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Short follicular phase of stimulation following corifollitropin alfa or daily recombinant FSH treatment does not compromise clinical outcome: a retrospective analysis of the Engage trial


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Abstract To evaluate whether a short follicular phase of ovarian stimulation compromises the chance of pregnancy, subjects from a double-blind, randomized trial treated with a single dose of corifollitropin alfa ($n = 756$) or daily recombinant FSH ($n = 750$) were categorized as early responders if three follicles ≥ 17 mm were reached and human chorionic gonadotrophin (HCG) was administered prior to or on stimulation day 8, and as normal responders if three follicles ≥ 17 mm were reached and HCG was administered after stimulation day 8. In the corifollitropin alfa and recombinant FSH groups, 23.2% and 29.1%, respectively, were early responders ($P = 0.01$). Regardless of the treatment group, the initial ovarian response was higher in early responders, but with two extra days of stimulation, the number and size of follicles on the day of HCG in the normal responders was similar to those of the early responders. The number of oocytes was similar in both response groups following corifollitropin alfa treatment (13.6 versus 14.5) and recombinant FSH treatment (12.8, both groups). The ongoing pregnancy rates were comparable for early and normal responders regardless of the treatment group, supporting successful outcome following a stimulation period of only 1 week. 

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KEYWORDS: corifollitropin alfa, infertility, ongoing pregnancy rate, ovarian stimulation, recombinant FSH, short follicular phase

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Introduction

Shortening of the follicular phase during the normal menstrual cycle may be related to an early follicular development during the luteal–follicular transition or to accelerated follicular development. A reduced length of the follicular phase results in early ovulation due to advanced selection of the dominant follicle in the early follicular phase while the follicular growth in the late follicular phase is unchanged (Klein et al., 2002; van Zonneveld et al., 2003). In women with a short follicular phase undergoing ovarian stimulation, (pre)treatment with a gonadotrophin-releasing hormone (GnRH) agonist prior to ovarian stimulation increased the length of follicular phase and partially restored fecundity (Cedrin-Durnerin et al., 2003).

As for women with a short follicular phase during their spontaneous menstrual cycle, one may suspect that IVF patients with a regular cycle but a short duration of stimulation prior to assisted reproduction technology have a reduced chance of pregnancy, possibly due to insufficient time for full follicle maturation or endometrial development. So far, the limited literature addressing the impact of a relatively short duration of stimulation has not suggested any difference in the success rates (Check et al., 2009; Martin et al., 2006).

Corifollitropin alfa is a new recombinant gonadotrophin that has the same pharmacological effect as daily FSH (Fauser et al., 2010), but a very different pharmacokinetic profile that allows a single dose to maintain multiple follicular development for the first 7 days of stimulation. Following corifollitropin alfa injection, FSH activity is initially higher than with daily FSH treatment; however, in a large randomized double-blind study (Engage), this did not lead to a different duration of stimulation or a different chance of ongoing pregnancy (Devroey et al., 2009). Interestingly, about one-third of women treated with corifollitropin alfa or daily recombinant FSH reached the criterion for triggering final oocyte maturation by stimulation day 8, whereas the overall median duration of stimulation was 9 days regardless of the treatment group. Women treated with corifollitropin alfa particularly benefit from a short duration of stimulation as further injections with daily FSH are not required and they may proceed immediately to triggering of final oocyte maturation following a single injection of this new gonadotrophin.

To evaluate whether a short follicular phase of stimulation in an ovarian stimulation cycle compromises the chance of pregnancy, a retrospective analysis of the Engage data was performed to compare the clinical outcomes of early responders (reaching the criterion for human chorionic gonadotrophin (HCG) and receiving HCG for triggering final oocyte maturation on or prior to stimulation day 8) with normal responders (reaching the criterion after stimulation day 8).

Materials and methods

The Engage trial (Devroey et al., 2009) was a randomized, double-blind, trial that was conducted from 2006–2008 to investigate the efficacy and safety of a single injection of corifollitropin alfa for the first 7 days of ovarian stimulation

using daily injections of recombinant FSH as a reference. This trial was carried out at 34 centres (20 in Europe and 14 in North America: 13 in the USA, one in Canada) and included 1506 women with a regular menstrual cycle, aged 18–36 years with an antral follicle count (AFC) ≤ 20 and a body weight of >60 kg. The Engage trial was approved by the Independent Medical Ethics Committee or Institutional Review Board for each centre as well as by the responsible health authority and was conducted in accordance with the principles of Good Clinical Practice. Written informed consent was provided by all subjects.

