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# 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

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## 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