Efficacy and safety of late-start Corifollitropin-alfa administration for controlled ovarian hyperstimulation in IVF: a cohort, case–control study

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Abstract

Objective To investigate efficacy and safety of a controlled ovarian stimulation (COS) protocol in which a single dose of Corifollitropin-alfa (CF α) was administered on day 4 of a GnRH-antagonist cycle.

Design Cohort case–control study.

Setting University Hospital.

Patients One hundred twenty-two normally cycling women expected to be normal responders to COS.

Interventions In 61 patients, CF α (100–150 μ g) was injected subcutaneously on day 4 of a spontaneous menstrual cycle; a GnRH-antagonist was added from day 8 (fixed protocol; 0.25 mg/day). If needed to complete follicular maturation, recombinant FSH (rFSH) daily injections (150/200 IU/day) were given from day 11. A control group of 61 matched women was stimulated with daily subcutaneous injections of rFSH (100–150 U/day) from day 4 of the cycle, and received GnRH-antagonist (0.25 mg/day) from day 8. IVF or ICSI was performed according to the sperm characteristics, and 1–2 embryos were transferred in utero under US guidance on day 2.

Main outcome measures Number of retrieved cumulus-oocyte complexes (COCs), clinical pregnancy rate (PR), implantation rate (IR), ongoing PR at 10 weeks, number of injections/cycle, ovarian hyperstimulation syndrome (OHSS) rate.

Results No cycle was cancelled and the mean number of retrieved COCs was comparable in patients and controls. About 60 % of CF-alfa treated women had no need of daily rFSH addition, and the mean number of injections/cycle was significantly lower in the CF-alfa group than in controls ($p<0.05$). The ongoing PR/transfer was 36.8 % in CF-alfa group and 37.5 % in controls. No patient developed severe OHSS, and the incidence of moderate OHSS was similar in cases and controls.

Conclusions CF α may be started on day 4 of the cycle obtaining results comparable to those of a COS using day 4-start daily rFSH, with significantly less injections and a similar risk of OHSS.

Keywords Corifollitropin alfa · Controlled ovarian stimulation · Mild ovarian stimulation · GnRH-antagonist · Recombinant FSH · Ovarian hyperstimulation syndrome

Capsule We report the IVF outcome of 122 patients stimulated either with Corifollitropin-alfa as a single injection on day 4 or with daily rFSH injection from day 4 of a GnRH-antagonist cycle.

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Introduction

Current treatments for controlled ovarian stimulation (COS) prescribe daily injections of gonadotropins (Gn) to maintain steady state levels in the blood sufficient to ensure the proper development of a suitable cohort of follicles. Prevention of premature ovulation, linked to the endogenous LH surge, can be accomplished either with gonadotropin-releasing hormone (GnRH) agonist or antagonists.

In comparison to the classical “long” protocol with GnRH-agonists, the GnRH antagonist “short” protocol has reduced

the impact of COS on patients' life by shortening the time needed to get complete follicular maturation. Further, GnRH-antagonists allowed to develop the so-called "mild" or "minimal" stimulation COS regimens, in which the initial follicular recruitment is accomplished by endogenous gonadotropins, and exogenous Gn are administered only from day 4–5 of the cycle onward (1–4). Aim of the "mild" COS is to obtain a patient-friendly treatment, with higher tolerability and without worsening IVF outcome.

Corifollitropin-alfa (CF α ; Elonva®, MSD, Germany) is a recombinant glycoprotein deriving from the addition of the carboxy-terminal peptide of the β -subunit of human chorionic gonadotropin (hCG) to the β -subunit of FSH (5). The carboxy-terminal peptide addition to FSH maintains the specific binding to FSH receptor and does not confer any LH activity to the molecule (5, 6), but changes its kinetic (7). After a single subcutaneous injection, CF α reaches peak serum levels after approximately 24 h, and having a long circulating half-life, provides a reliable FSH stimulus able to initiate and sustain multiple follicular development for 7 days (7–11).