The treatment regimen of the Engage trial has been described previously (Devroey et al., 2009). None of the patients were pretreated or scheduled by means of oral contraceptives. At menstrual cycle day 2 or 3, subjects received either a single dose of 150 μ g corifollitropin alfa (Elonva; Organon, The Netherlands; $n = 756$) or daily 200 IU recombinant FSH (follitropin beta, Puregon Pen; Organon; $n = 750$) for the first 7 days of ovarian stimulation, followed by daily recombinant FSH in a GnRH antagonist (ganirelix, Orgalutran; Organon) protocol. Patients were to return daily to the clinic for an ultrasound from stimulation day 5 up to and including the day of HCG, although an ultrasound on day 6 and 7 was optional. Final oocyte maturation was to be triggered with HCG as soon as three follicles ≥ 17 mm were visible on ultrasound or the day thereafter.

Serum hormone concentrations (FSH, LH, oestradiol, inhibin B and progesterone) were measured on stimulation days 1, 5, 8 and on the day of HCG by a central laboratory, as previously described (Fauser et al., 2010).

In the current retrospective analysis of the Engage trial, subjects who reached at least three follicles ≥ 17 mm and received HCG prior to or on stimulation day 8 were categorized as 'early responders' whereas those who reached at least three follicles ≥ 17 mm after stimulation day 8 and received HCG were categorized as 'normal responders.' If HCG was given within 6 h after midnight, the day of HCG administration was considered to be the day before. Subjects who did not reach the criterion for HCG administration or did not receive HCG were excluded from the analyses. The data used in the current analyses reflect minor corrections to the previously published Engage trial data (Devroey et al., 2009).

Baseline characteristics, ovarian response and ongoing pregnancy rates were analysed per started cycle for the early and normal responders. Women who did not reach the oocyte retrieval stage were included in the analysis as having 0 oocytes retrieved and 0 embryos obtained and were considered in the analysis as being not (ongoing) pregnant. *P*-values were based on an analysis of variance (ANOVA) *F*-test for comparing means, Wilcoxon rank sum test for comparing medians and chi-squared test for comparing percentages.

To address differences in clinical outcomes that may be skewed by different proportions of subjects from IVF centres, located either in Europe or in North America (Baker et al., 2010; Boostanfar et al., 2012), the ongoing pregnancy rates were also presented by region. Additionally, for ongoing pregnancy, the odds ratio of early to normal responders was estimated using logistic regression. Region (Europe, North America) and treatment group (corifollitropin alfa, recombinant FSH) were added to the logistic model to

obtain an estimated odds ratio adjusted for these covariates.

Results

Incidence of early response to ovarian stimulation

There were 715 and 733 subjects that reached the HCG criterion (at least three follicles ≥ 17 mm) and received HCG in the corifollitropin alfa and recombinant FSH arms, respectively. Of those who reached the criterion for HCG administration and received HCG, 23.2% ($n = 166$) in the corifollitropin alfa arm and 29.1% ($n = 213$) in the recombinant FSH arm were early responders, a difference that was significant ($P = 0.01$).

In the early responder group, the percentage of women who reached the HCG criterion of at least three follicles ≥ 17 mm at stimulation days 5, 6, 7 or 8 was 1.2%, 1.8%, 13.3% and 83.7% in the corifollitropin alfa treatment arm and 0.5%, 4.7%, 18.3% and 76.5% in the recombinant FSH arm, respectively.

In the early responder group, 152 (91.6%) and 195 (91.5%) subjects in the corifollitropin alfa and recombinant FSH treatment arms, respectively, received HCG the same day that at least three follicles ≥ 17 mm were observed by ultrasound. In total, 6.6% and 8.5% of subjects received HCG 1 day later, whereas 1.8% and 0.0%, respectively, received HCG more than 1 day later.

Subject characteristics

Compared with subjects who received HCG after day 8, early responders in the corifollitropin alfa group were of similar age and had a similar body mass index (BMI), menstrual cycle length, duration of infertility, AFC and serum FSH concentration on stimulation day 1 (Table 1). These characteristics were also similar in the recombinant FSH group with the exception of a lower BMI ($P < 0.01$), a lower

serum FSH concentration on stimulation day 1 ($P < 0.01$) and a higher AFC in the early responder group ($P < 0.01$).

