Reproductive BioMedicine Online (2016) ■■, ■■–■■

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ARTICLE

Corifollitropin alfa versus recombinant follicle-stimulating hormone: an individual patient data meta-analysis

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Abstract A meta-analysis was conducted of individual patient data ($n = 3292$) from three randomized controlled trials of corifollitropin alfa versus rFSH: Engage (150 μg corifollitropin alfa $n = 756$; 200 IU rFSH $n = 750$), Ensure (100 μg corifollitropin alfa $n = 268$; 150 IU rFSH $n = 128$), and Pursue (150 μg corifollitropin alfa $n = 694$; 300 IU rFSH $n = 696$). Women with regular menstrual cycles aged 18–36 and body weight >60 kg (Engage) or ≤60 kg (Ensure), or women aged 35–42 years and body weight ≥50 kg (Pursue), received a single injection (100 μg or 150 μg) of corifollitropin alfa (based on body weight and age) or daily rFSH. The difference (corifollitropin alfa minus rFSH) in the number of oocytes retrieved was +1.0 (95% CI: 0.5–1.5); vital pregnancy rate: −2.2% (95% CI: −5.3%–0.9%); ongoing pregnancy rate: −1.7% (95% CI: −4.7%–1.4%); and live birth rate: −2.0% (95% CI: −5.0%–1.1%). The odds ratio for overall OHSS was 1.15 (95% CI: 0.82–1.61), and for moderate-to-severe OHSS: 1.29 (95% CI: 0.81–2.05). A single dose of corifollitropin alfa for the first 7 days of ovarian stimulation is a generally well-tolerated and similarly effective treatment compared with daily rFSH.

KEYWORDS: corifollitropin alfa, GnRH antagonist, ovarian hyperstimulation syndrome, ovarian stimulation, pregnancy

http://dx.doi.org/10.1016/j.rbmo.2016.04.005
1472-6483/

Please cite this article in press as: Georg Griesinger, et al., Corifollitropin alfa versus recombinant follicle-stimulating hormone: an individual patient data meta-analysis, Reproductive BioMedicine Online (2016), doi: 10.1016/j.rbmo.2016.04.005

Introduction

Corifollitropin alfa is a recombinant gonadotrophin with sustained follicle-stimulating activity, such that a single dose is able to initiate and sustain the growth of multiple follicles for the first 7 days of ovarian stimulation (Fauser et al., 2009). Three separate randomized, double-blind, phase III trials of women undergoing ovarian stimulation with either corifollitropin alfa or recombinant FSH (rFSH), Engage (Devroey et al., 2009), Ensure (Corifollitropin alfa Ensure Study Group, 2010) and Pursue (Boostanfar et al., 2015) showed that a single injection of corifollitropin alfa for the first 7 days of ovarian stimulation was either equivalent (Engage and Ensure) or non-inferior (Pursue) to daily injections of rFSH regarding the number of oocytes retrieved, and equivalent (Engage) or non-inferior regarding vital pregnancy rates (Pursue), equivalent (Engage) or non-inferior (Pursue) regarding ongoing pregnancy rates, and non-inferior regarding live-birth rates (Pursue). In addition, there were no significant differences in the incidence of ovarian hyperstimulation syndrome (OHSS) between corifollitropin alfa and rFSH in the three trials.

Each individual trial was sufficiently powered to yield conclusions relevant to the doses, populations and hypotheses studied; however, the meta-analysis of data from the three studies permits conclusions based on a much larger sample, while adjusting for confounding factors and exploring heterogeneity. Thus, the results would be expected to yield more precise estimates of treatment efficacy and safety and broader external validity relative to those from the individual trials. In contrast to conventional meta-analyses wherein aggregate study level data are synthesized, the present meta-analysis models individual patient data, while simultaneously accounting for clustering of patients within studies and dosing groups. This approach allows for adjustments of the outcomes of interest according to baseline prognostic factors, an aspect that is not possible in conventional meta-analyses (Pouwer et al., 2015).