A single subcutaneous injection of CF α on day 2 of the menstrual cycle was tested in two large, randomized, double-blind, phase III trials that demonstrated that CF α is as effective as seven daily injections of rFSH when used in a COS protocol with GnRH-antagonist (12, 13). Based on the results of the phase II dose-finding study, in view of the inverse relationship between exposure and body weight, the recommended dose of CF α was established at 100 μ g for subjects with body weight below 60 kg and 150 μ g for subjects above 60 kg. (9, 10).

The ease of using a single CF α injection instead of seven daily rFSH injections was shown to increase both patients' satisfaction and their compliance to treatment (14). In the long run, this may lead to a higher cumulative IVF effectiveness, as it may reduce the proportion of couples that prematurely withdraw from IVF program because of emotional and/or physical distress. The idea of administering CF α on day 4 of the cycle (instead than on day 2) combines the long-acting properties of the drug with the "mild" stimulation philosophy, aiming at performing COS with the lowest number of injections and the highest tolerability.

To date, the late-start CF α regimen was tested only in a small pilot study in which 27 women were randomized to receive CF α on day 4 and were compared to 25 women receiving it on day 2 of a GnRH-antagonist cycle (4). The study showed that the two protocols had comparable effectiveness, but raised the doubt that the late CF α administration could increase the rate of ovarian hyperstimulation syndrome (OHSS), being associated with a higher number of follicles >11 mm on the day of ovulation trigger (4).

Herein we show a series of 61 patients at their first IVF cycle that were treated with CF α administered on day 4 (late-start), comparing their outcome with that of 61 properly

matched controls who received daily rFSH injections from day 4 of the cycle; aim of our study was to check the efficacy and safety of the late-start CF α regimen in comparison with a "mild" stimulation regimen using daily rFSH.

Materials and methods

Patients

We studied patients entering our IVF program from June 2013 to March 2014. The inclusion criteria were the following: a) age 25–40 years, b) regular menstrual cycles (26–34 days), c) circulating day 3 follicle-stimulating hormone (FSH) level <10 IU/L, d) anti-Mullerian hormone (AMH) serum level of 1.2–4.5 ng/ml, e) antral follicle count (AFC) between 6 and 24. Exclusion criteria were: a) polycystic ovary syndrome (PCOS) diagnosed according to Rotterdam criteria (15); b) irregular cycle length (<26 or >34 days), c) circulating day 3 FSH $\geq$ 10 IU/L, d) circulating AMH levels <1.2 or >4.5 ng/ml, e) AFC <6 or >24, f) signs or symptoms of hyperandrogenism, g) hyperprolactinemia, h) signs or symptoms of thyroid dysfunction, and i) a history, signs or symptoms of any other endocrine disease.

Ninety-two patients matched the inclusion criteria and were proposed to join the study and to receive the new COS protocol. Among them, 61 gave their written, informed consent accepting to be stimulated with the late-start CF α protocol and were included in the study.

As controls, we included a group of 61 women with properly matched clinical, hormonal and US characteristics, who received daily injections of rFSH (100–150 IU/day) from day 4 of the menstrual cycle in the same time interval. The study was approved by the local ethical committee as a cohort case-control study.

As the expected rate of severe OHSS among normal responders undergoing IVF is 1.5–2 % (approximately 1 out of 60) and that of moderate OHSS 5–6 % (approximately 4 out of 60), we estimated to include in the study at least 60 patients (plus the same number of controls) in order to have the chance not only to observe the incidence of risk factors for OHSS (e.g., peak estradiol level >3000 pg/ml, number of follicles >11 mm the day of hCG administration, etc.) as already done in other studies (16), but also to calculate the actual incidence of severe and moderate OHSS among our patients.

Late-start CF α protocol

The late-start CF α protocol was performed administering a single subcutaneous injection of CF α (Elonva®, MSD, Germany) (100 μ g to patients $\leq$ 60 kg, 150 μ g to patients with body weight >60 kg, respectively, as recommended by the manufacturer) on the fourth day of a spontaneous menstrual

cycle. No patients were treated with oral contraceptives before COS. The GnRH-antagonist ganirelix (Orgalutran, MSD, Germany) was added as 0.25 mg daily subcutaneous injections from day 8 of the cycle, according to a fixed schedule.