There were differences in the distribution of subjects who were early or normal responders from centres in Europe and North America, with considerably more early responders from North America than from Europe in the corifollitropin alfa group ($P = 0.01$) (Table 1).

Ovarian response to stimulation

Comparing the number of stimulation days, in each treatment group, early responders required 2 days less stimulation than normal responders. The mean \pm SD duration of stimulation was 7.9 ± 0.3 days in early responders versus 10.1 ± 1.2 days in normal responders in the corifollitropin alfa group and 7.8 ± 0.5 days versus 9.8 ± 1.0 days in the recombinant FSH group (Table 2).

The number and size of growing follicles during stimulation is presented per treatment group for early and normal responders in Figure 1 and Table 2. While in both treatment arms the number of follicles ≥ 11 mm was numerically higher in the first week of stimulation in the early responders compared with other responders, on the day of HCG administration the number and size of follicles was similar in both response groups (Table 2). The hormone profiles during stimulation for early responders and normal responders are shown in Figures 2 and 3. In both treatment arms, serum FSH and LH concentrations were similar in early responders and normal responders (Figure 2). In line with the higher number of growing follicles ≥ 11 mm, early responders had higher serum oestradiol ($P < 0.01$, both treatment groups) and inhibin B concentrations ($P < 0.01$, recombinant FSH group only) on stimulation days 5 and 8 than normal responders (Figure 3). Serum progesterone concentrations in early responders were higher ($P < 0.01$) on stimulation day 8, particularly in the recombinant FSH treatment group (Figure 3).

The number of oocytes retrieved was similar in early and normal responders in each treatment arm. The mean \pm SD number of embryos obtained in the corifollitropin alfa arm

Table 1 Baseline characteristics of early responders and normal responders for all subjects who reached the criterion for HCG administration.

	Corifollitropin alfa		Recombinant FSH	
	Early responders ($n = 166$)	Normal responders ($n = 549$)	Early responders ($n = 213$)	Normal responders ($n = 520$)
Age (years)	31.4 ± 3.4	31.5 ± 3.3	31.3 ± 3.2	31.7 ± 3.3
BMI (kg/m^2)	24.7 ± 2.7	24.9 ± 2.8	24.3 ± 2.5^a	25.1 ± 2.8^a
Serum FSH on day 1 (IU/l)	$6.2 (4.4-9.0)$	$6.4 (4.1-10.0)$	$5.9 (4.0-8.2)^a$	$6.5 (4.4-10.4)^a$
Antral follicle count (<11 mm)	12.1 ± 4.5	12.5 ± 4.5	13.2 ± 4.6^a	12.1 ± 4.3^a
Duration of menstrual cycle (days)	28.5 ± 1.8	28.5 ± 1.7	28.5 ± 1.7	28.4 ± 1.8
Duration of infertility (years)	3.2 ± 2.5	3.4 ± 2.5	2.9 ± 1.8	3.4 ± 2.3
Location				
Europe	64 (38.6) ^b	272 (49.5)	91 (42.7)	247 (47.5)
North America	102 (61.4) ^b	277 (50.5)	122 (57.3)	273 (52.5)

Values are mean \pm standard deviation, median (5–95th percentile range) or n (%).

^a $P < 0.01$.

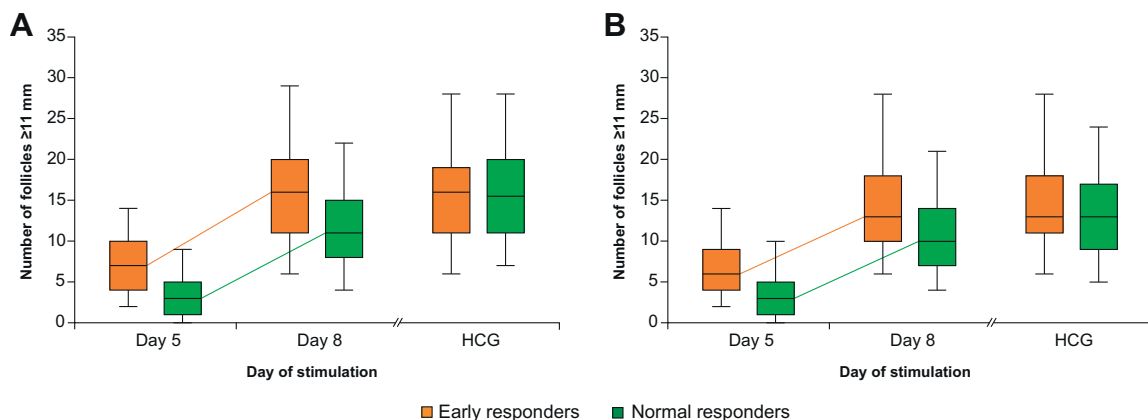
^b $P = 0.01$, Europe versus North America.

