A comparison of live birth rates and cumulative ongoing pregnancy rates between Europe and North America after ovarian stimulation with corifollitropin alfa or recombinant follicle-stimulating hormone

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Objective: To compare live birth rates after fresh embryo transfer (ET) and cumulative ongoing pregnancy rates after fresh ET and frozen-thawed (ET) between continents and overall after one treatment cycle with corifollitropin alfa or recombinant FSH.
Design: Double-blind, multicenter, randomized controlled trial.
Setting: Fourteen centers in North America (NA); 20 in Europe (EU).
Patient(s): 804 NA patients and 702 EU patients.
Intervention(s): Patients >60 kg received a single dose of corifollitropin alfa or daily rFSH for the first 7 days of controlled ovarian stimulation.
Main Outcome Measure(s): Live birth rates.
Result(s): Within each continent no differences were noted between the two treatment groups; however, between continents, the cumulative ongoing pregnancy rate and live birth rate were considerably higher in NA than in EU. The live birth rate in NA was 39.2% in both treatment groups compared with 31.5% and 28.8% in EU after corifollitropin alfa and rFSH treatment, respectively. Considering the number of embryos transferred, the live birth rate per ET was still higher in NA than in EU (42.7% v.s 36.8% with corifollitropin alfa and 41.6% vs. 30.9% with rFSH). Overall live birth rates after fresh ET were 35.6% and 34.4% (estimated difference 1.1% [95% confidence interval −3.7–5.8]), and the estimated cumulative live birth rates were 43.4% and 41.3% with corifollitropin alfa and rFSH, respectively.
Conclusion(s): Live birth rates and cumulative pregnancy rates were higher in NA than in EU after treatment with either corifollitropin alfa or daily rFSH; both treatment protocols provided equal success rates.
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Key Words: Live birth rates, cumulative pregnancy rates, corifollitropin alfa, GnRH antagonist, North America, Europe

There is no uniform definition of success after in vitro fertilization (IVF), but preferred clinical outcome is often indicated as "delivery with at least one live born child" or "birth of a singleton healthy child at term" (1). The effectiveness of IVF treatment regimens is frequently presented as the ongoing pregnancy rate per started cycle, which is the number of pregnancies as a percentage of all treatment cycles, including cycles without embryo transfer (ET) (2). However, it is the live birth rate per started cycle that really matters in the end, which is the percentage of all treatment cycles that lead to live born infants adjusted for miscarriage and stillbirth (3). Alternatively, ongoing pregnancy rates may be presented as cumulative figures, including the number of pregnancies obtained from embryos cryopreserved during the treatment cycle. Both percentages provide a better estimate of the patient's chance of becoming

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pregnant and of taking home a live born infant after a single treatment cycle. Apart from the stimulation protocols, many other factors determine the success rates of IVF units, including the patient population treated, the quality of the IVF laboratory, and the number of embryos transferred. In multicenter randomized controlled trials, the same stimulation protocol is applied to a cohort of similar patients in a large number of IVF units, often in different geographic locations. Comparison of the success rates indicate that ongoing pregnancy rates per started cycle may vary between continents and between IVF units within one continent, which complicates trial designs and analyses to demonstrate or exclude a potential difference in pregnancy rates between two treatment regimens (4). Such variability should be taken into account at trial design (randomization) by achieving a close balance of the two treatment groups per IVF unit in terms of number of patients treated.

The novel sustained follicle stimulant corifollitropin alfa (5) was compared with daily recombinant FSH (rFSH) in inducing multifollicular development in women undergoing controlled ovarian stimulation (COS) in a very large, multinational, double-blind, randomized, comparative trial (Engage trial) including 1,506 patients aged $\leq$36 years undergoing ovarian stimulation before IVF/intracytoplasmic sperm injection (ICSI). The global study was unique because it concerned a fixed treatment protocol among a cohort of similar patients cycling in 14 IVF units in North America (NA) and 20 IVF units in Europe (EU) and resulted in highly similar ongoing pregnancy rates between the two treatment groups (2, 6).