The objective of this meta-analysis was therefore to evaluate the overall efficacy and safety of corifollitropin alfa compared with rFSH for the first 7 days of ovarian stimulation with respect to the number of oocytes retrieved, pregnancy rates, live-birth rates, and the incidence of OHSS using individual patient data from 3292 subjects from the Engage, Ensure and Pursue clinical trials.

Materials and methods

Study population

Women included in this meta-analysis participated in one of three randomized controlled trials (n = 3292). In Engage, women aged 18–36 years with a body weight >60 kg were randomized to 150 μg corifollitropin alfa (n = 756) or 200 IU rFSH (n = 750) (Devroey et al., 2009, trial registration number NCT00696800). In Ensure, women aged 18–36 years with lower body weight (≤60 kg) were randomized to 100 μg corifollitropin alfa (n = 268) or 150 IU rFSH (n = 128) (Corifollitropin alfa Ensure Study Group, 2010, trial registration number NCT00702845). In Pursue, older women (aged 35–42 years) with a body weight ≥50 kg were randomized to 150 μg corifollitropin alfa (n = 694) or 300 IU rFSH (n = 696) (Boostanfar et al., 2015, trial registration number NCT01144416). All three trials used a gonadotrophin-releasing hormone (GnRH) antagonist protocol. Complete details of the treatment regimens for each trial have been published previously (Corifollitropin alfa Ensure Study Group, 2010; Boostanfar et al., 2015; Devroey et al., 2009). All three trials were conducted in accordance with principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies, and written informed consent was provided by all subjects.

The endpoints for this individual patient data meta-analysis were the number of retrieved oocytes, the vital pregnancy rate (presence of at least one fetus with heart activity 5 weeks after embryo transfer), the ongoing pregnancy rate (presence of at least one fetus with heart activity at least 10 weeks after embryo transfer or live birth), the live-birth rate per started cycle, and the incidence of OHSS (overall and moderate or severe). The analysis included all women who started the stimulation cycle.

Statistical analysis

The differences between the outcomes for corifollitropin alfa and rFSH with their 95% confidence intervals (CI) were obtained from a linear model (number of oocytes retrieved), a generalized linear model (vital and ongoing pregnancy rates and live-birth rates), or a logistic regression model (OHSS), each with factors for treatment and study. Additionally, a cluster adjustment was included for IVF centre in the analysis of number of oocytes retrieved, and a cluster adjustment for region (Asia, Europe, or North America) was included for pregnancy outcomes. Age and weight were included as continuous covariates in all models. Heterogeneity was assessed by adding the interaction of trial and treatment to the model. The threshold for heterogeneity was $P < 0.05$.

Results

Number of oocytes retrieved

Treatment differences (corifollitropin alfa minus rFSH) based on the mean number of oocytes retrieved were +2.5, +1.2 and +0.5 in Ensure, Engage and Pursue, respectively. The overall difference was +1.0 (95% CI, 0.5–1.5; linear regression model adjusting for trial, centre, age and weight; **Figure 1**). The test for heterogeneity reached marginal significance ($P = 0.049$).

Vital and ongoing pregnancy rates and live birth rate

The differences in vital pregnancy rates (corifollitropin alfa minus rFSH) were −9.6%, +1.1% and −3.0% in Ensure, Engage and Pursue, respectively. The overall difference was −2.2% (95% CI: −5.3% to 0.9%; **Figure 1**). The test for heterogeneity was not significant. The differences in ongoing pregnancy rates (corifollitropin alfa minus rFSH) were −9.2%, +1.1% and −1.9% in Ensure, Engage, and Pursue, respectively. The