Table 2 Efficacy outcomes for early responders and normal responders for all subjects who reached the criterion for HCG administration.

	<i>Corifollitropin alfa</i>		<i>Recombinant FSH</i>	
	<i>Early responders</i> (n = 166)	<i>Normal responders</i> (n = 549)	<i>Early responders</i> (n = 213)	<i>Normal responders</i> (n = 520)
Duration of stimulation (days)	7.9 ± 0.3	10.1 ± 1.2	7.8 ± 0.5	9.8 ± 1.0
Follicles ≥11 mm on stimulation day 5	7.4 ± 3.9	3.5 ± 3.3	7.0 ± 4.0	3.7 ± 3.5
Follicles on stimulation day 8				
≥11 mm	16.3 ± 7.1	11.9 ± 5.7	14.5 ± 6.3	10.6 ± 5.3
≥15 mm	9.8 ± 5.1	3.8 ± 3.5	9.0 ± 4.0	3.9 ± 3.2
≥17 mm	5.8 ± 3.4	1.2 ± 1.8	5.7 ± 2.8	1.5 ± 1.9
Follicles on day of HCG				
≥11 mm	16.0 ± 7.1	16.1 ± 6.8	14.4 ± 6.2	13.8 ± 6.0
≥15 mm	9.6 ± 5.0	9.8 ± 4.6	8.7 ± 3.9	8.7 ± 4.0
≥17 mm	5.7 ± 3.3	5.8 ± 3.2	5.5 ± 2.7	5.7 ± 3.0
Oocytes retrieved	13.6 ± 7.2	14.5 ± 8.1	12.8 ± 6.4	12.8 ± 6.8
Day 3				
Embryos obtained	7.3 ± 4.4 ^a	8.8 ± 5.8 ^a	7.1 ± 4.5	7.7 ± 4.8
GQE obtained	4.3 ± 3.6	4.8 ± 4.5	4.2 ± 3.5	4.6 ± 4.0
Transfers				
Embryos	1.7 ± 0.6	1.6 ± 0.6	1.7 ± 0.5	1.6 ± 0.6
GQE	1.3 ± 0.8	1.2 ± 0.8	1.4 ± 0.8	1.3 ± 0.7
Ongoing pregnancy rates				
Overall	43.4	38.8	39.0	38.8
In Europe	34.4	32.0	24.2	32.0
In North America	49.0	45.5	50.0	45.1

Values are mean ± SD or n (%). GQE = good-quality embryos; HCG = human chorionic gonadotrophin; ITT = intent-to-treat.

^a*P* < 0.01.

**Figure 1** Number of follicles ≥11 mm during stimulation with corifollitropin alfa (A) and recombinant FSH (B) in early and normal responders. Horizontal lines indicate medians, boxes indicate interquartile ranges and whiskers indicate 5th and 95th percentiles. HCG = day of human chorionic gonadotrophin.

was 7.3 ± 4.4 and 8.8 ± 5.8 ($P < 0.01$) and in the recombinant FSH arm was 7.1 ± 4.5 and 7.7 ± 4.8 in early and normal responders, respectively (Table 2). The number

of embryos (and good-quality embryos) transferred was similar in early and normal responders and in each treatment arm (Table 2).