The ovarian response to COS was monitored performing trans-vaginal US assessment and serum estradiol measurement every 2–3 days from stimulation day 8. Daily injections of rFSH (Puregon, MSD, Germany; 150 IU/day to patients with body weight ≤ 60 kg, 200 IU/day to patients >60 kg) were administered from day 11 when the conditions to trigger ovulation were not yet reached. Ovulation was triggered by injecting subcutaneously 10,000 IU of hCG (Gonasi HP, Ibsa, Switzerland), when at least three leading follicles reached 17 mm diameter, with appropriate E2 levels.

Control daily rFSH protocol

The late-start rFSH protocol was performed administering daily subcutaneous injections of rFSH (Puregon®, MSD, Germany) (100–150 IU/day according to age, AMH levels and AFC) from day 4 of a spontaneous menstrual cycle. The GnRH-antagonist ganirelix (Orgalutran, MSD, Germany) was then added as 0.25 mg daily subcutaneous injections from day 8 of the cycle, according to a fixed schedule. Ovarian response assessment schedule and ovulation trigger criteria were the same as above.

IVF procedure

Oocyte pick-up (OPU) was performed by transvaginal US-guided aspiration approximately 36 h after hCG injection, under local anaesthesia (paracervical block). Mature metaphase II (MII) oocytes were retrieved from the cumulus-oocyte complexes (COCs) and later inseminated either using IVF or ICSI, according to semen quality after in vitro processing. After 48 h of in vitro culture, embryo morphology was evaluated using the 10-points scale score by Holte et al. (16) and the two best scored embryos were transferred in utero using a soft catheter (Sydney, Cook, Australia) under US guidance. No more than two embryos were transferred in order to avoid triplet pregnancies; if more than two good scored embryos were obtained, they were frozen and kept in liquid nitrogen until further use. A single embryo was transferred when it was the only available.

The luteal phase was supported administering 180 mg/day natural progesterone intravaginally (Crinone 8, Merck-Serono, Germany) for 15 days starting the day of ET. Pregnancy was assessed by serum hCG after 14 days from ET and then confirmed when one or two gestational sacs were visualized by transvaginal US after two further weeks. Pregnant patients were further controlled by transvaginal US at 10 weeks gestational age in order to assess the ongoing pregnancies at 10 weeks.

Statistical methods

The main outcome measures were: (a) concerning COS: number of retrieved COCs, number of injections/cycle; (b) concerning IVF outcome: clinical (US-detected) pregnancy rate (PR), implantation rate (IR), ongoing PR at 10 weeks; (c) concerning safety: peak estradiol level, number of follicles <10 mm diameter the day of hCG, incidence of severe or moderate OHSS.

The enrolled patients were quite homogeneous for clinical and endocrine characteristics, and the parameters that were considered as main outcomes resulted to be normally distributed at the Kolmogorov-Smirnov test. Therefore, data were expressed as mean $\pm$ standard deviation (SD) of the mean or as counts and percentages. Significance of between-group differences was assessed using the Student's *t*-test for unpaired data. Qualitative data were analyzed by means of Chi-square test. All the tests were two tailed with a significance level set at 5 % ($p < 0.05$).

Results

The clinical characteristics of the 122 patients are shown in Table 1. No significant differences were observed between cases and controls as far as all the clinical, hormonal and US features were concerned. Even the distribution of infertility causes and the proportion of IVF and ICSI treatments were similar among cases and controls. The overall age, BMI, cycle length and basal endocrine and ultrasound characteristics of the whole group of patients corresponded to those of expected normal responders to COS.