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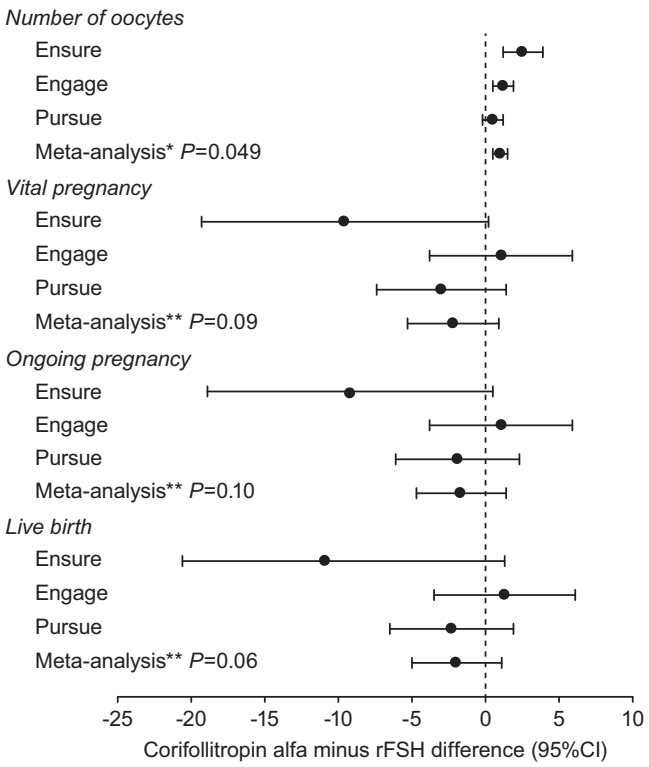

Figure 1 Pooled estimates for the differences in oocyte numbers and pregnancy and live-birth rates between corifollitropin and rFSH. *Adjusted for trial, centre, age, and body weight; **Adjusted for trial, region, age, and body weight. *P*-values describe the test for heterogeneity ($P < 0.05$ indicates heterogeneous differences across trials).

overall difference was −1.7% (95% CI: −4.7% to 1.4%; Figure 1). The test for heterogeneity was not significant. The differences in live-birth rates (corifollitropin alfa minus rFSH) were −10.9%, +1.3% and −2.3% in Ensure, Engage and Pursue, respectively. The overall difference was −2.0% (95% CI: −5.0% to 1.1%, generalized linear model; Figure 1). The test for heterogeneity did not reach significance, but a trend toward significance was noted.

Ovarian hyperstimulation syndrome

The odds ratio (OR) for the development of any grade of OHSS (corifollitropin alfa: rFSH; 148 events) ranged from 1.01 to 1.48 in the individual trials. The overall OR for OHSS of any grade was 1.15 (95% CI: 0.82–1.61, logistic regression model; Figure 2). There was no heterogeneity among studies. The OR for moderate or severe OHSS (11, 51 and 15 cases in Ensure, Engage and Pursue, respectively) ranged from 0.50 to 2.21. The overall OR for moderate or severe OHSS was 1.29 (95% CI: 0.81–2.05, logistic regression model; Figure 2). No heterogeneity was noted ($P = 0.14$).

Discussion

The Engage, Ensure and Pursue trials conducted in women undergoing ovarian stimulation using a GnRH antagonist protocol demonstrated that a single injection of corifollitropin alfa for the first 7 days of ovarian stimulation was equivalent or non-inferior to daily injections of rFSH with respect to the number of oocytes retrieved, vital pregnancy rates, ongoing pregnancy rates, and live-birth rates. In addition, the incidence of OHSS was generally similar between the two treatments in each study. The present meta-analysis used individual patient data from these three clinical trials to compare the efficacy and safety of corifollitropin alfa versus rFSH. Overall, the results of this meta-analysis are consistent with those from the individual trials.