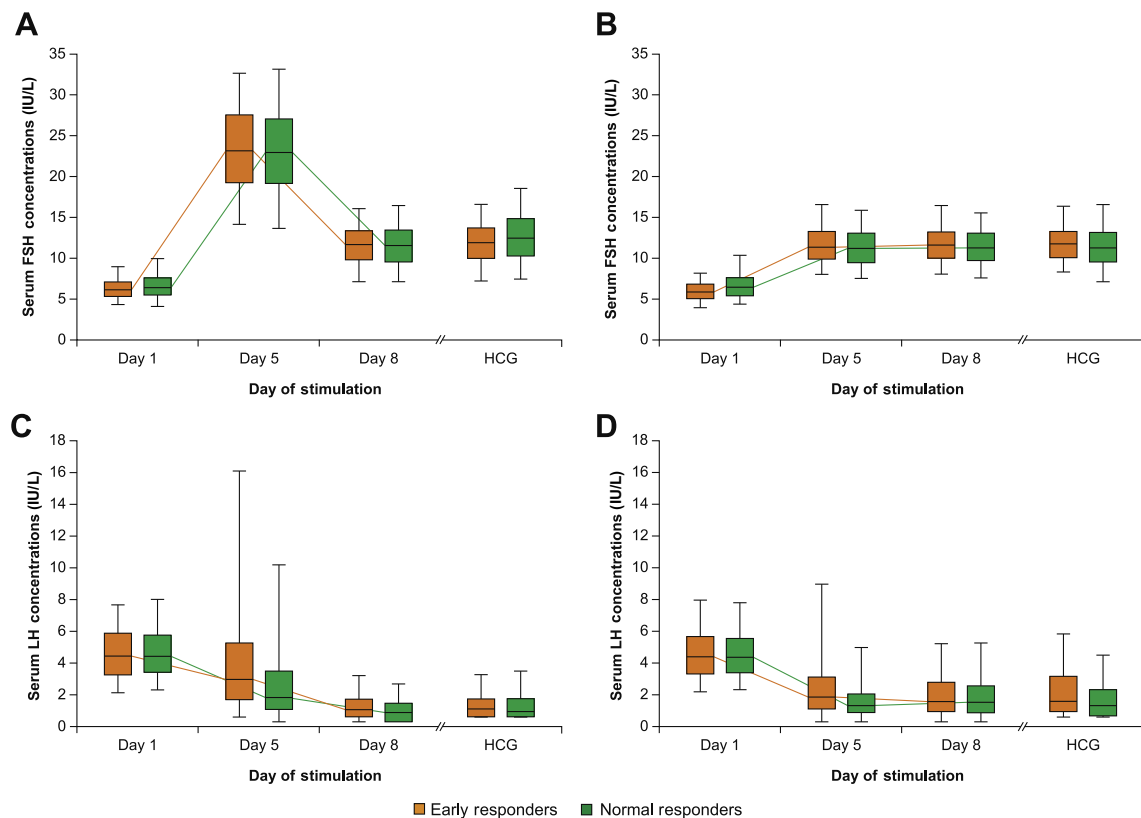


Figure 2 Serum FSH (A and B) and LH (C and D) concentrations during stimulation with corifollitropin alfa (A and C) or recombinant FSH (B and D) in early responders and normal responders. Horizontal lines indicate medians, boxes indicate interquartile ranges and whiskers indicate 5th and 95th percentiles. HCG = day of human chorionic gonadotrophin.

Ongoing pregnancy rates

The ongoing pregnancy rates in early and normal responders were similar in both treatment arms. The ongoing pregnancy rates were, respectively, 43.4% and 38.8% in the corifollitropin alfa treatment arm and 39.0% and 38.8% in the daily recombinant FSH treatment arm. Subset analysis of the pregnancy rates per region confirmed that the pregnancy rates were similar in both response groups (Table 2). The estimated odds ratio for ongoing pregnancy for early to normal responders adjusted for treatment group and region was 1.04 (95% confidence interval 0.82–1.33).

Although there were very few subjects, overall three ongoing pregnancies among eight subjects were established in those who reached the criterion and received HCG as early as stimulation day 6 in either treatment group. In total, 20 out of 44 subjects who reached the HCG criterion and received HCG on stimulation day 7 had an ongoing pregnancy.