Table 1 Clinical characteristics of the 122 patients treated either with Corifollitropin alpha ($n=61$) or with daily rFSH ($n=61$). Data are expressed as mean $\pm$ SD

	CF alfa	rFSH	<i>p</i>
Age (years)	33.8 $\pm$ 3.6	32.8 $\pm$ 3.7	ns
BMI (Kg/m ²)	22.9 $\pm$ 3.6	22.2 $\pm$ 3.0	ns
Duration of infertility (years)	2.4 $\pm$ 1.1	2.5 $\pm$ 0.9	ns
Cycle length (days)	29.3 $\pm$ 4.1	28.8 $\pm$ 1.5	ns
FSH on day 3 (IU/l)	6.8 $\pm$ 1.8	6.8 $\pm$ 1.9	ns
AMH (ng/ml)	2.7 $\pm$ 1.4	3.6 $\pm$ 2.2	ns
Antral Follicle Count (AFC)	16 $\pm$ 4.9	19.2 $\pm$ 4.6	ns
Cause of infertility (%)	—	—	ns
- male	62	67	
- tubal	15	11	
- unexplained	23	22	
IVF (%)	45.9	47.5	ns
ICSI (%)	54.1 %	52.5	ns

All COS cycles arrived to OPU (Table 2); among both cases and controls there were no cancelled cycles due to insufficient (<3 growing follicles) or too high (>20 follicles with diameter >9 mm) ovarian response at the first checkpoint (day 8 of the cycle). Four patients (6.5 %) whose husband was affected by a severe dyspermia, however, did not undergo ET because none of their eggs fertilized normally or developed into embryos of acceptable morphology.

The outcome of COS in both patients' groups is shown in Table 2. Starting on day 4, the average stimulation length resulted to be rather short (averagely about 7.5 days) in both groups. About 60 % of the patients treated with CF-alfa did not need the addition of daily rFSH from day 11 onward, and those who received the addition of daily rFSH reached the criteria allowing ovulation trigger with a low mean dose (255 ± 120 IU). Significantly less injections/cycle were necessary in the CF-alfa group than in controls (7.8 ± 3.8 vs. 14.8 ± 4.4 , $p < 0.05$). The serum E2 level on day 8 of the cycle was significantly higher in CF-alfa group than in controls, but the final peak E2 level, as well as the number of follicles above 11 mm diameter the day of hCG administration, were comparable in the two groups.

A comparable number of COCs (averagely about 8.5) were retrieved in both patients' groups (Table 3); the harvested mature (MII) oocytes, however, were more in the CF-alfa group than in controls (7.5 ± 3.8 vs. 5.9 ± 3.3 , $p < 0.05$). The fertilization rate was not significantly different in the two groups and the morphological score of the obtained embryos was comparable. Embryos were cryopreserved in a similar proportion of cases (Table 3).

The clinical pregnancy rates per ET and per started cycle, as well as the implantation rate were slightly, but not significantly, higher in the CF-alfa group than in the control group (43.8 % vs 40.3 %, 41 % vs. 36 %, and 31.8 % vs. 28.1 %, respectively).

Differently, the twinning rate was significantly higher in the CF-alfa group (40 % vs. 8 %, $p < 0.05$). Even the abortion rate, however, was significantly higher among patients treated with CF-alfa (16 % vs. 3 %, $p < 0.05$) and therefore the ongoing pregnancy rate (OPR) at US examination performed at 10 weeks gestational age was comparable in both groups (36.8 % vs. 37.5 %) (Table 3). To date, none of the patients that had frozen embryos requested to get them thawed and transferred.

None of the patients included in the study developed symptoms or signs of early or late severe OHSS, and none needed hospitalization; the incidence of moderate OHSS was comparable in both groups (4.9 % vs. 5.4 %) (Table 3). No other serious adverse effect was noticed.

Discussion

The late-start, "mild" stimulation COS regimens are subjectively better tolerated (less abdominal discomfort and swelling) (15), shorter, and consequently probably cheaper than standard protocols (2, 3, 17). In comparison to the "classical" COS, they compensate the slightly reduced "per attempt" effectiveness with the improved tolerability, that lowers the drop-out rate and finally increases the number of attempts, leading to a comparable cumulative yearly success rate (18).