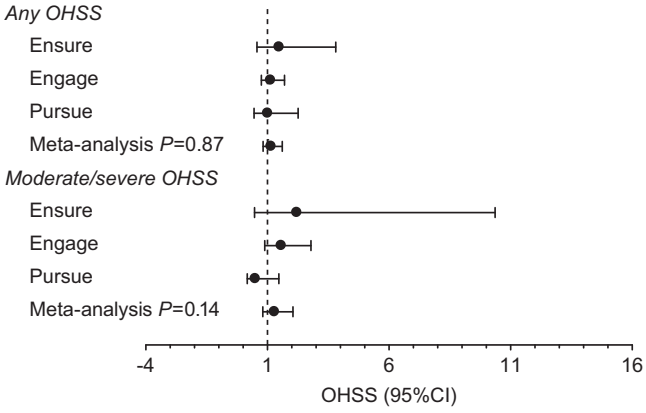

Figure 2 Odds ratios for the development of ovarian hyperstimulation syndrome (OHSS), adjusted for the logistic regression model. *P*-values describe the test for heterogeneity ($P < 0.05$ indicates heterogeneous odds ratios across trials).

The number of retrieved oocytes was a key endpoint of the individual trials, as this measure serves as a reliable indicator of pharmacologic treatment effect. For this endpoint, equivalent efficacy is declared if corifollitropin alfa provides no less than three oocytes (a difference that is considered to be clinically significant) and no more than five oocytes (potentially increasing the risk of OHSS) compared with rFSH. The meta-analysis results showed that women receiving corifollitropin alfa had, on average while accounting for important baseline factors such as age and body weight, one additional oocyte retrieved compared with women receiving rFSH; this difference was not statistically significant (95% CI, 0.5–1.5). There was marginally significant heterogeneity ($P = 0.049$) between the trials observed for the number of retrieved oocytes. This observation is primarily due to the inclusion of women with low body weight from the Ensure trial, who received lower doses of corifollitropin alfa (100 μg) and rFSH (150 IU/d) compared with the higher-weight women in Engage. The different dosages of corifollitropin alfa provided similar drug exposure and therefore, similar ovarian response in both studies, but the lower daily doses of rFSH in Ensure resulted in fewer retrieved oocytes than in Engage (10.6 oocytes versus 12.5 oocytes, respectively). Consequently, the estimated between-treatment difference for the number of retrieved oocytes was 2.5 oocytes in Ensure versus 1.2 oocytes in Engage. In the Pursue study in older women, an average of 10.7 oocytes and 10.3 oocytes were obtained after stimulation with corifollitropin alfa versus rFSH, respectively. Although these rates were considerably lower for both treatment groups in Pursue compared with rates observed in Engage, the

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absence of any meaningful between-treatment difference suggests that these reductions were related to the older age of the study participants. In other words, both the dose of 150 μg corifollitropin and the daily dose of 300 IU rFSH were already at the upper margin of the therapeutic window in this older-age patient group.

Pregnancy outcomes and live-birth rates were also endpoints in the individual trials, as these measures provide an estimate of treatment success. The meta-analysis results demonstrated equivalent efficacy for corifollitropin alfa and rFSH with respect to pregnancy outcomes and live-birth rates among women with different baseline characteristics, such as age and body weight. For these endpoints, there was no significant heterogeneity noted. These meta-analysis results are consistent with those from the individual trials. The Engage trial, which was powered to exclude a pre-defined inferiority margin of more than 8% reduction in ongoing pregnancy rates as the primary study end-point, demonstrated non-inferior ongoing pregnancy rates in patients treated with corifollitropin alfa compared with daily rFSH (38.9% and 38.1%, respectively). The Ensure trial was not powered to assess non-inferiority in the ongoing pregnancy rates. In Ensure, the ongoing pregnancy rates for corifollitropin alfa and daily rFSH were 25.4% and 34.4%, respectively. The between-treatment difference was not statistically significant and considered to be a chance finding, given that the other efficacy outcomes were similar between the treatments. In these two trials, the vital pregnancy rates in the corifollitropin alfa and daily rFSH treatment arms, respectively, were 39.9% versus 39.1% in Engage and 25.7% versus 35.2% in Ensure. In Pursue, treatment with corifollitropin alfa was proven non-inferior to daily rFSH with respect to vital pregnancy rates (23.9% versus 26.9%, respectively), ongoing pregnancy rates (22.2% versus 24.0%, respectively), and live-birth rates (21.3% versus 23.4%, respectively). Although the pregnancy rates and live-birth rates were generally lower for both treatment groups in Pursue compared with the other trials, the lack of meaningful between-treatment differences suggests that these reductions were related to the older age of the study participants. The lack of association of a higher oocyte number with a higher pregnancy rate is consistent with a number of randomized controlled trials (Sterrenburg et al., 2011), in which a higher number of oocytes as a consequence of a higher dose stimulation did not translate into a higher pregnancy rate.

