ensure trials, patients with OHSS symptoms were younger than those who did not develop OHSS. This is in line with previous studies, which show a trend towards increased risk of OHSS in younger women (Delvigne and Rozenberg, 2002). The higher AFC in the OHSS group is also in line with previous publications, which indicate that increased AFC may be a predictor for hyper-response (Kwee et al., 2007; Verhagen et al., 2008).

Ovarian response characteristics of patients with OHSS compared with those without OHSS include an increased number of follicles $\geq$11 mm and higher serum oestradiol concentrations on the day of HCG, and higher number of oocytes retrieved (Humaidan et al., 2010b; Mathur et al., 2000; Verwoerd et al., 2008). These associations were observed for both the corifollitropin alfa and rFSH treatment groups. The characteristics of women with OHSS in the corifollitropin alfa treatment arms were indistinguishable from women with OHSS in the rFSH treatment arms.

Stepwise logistic regression supports these discussion points, since treatment group and FSH concentration on day 8 did not contribute to or appear in the final model, whilst FSH concentration on day 1 (which partly reflects the ovarian age) and serum oestradiol on the day of HCG did. The number of oocytes appeared to be more important than the number of follicles on day of HCG, but these are of course highly correlated. Whilst colinearity may be expected between serum oestradiol concentrations and the number of oocytes retrieved, both remained independent in the final model. On the other hand, the fact that AFC itself did not appear in the final model does not imply that AFC has no predictive value at all, only that it did not add much to other, possibly correlated, factors already included in the model.

OHSS is a potentially serious complication of ovarian stimulation for IVF/ICSI, but preventive measures can be taken to minimize this risk both following corifollitropin alfa or daily FSH treatment. These include careful monitoring of the ovarian reserve prior to stimulation and the ovarian response during stimulation, especially for patients who have not previously undergone IVF treatment and whose response to ovarian stimulation is unknown. Thus, ultrasonographic assessments of follicular development and determination of serum oestradiol concentrations prior to and during ovarian stimulation treatment should be performed. In the case of too high an ovarian response during stimulation treatment cycles, adjustments, as described earlier (Humaidan et al., 2010b), can be made within both corifollitropin alfa and rFSH treatment regimens to reduce the related risk of OHSS. Last but not least, it is not recommended to treat potential high responder patients with corifollitropin alfa or to apply corifollitropin alfa in a long GnRH agonist protocol, as a small uncontrolled study (Fatemi et al., 2010) suggests a higher ovarian response than in combination with a GnRH antagonist.

In conclusion, patients who developed OHSS had a higher ovarian reserve and higher ovarian response without any notable differences between the two treatment groups. Despite a higher ovarian response with a single injection of corifollitropin alfa compared with daily rFSH for the first 7 days of ovarian stimulation, the incidence of OHSS was not statistically different between the two treatment regimens. This study combines the first two controlled phase-3 trials but another large randomized controlled trial of corifollitropin alfa is underway (NCT01144416); thus, the conclusions of this current combined analysis need to be confirmed in the near future. Preferably this new meta-analysis should be performed by using individual patient data rather than by using summary statistics of published manuscripts.

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Appendix

Engage Investigators: *Belgium:* Devroey, UZ Brussel, Centre for Reproductive Medicine, Brussels; Dhont, University Hospital Ghent, Department of Gynecology. *Canada*: Leader, The Ottawa Fertility Centre, Ottawa, Ontario. *Czech Republic*: Mardešić, Sanatorium Pronatal, Prague; Mrázek, ISCARE IVF a.s., Prague. *Denmark*: Blaabjerg, Herlev Hospital, Fertility Clinic, Herlev. *Finland*: Tapanainen, Naistentautien klinikka, Oulun yliopistollinen sairaala (OYS), Oulu; Varila, Väestöliitto, Tampereen klinikka, Tampere. *France*: Barrière, Hôpital de la mère et de l'enfant, Nantes; Hedon, Hôpital Arnaud de Villeneuve, Montpellier. *The Netherlands*: Fauser and Sterrenburg, University Medical Centre, Department of Reproductive Medicine and Gynecology, Utrecht. *Norway*: Kahn, Sykehuset Telemark HF, Skien; Von Düring, St. Olavs Hospital HF, Trondheim. *Spain*: Bajo Arenas, Ginefiv, Madrid; Barri, Institut Universitari Dexeus, Barcelona; Fernández-Sánchez, IVI Sevilla, Sevilla. *Sweden*: Bergh, Kvinnokliniken, Sahlgrenska Universitetssjukhuset, Göteborg; Hillensjö, Fertilitetscentrum, Carlanderska Sjukhuset, Göteborg. *United Kingdom*: Balen, Assisted Conception Unit, Leeds General Infirmary; Ledger, Assisted Conception Unit, Jessop Wing, The Hallamshire Hospital, Sheffield; Matthews, Bourn Hall Clinic, Cambridge. *United States of America*: Abuzeid, IVF Michigan, Rochester Hills (MI), Alper, Boston IVF, Waltham (MA); Boostanfar, untington Reproductive Centre, Westlake Village (CA); Doody, Centre for Assisted