Discussion

The current analysis indicates that women with a short duration of stimulation of only 6–8 days have the same chance of ongoing pregnancy as those with a longer duration of stimulation, regardless of treatment with either corifollitropin alfa or daily recombinant FSH. The percentage of early responders was lower in subjects treated with corifollitropin

alfa than in subjects treated with recombinant FSH, whereas the pharmacokinetics of corifollitropin alfa would suggest a reverse finding. Following a single injection of corifollitropin alfa, high serum FSH activity peaks 2 days thereafter, whereas daily injections of recombinant FSH take about 5 stimulation days to reach a steady state of serum FSH (Fauser et al., 2009).

Thus, the higher FSH activity following corifollitropin alfa treatment does increase the incidence of accelerated follicular development. The lower incidence of early responders following corifollitropin alfa treatment in this study may be a chance finding; however, in another randomized controlled trial (Corifollitropin alfa Ensure Study Group, 2010) the incidence of subjects who reached the criterion for HCG was also slightly lower in the corifollitropin alfa group than in the reference group of daily 150 IU recombinant FSH (32.8% versus 39.8%). Because in both trials the median duration of stimulation was 9 days in both treatment groups and corifollitropin alfa recruited more follicles than daily recombinant FSH, these data suggest a differential effect of exogenous FSH on follicular recruitment and on the time required for folliculogenesis.

Interestingly, women with a short duration of stimulation initially had a faster ovarian response but the final cohort of recruited follicles was not different from the normal responders. Thus, early responders had a normal magnitude of ovarian response and were not typically high responders. These findings confirm that the time interval needed for follicular development is not a critical factor, either for oocyte