The long-acting rFSH molecule CF α was made available for clinical use a few years ago and was proven effective in inducing multiple follicular development in IVF patients with

Table 2 Outcome of COS using either Corifollitropin alfa ($n=61$) or daily rFSH ($n=61$). Data are expressed as mean $\pm$ SD

	CF alfa	rFSH	P
Cancelled cycles (%)	—	—	
Length of follicular phase (days)	12.6 $\pm$ 2.1	12.6 $\pm$ 1.8	ns
Length of ovarian stimulation (days)	7.9 $\pm$ 2.8	7.4 $\pm$ 3.0	ns
Days of GnRH-antagonist administration	5.1 $\pm$ 1.9	4.9 $\pm$ 1.6	ns
Cycles with no need of daily rFSH addition (%)	60.6	—	—
Total added rFSH dose (IU)	255 $\pm$ 120	—	—
Total n. of injections (rFSH + GnRH-antagonist)/cycle ^a	7.8 $\pm$ 3.8 ^a	14.8 $\pm$ 4.4	<0.05
Serum E2 on day 8 (pg/ml)	744 $\pm$ 317	492 $\pm$ 305	<0.05
Serum peak E2 (pg/ml)	1431 $\pm$ 471	1547 $\pm$ 667	ns
Follicles >11 mm diameter on hCG day	13.9 $\pm$ 5.6	11.7 $\pm$ 7.4	ns

^a the injection of hCG to trigger ovulation was not counted

Table 3 Outcome of OPU and of IVF cycle using either Corifollitropin alfa ($n=61$) or daily rFSH ($n=61$). Data are expressed as mean $\pm$ SD

	CF alfa	rFSH	P
Retrieved COCs	8.9 $\pm$ 4.1	8.0 $\pm$ 4.3	ns
MI I oocytes	7.5 $\pm$ 3.8	5.9 $\pm$ 3.3	<0.05
Inseminated oocytes	6.6 $\pm$ 2.8	5.5 $\pm$ 2.7	ns
Fertilization rate (%)	73.2	62.2	ns
Embryos available for ET or freezing	4.2 $\pm$ 2.2	3.2 $\pm$ 2.4	ns
Embryo morphological score	7.4 $\pm$ 2.6	6.1 $\pm$ 3.6	ns
Transferred embryos	1.8 $\pm$ 0.4	1.6 $\pm$ 0.6	ns
Cycles with embryo freezing (%)	15.8	14	ns
Clinical pregnancy rate/started cycle (%)	41	36	ns
Clinical pregnancy rate/ET (%)	43.8	40.3	ns
Implantation rate (%)	31.8	28.1	ns
Twinning rate (%)	40	8	<0.05
Abortion rate (%)	16	3	<0.05
Ongoing PR/started cycle at 10 weeks	34.4	34.4	ns
Ongoing PR/ET at 10 weeks	36.8	37.5	ns
Severe OHSS rate (%)	0	0	ns
Moderate OHSS rate (%)	4.9	5.4	ns

clinical characteristics of expected normal (12, 13) or poor (19, 20) responders, in association with GnRH-antagonists and either rFSH (12, 13, 19) or hMG (20).

CF α has the ideal kinetic to be applied in late-start protocols, when exogenous gonadotropin administration is started on day 4 of the menstrual cycle. Circulating FSH peak is reached approximately 24 h after CF α is injected subcutaneously, more quickly than after repeated rFSH daily injections, and sustained FSH levels are maintained for 7 days due to the long half-life of the molecule (7, 10, 11). In practical terms, when CF α is injected on day 4 of the cycle, blood FSH peak is reached on day 5 and steady FSH levels are maintained until day 11, when only some patients would need further FSH administration to complete follicular growth.

In the present study, administering CF α on day 4 of a spontaneous cycle we observed that 60.6 % of the patients had no need of further daily rFSH injections. This proportion is similar to that reported in a small pilot study that compared day 4 vs. day 2 CF α administration: 56 % of patients had no need of rFSH addition in the day 4 group vs. 20 % in the day 2 group (4). Differently, in the large Ensure (13) and Engage (12) trials, in which CF α was given on day 2, only 38 % and 30 % of patients, respectively, had no need to continue ovarian stimulation with daily rFSH addition after the down of CF α effect. These data strongly suggest that day 4 protocol significantly lowers the need of rFSH addiction in comparison with day 2 regimen. Herein we also show that the late administration of CF α allows to add GnRH-antagonist from day 8 of the cycle instead than from day 5, as suggested when CF α is given on day 2 to expected normal responders (12, 13); this is another issue that further lowers the number of injections. In the present study, the late-start CF α protocol enabled us to complete COS with an average total number of injections of 7.8 ± 3.8 (range 4–11), which is definitely low in comparison with a standard COS, lower than observed after day 2 CF α administration (12, 13), and significantly lower than observed in case of daily rFSH administration from day 4 of the cycle. This could possibly increase the patients' satisfaction and compliance to treatment and, on the other side, decrease the economical costs of IVF for medications.