Patients who became pregnant in the Engage trial were followed to delivery to compare the live birth rates after COS with corifollitropin alfa and daily rFSH. Patients who did not become pregnant after fresh ET but who had cryopreserved embryos were followed when they underwent frozen-thawed embryo transfer (FTET) cycles, which offered the opportunity to assess whether the final success rates resulting from a single treatment cycle of corifollitropin alfa is at least similar to that of a single treatment cycle of daily rFSH.

This report presents the live birth rates as well as the cumulative ongoing pregnancy rates from a single treatment cycle with corifollitropin alfa or daily rFSH. These success rates are evaluated per continent and overall per treatment group.

MATERIALS AND METHODS

Intervention Trial

Details of the design of the Engage trial have been described previously (2, 6). This intervention trial was a multicenter, randomized, double-blind double dummy, noninferiority clinical trial (n = 1,506), involving 14 centers in NA (13 centers in USA and one in Canada) and 20 centers in EU (three in Spain, three in UK, two in Belgium, two in Czech Republic, two in Finland, two in France, two in Norway, two in Sweden, one in Denmark, and one in The Netherlands). The trial included women with an indication for COS before IVF or ICSI; aged 18–36 years with a body weight of 60–90 kg, a body mass index of 18–32 kg/m^2, a regular menstrual cycle of 24–35 days, and partners having ejaculatory sperm. The primary efficacy outcome of this trial was ongoing pregnancy rate defined as presence of at least one fetus with heart activity $\geq$10 weeks after ET. All patients who received at least one dose of corifollitropin alfa (Elonva; N.V. Organon) or rFSH (Puregon/Follistim AQ Cartridge; N.V. Organon) in the intervention trial and who became pregnant were eligible for entry into the pregnancy follow-up trial. Patients from whom embryos were cryopreserved during the intervention trial and for which at least one embryo was thawed for use in a subsequent FTET cycle were eligible for the follow-up to collect the outcome of FTET cycles. Both follow-up trials were conducted in accordance with principles of Good Clinical Practice and were approved by the appropriate Institutional Review Boards and regulatory agencies. Written informed consent was provided by each subject.

Pregnancy Follow-up After Fresh ET

This prospective trial (NCT 00703014) began once the first patient signed informed consent as part of consent for the Engage trial, but actual enrollment started when the first ongoing pregnancy was established. In total, 275 of 294 pregnant patients in the corifollitropin alfa group and 266 of 286 pregnant patients in the rFSH group were enrolled in the pregnancy follow-up trial. The study was completed in March 2009. The primary efficacy outcome was the live birth rate after fresh ET after a single treatment cycle. The live birth rate was calculated as the number of patients with at least one live born infant relative to the total number of patients who started treatment (per started cycle) or who had ET (per ET). The health of infants born after corifollitropin alfa treatment and after rFSH treatment, including any major or minor malformation, was also collected but will be reported separately.

Follow-up After FTET Cycles

Patients who consented to participate in the follow-up with embryos cryopreserved in the Engage trial, of which at least one embryo was thawed for use in a subsequent FTET cycle, were included in this prospective study (NCT 00702273). Each study site was allowed to follow its routine procedure for FTET cycles, and thawed embryos could be replaced in natural cycles or in supplemented cycles. The study was completed in May 2009. The primary efficacy outcome was the cumulative ongoing pregnancy rate, defined as the percentage of patients who had an ongoing pregnancy $\geq$10 weeks after either fresh ET or one or more FTET cycles.

Other efficacy assessments were the number and quality of embryos transferred after thawing, and FTET cycle outcomes including miscarriage, ectopic pregnancy, intrauterine pregnancy (including vital pregnancy at 5–6 weeks after ET), and ongoing pregnancy $\geq$10 weeks after ET.

Statistical Methods

Treatment differences for ongoing pregnancy rate, live birth rate, and cumulative ongoing pregnancy rate were estimated with the use of a generalized linear model with identity link. Treatment group (corifollitropin alfa vs. rFSH), continent (NA vs. EU), age group ($<$32 y vs $\geq$32 y), and previous IVF cycle