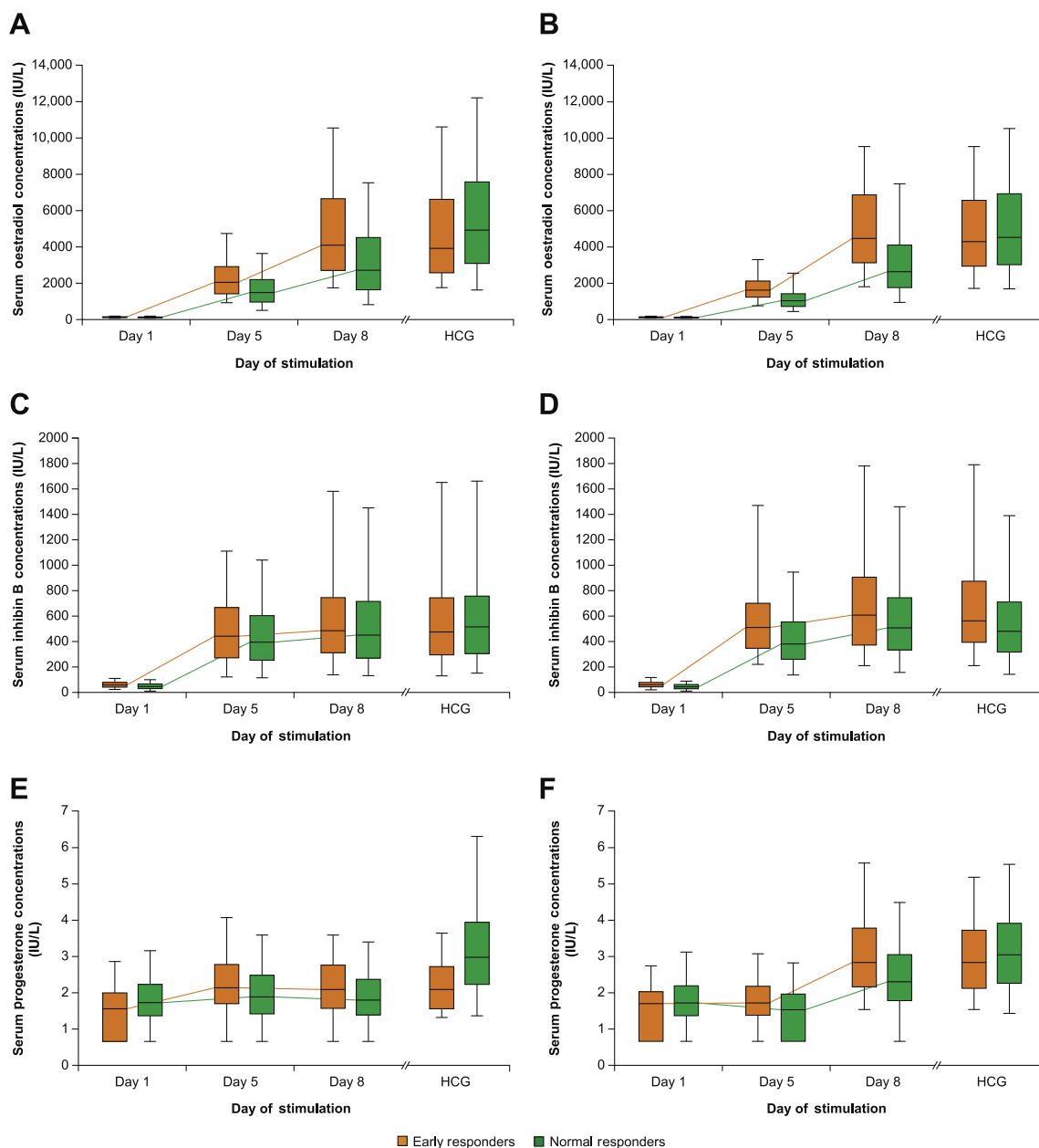


Figure 3 Serum oestradiol (A and B), inhibin B (C and D) and progesterone (E and F) concentrations during stimulation with corifollitropin alfa (A, C, E) or recombinant FSH (B, D, F) in early responders and normal responders. Horizontal lines indicate medians, boxes indicate interquartile ranges and whiskers indicate 5th and 95th percentiles. HCG = day of human chorionic gonadotrophin.

or embryo quality or for endometrial development (Martin et al., 2006).

The current study documented that early and normal responders have a similar chance of pregnancy and that only 1 week of stimulation is sufficient to prepare the endometrium for implantation. These findings are in agreement with those of Alport et al. (2011), who found no association between the length of stimulation and pregnancy outcome, although the analysis indicated that a short ovarian stimulation may be associated with a suboptimal number of follicles.

In this study, there were no notable differences in demographic and fertility characteristics between subjects who were early responders and those who were normal

responders, apart from a lower BMI, lower FSH and higher AFC in early responders in the recombinant FSH treatment group. However, this difference did not result in significantly more oocytes in early responders compared with normal responders. There was no difference between the menstrual cycle length of early and normal responders in either treatment group. With no significant differences in age or ovarian reserve observed, the reason why a proportion of women have a relatively short follicular phase during ovarian stimulation is difficult to understand but may be related to polymorphisms in genes involved in FSH signalling or folliculogenesis, which influence the response to exogenous gonadotrophin administration (Altmäe et al., 2011) or due

to an early follicle development during the luteal–follicular transition.

The percentage of early responder subjects in this study (23.2% and 29.1% in the corifollitropin alfa and recombinant FSH arms, respectively) may be unique for the GnRH antagonist protocol if related to an early luteal–follicular transition. Accordingly, the percentage of early responders may turn out to be much lower following pretreatment by oral contraceptives or following down-regulation in a long GnRH agonist protocol. The finding of a higher proportion of early responder subjects from North America compared with Europe suggests differences between the baseline characteristics of participants from these two regions. Subjects from North America were reported to be of similar age but had a lower incidence of primary infertility and less frequently a previous IVF cycle than those from Europe (Boostanfar et al., 2012). However, these differences do not explain the higher incidence of early responders in North America. Ongoing pregnancy rates in subjects in North America were higher than in subjects from Europe. This has been reported previously (Boostanfar et al., 2012) and could be due to better embryo selection procedures and more frequent double-embryo transfer rather than single-embryo transfer in North American IVF centres.

On the day of HCG, following two extra days of stimulation in the normal responder groups, the number of follicles ≥ 11 mm was similar in both response groups in each treatment arm, despite the more rapid initial ovarian response in terms of follicular development in the early responders. On the day of HCG, serum oestradiol, inhibin B and progesterone concentrations were also very similar, whereas during stimulation, higher hormone concentrations were observed in early responders. Overall, these data indicate that early responders are not typically high responders, but are subjects with either advanced follicle growth at the early follicular phase or with accelerated follicle growth during stimulation.

In conclusion, this large retrospective analysis showed that early responders receiving HCG prior to or on stimulation day 8 have advanced follicular development but the final number and size of preovulatory follicles is comparable to those of normal responders. A short follicular phase of stimulation did not affect the number of oocytes retrieved, the number of good-quality embryos obtained or the ongoing pregnancy rates.

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