OHSS is a potentially lethal iatrogenic complication of ovarian stimulation. Compared with long GnRH agonist protocols, the risk of severe OHSS is reduced by approximately 50% using GnRH antagonists for co-treatment during ovarian stimulation prior to IVF or intracytoplasmic sperm injection (Al Inany et al., 2011; Kolibianakis et al., 2006). Nevertheless, moderate to severe OHSS may still occur in GnRH antagonist protocols. The meta-analysis results, adjusted for age and body weight, show that the odds ratio for development of moderate to severe OHSS was generally similar with corifollitropin alfa and rFSH, and there was no significant heterogeneity observed for the incidence of OHSS.

The major strength of this meta-analysis is that it provides a more robust conclusion compared with the individual studies due to the increase in the sample size of the study population ($n = 3292$). Indeed, it has been recognized that a meta-analysis of individual patient data is more robust than a meta-analysis of published data from different trials (Stewart and Parmar, 1993; van Walraven, 2010). In addition, the range of subjects included in the trials for this meta-analysis potentially represents the general population of women undergoing ovarian stimulation prior to IVF (women 18 to 36 years of age with a range of body weights, and older women up to 42 years of age). Nevertheless, the validity of the efficacy and safety results of this meta-analysis are limited to the study populations of the individual trials, which included normal responders and excluded patients with known risk factors for a hyper- or hypo-response to ovarian stimulation. Accordingly, further research is needed to determine the efficacy and safety of corifollitropin alfa in other patient populations, such as women with diminished ovarian reserve and response, respectively.

In conclusion, a single dose of corifollitropin alfa for the first 7 days of ovarian stimulation has a similar efficacy and safety profile compared with seven daily injections of rFSH. Corifollitropin alfa resulted in an average of one oocyte more than rFSH. Treatment differences between corifollitropin alfa and rFSH in pregnancy and live-birth rates were small and not statistically significant. Moreover, treatment was generally well-tolerated, with a generally similar incidence of OHSS between the corifollitropin alfa and rFSH treatment groups. Based on the pharmacokinetics of corifollitropin alfa, only a single injection is required to sustain multi-follicular growth for up to seven days (Fauser et al., 2009), thereby avoiding a significant number of injections relative to rFSH over the course of treatment. The potential benefits to the patient from this simplified treatment option remain to be explored in non-blinded trials and clinical use.

Acknowledgement

The authors thank E M Kolibianakis and A Beltsos for valuable comments on earlier versions of this article, and P Verweij for statistical support of the analysis. Medical writing and editorial assistance was provided by K Lewis and J Rotonda of Merck & Co., Inc., Kenilworth, NJ, USA. Financial support for this study was provided by Merck & Co. Inc., Kenilworth, NJ, USA.

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Authors' roles: GG, RB, KG, DG, CMS, and BJS are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, and interpretation of data in addition to drafting the manuscript and/or revising/reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration: GG has received consulting fees from Ferring, Glycotope, Serono, MSD, Finox, Vitrolife, IBSA and ReprodWissen; board membership fee from MSD; and speakers' bureau fees from Ferring, Serono, MSD, Vitrolife and IBSA. RB has received consultancy fees and research grant support to his institution from Merck and Co., Inc. DG and CMS are employees of Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock/stock options in the company. KG and BJS are former employees of Merck Sharp and Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may hold stock/stock options in the company.

Received 10 November 2015; refereed 1 April 2016; accepted 14 April 2016.