The so-called “mild” protocols (1), in which exogenous gonadotropins are started some days after the beginning of the cycle, allow initial follicle recruitment by endogenous FSH (21, 22). Compared to the “classical” COS regimens, they show a lower follicular recruitment, and were repeatedly shown to lead to a lower oocyte yield (23–25). Indeed the mean number of retrieved MII oocytes in the present series was lower than reported in Engage (12) and Ensure (13) trials (7.5 vs. 13.8 and 12.7, respectively), but it was significantly higher than the one obtained in the control group (5.9), composed of patients who received daily rFSH from day 4. Anyway, the number of MII oocytes in CF-alfa group was sufficient to get an ongoing pregnancy rate/ET (36.8 %)

comparable to that of the two larger studies (43.8 % and 31.7 %, respectively) and to that of the daily rFSH control group (40.3 %). Interestingly enough, a recent post hoc analysis of the Engage trial confirmed that after CF α stimulation the ongoing PR/ET of patients in which 6–9 oocytes were retrieved was comparable to that of patients that obtained 10–13 oocytes (26). Indeed the results presented herein are similar to those reported in a study previously published by our group, in which a low dose of daily rFSH (150 IU) was administered from day 4 to expected normal responder, non-PCO women: in that trial, in fact, a mean of 9.9 MII oocytes were retrieved and an ongoing PR/ET at 10 weeks of 35.9 % was obtained (27).

It must be remarked that in the present study, an unacceptably high twinning rate (40 %), unusual for our IVF Unit, was observed in the CF-alfa group; actually it was significantly higher than in the control group, despite the embryo morphological score was comparable in the two groups. We can not understand if this observed outcome was due to embryo quality or to endometrial receptiveness, but in any case, in light of the observed results we would definitely recommend to associate the use of CF α with elective single embryo transfer, eventually extending embryo culture to the blastocyst stage.

As far as safety is concerned, the pooled analysis of three large clinical trials (12, 13, 28) showed that the incidence of severe OHSS was consistent with that expected in the relatively young patient population and was similar for patients receiving CF α (1.8 %) or daily rFSH (1.3 %) (26). In a recent pilot study comparing CF α given on day 2 vs. day 4 in young expected normal responders, the proportion of patients with more than 20 follicles >11 mm diameter the day of ovulation trigger was found to be higher in the day 4 group, raising the suspect that day 4 administration could be associated with a higher risk of OHSS (4). Analyzing a larger series, we could not confirm that finding: neither US, nor peak estradiol levels were significantly higher in the CF-alfa treated group than in the group receiving daily rFSH. Even if all patients in our series received hCG trigger (and not GnRH-agonist trigger), none of them developed severe OHSS. Also the incidence of moderate OHSS was similar in CF-alfa patients and in controls, and overall it was not higher than expected in rather young, normal responding women. The difference between our data and those of Blockeel et al. (4) could depend on the age of the included patients, that was higher in our series (34 vs. 30.7 years), and/or on the ovarian response to COS, that was lower in our patients' group (8.9 vs. 14.7 retrieved COCs).

With the limitations of the relatively small number of observations, the present cohort case–control study suggests that the administration of CF α on day 4 of the cycle with the sequential addition of daily GnRH-antagonist from day 8 and (eventually) daily rFSH from day 11 may result in a satisfactory IVF outcome without increasing the risk of OHSS.

The administration of CF α in a late-start, “mild stimulation” regimen may further reduce the stressing impact of COH on IVF patients increasing their compliance. Our research group is presently starting a large RCT to further test the potential of this new COH protocol in comparison both with the day 2 start CF- α protocol, and with the daily rFSH day 4 start regimen.

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