Reproduction, Bedford (TX); Frattarelli, Reproductive Medicine Associates of New Jersey, Morristown (NJ); Grunfeld, Reproductive Medicine Associates of New York, New York (NY); Karande, Karande and Associates SC, Hoffman Estates (IL); Kort, Reproductive Biology Associates, Atlanta (GA); Levy, Shady Grove Fertility Reproductive Science Centre, Rockville (MD); Lifchez, Fertility Centres of Illinois, Chicago (IL); Pang, Reproductive Science Centre of Boston, Lexington (MA); Schoolcraft, Colorado Centre for Reproductive Medicine, Englewood (CO); Yeko, The Reproductive Medicine Group, Tampa (FL).

Ensure Investigators: *Austria*: Obruca, Kinderwunschzentrum Privatspital Goldenes Kreuz, Vienna; Schenk, Kinderwunsch Institut Schenk GmbH, Dobl; Tews, Landes-Frauen-Und Kinderklinik Linz, Linz. *Czech Republic:* Mardešić, Sanatorium Pronatal, Prague; Mrázek, ISCARE I.V.F. a.s, Prague. *Denmark*: Meinertz, The Fertility Clinic, Hvidovre Hospital, Hvidovre. *France*: Hedon, Hôpital Arnaud de Villeneuve, Montpellier; Barrière Hôpital de la mère et de l'enfant, Nantes. *South Korea*: Kim, Asan Medical Centre, Seoul; Koong, Kwandong University, Cheil General Hospital, Seoul; Yoon, CHA General Hospital, Seoul. *Poland*: Koziol, Przychodnia Lekarska 'Novum', Warsaw; Kuczynski, Centrum Leczenia Nieplodnosci Malzenskiej 'Kriobank', Bialystok. *Spain*: Bernabeu, Instituto Bernabeu, Alicante; Balda, Hospital Universitario '12 de Octubre', Madrid. *Sweden*: Bergh, Kvinnokliniken, Sahlgrenska Universitetssjukhuset, Göteborg; Hillensjö, Fertilitetscentrum Carlanderska Sjukhuset, Göteborg. *Taiwan:* Huang, Chang Gung Memorial Hospital Linkou, Tao Yuan; Yang, National Taiwan University Hospital, Taipei.

Trust Investigators: *Argentina*: Papier, CEGyR Buenos Aires; Vilela, IFER Buenos Aires; Blaquier, FERTILAB Riobamba, Buenos Aires; Ruhlmann, San Isidro Medicina, San Isidro; Botti, PROAR, Rosario; Pasqualini, Halitus, Buenos Aires. *Australia*: Rombauts, Monash IVF, Clayton, Victoria; Hale, Melbourne IVF, East Melbourne, Victoria; Watkins, Tasmania IVF, Hobart; Norman, Repromed, Dulwich, SA and University of Adelaide; Illingworth, IVF Australia, Westmead, NSW. *Brazil*: Petracco, Hospital de Sao Lucas, Porto Alegre-RS; Ferriani, Hospital das Clinicas de Faculdade de Medicina de Ribeirao Preto, Ribeirao Preto; *Chile*: Devoto, Instituto de Investigacion Materno Infantil (IDIMI), Santiago; Zegers-Hochschild and Camus, Clinica las Condes, Santiago; *Germany*: Schultze-Mosgau, Universitätklinikum Lübeck, Lübeck; Dieterle, Kinderwunschcentrum Dortmund, Dortmund; Fiedler, Kinderwunsch Centrum München, München. *Denmark*: Nyboe Andersen, Rigshospitalet, København Ø. *France*: Salle, Groupement Hospitalier Est Hopital Femme Mere Infant PMA, Bron; Hazout, Clinique de la Muette, Paris. *Hungary*: Konc, St Janos Hospital and Outpatient Institute, Budapest. *Italy*: La Sala, Arcispedale S. Maria Nuova, Reggio Emilia; De Placido, Azienda Universitaria Policlinico Federico II, Napoli. *Netherlands*: Laven, Erasmus Medisch Centrum, Rotterdam; Lambalk, Academisch Ziekenhuis Vrije Universteit Amsterdam, Amsterdam; Jansen, Reinier de Graaf Groep, Voorburg; Cohlen, Isala Klinieken (locatie Sophia), Zwolle. *Norway*: Tanbo, Rikshospitalet HF, Oslo. *Sweden*: Wramsby, IVF Kliniken St. Görans, Stockholm.

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