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A pilot study comparing corifollitropin alfa associated with hp-HMG versus high dose rFSH antagonist protocols for ovarian stimulation in poor responders

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ABSTRACT

Does corifollitropin alfa associated with hp-HMG protocol from the beginning of ovarian stimulation perform better than high dose rFSH alone for ovarian stimulation with GnRH antagonist in poor responders? This retrospective, monocentric, case-control pilot study was conducted in 65 poor responders (Bologna criteria) undergoing 2 consecutive IVF cycles. All patients underwent a first ovarian stimulation cycle with high dose rFSH (≥ 300 IU/day) alone in antagonist protocol, unfortunately leading to poor ovarian response and no pregnancy. The following cycle was performed with 150 μ g of corifollitropin alfa associated with daily injections of hp-HMG from the beginning of the cycle. The primary outcome was the number of mature oocytes retrieved. The secondary outcomes were ovarian stimulation cancellation and embryo transfer rate per initiated cycle. The number of mature oocytes was not significantly different between the 2 groups. However, cycle cancellation rate was significantly lower and the proportion of cycles with embryo transfer was significantly higher with corifollitropin + hp-HMG protocol, leading to an encouraging clinical pregnancy rate of 24.1% per oocyte retrieval. This pilot study based on corifollitropin alfa associated with hp-HMG from the onset of stimulation appears to be promising for ovarian stimulation in poor responders.

Introduction

While infertility is generally considered to concern 10 to 15% of couples trying to conceive, the proportion of women with advanced reproductive age and/or premature ovarian failure tends to rise (Devine et al., 2015; Papathanasiou, Searle, King, & Bhattacharya, 2016). These patients often have to face poor ovarian response to controlled ovarian stimulation (COS), with low number of oocytes retrieved, higher risk of cycle cancellation, and finally suffer from relatively poor prognosis in IVF (in vitro fertilization) cycles (Bozdag, Polat, I. Yarali, & H. Yarali, 2017; Busnelli et al., 2015; Busnelli & Somigliana, 2018). Ovarian stimulation in poor responders remains one of the main challenges in ART (assisted reproductive technologies). In 2011, the European Society of Human Reproduction and Embryology proposed new criteria (the Bologna Criteria) in order to better define the status of 'poor responders' (Ferraretti et al., 2011). They incorporated age, ovarian reserve tests (anti-Müllerian hormone

(AMH) level or antral follicle count (AFC)) and ovarian response in previous IVF/ICSI (intra cytoplasmic sperm injection) cycles. However, these criteria still remain questioned and have not been systematically used in all the studies available in the literature (Papathanasiou et al., 2016).

In 2016, the working group POSEIDON has suggested a reconsideration of the population of poor responders proposing four subgroups (Humaidan, Alviggi, Fischer, & Esteves, 2016; Poseidon Group et al., 2016), but for now most studies are still performed using Bologna criteria. Several approaches have been proposed for ovarian stimulation in these patients, such as increasing rFSH (recombinant follicle stimulating hormone) daily doses (Dercourt, Barrière, & Freour, 2016), or conversely mild stimulation protocols (Siristatidis et al., 2017) or even natural cycle IVF (Lainas et al., 2015). Some authors also recommended adjuvant therapies, such as pre-treatment with androgens to enhance follicular recruitment (Doan, Quan,

& Nguyen, 2017; Nagels, Rishworth, Siristatidis, & Kroon, 2015). However, no evidence can be drawn from the huge amount of literature on which regimen may constitute the best approach to improve ovarian stimulation and pregnancy rate in this group of patients.

A few years ago, corifollitropin alfa became available for ovarian stimulation. This recombinant hormone consists of an FSH alfa subunit, associated with FSH beta subunit fused with the C-terminal peptide of human chorionic gonadotropin (hCG) beta subunit. Corifollitropin alfa acts like a long-acting FSH, with a single dose keeping circulating FSH level above the threshold necessary to support multi-follicular growth for 7 days, thus replacing the first 7 daily injections of rFSH. The single-dose pharmacokinetic profile of corifollitropin alfa is characterized by highest FSH activity during the first 2 days of stimulation, followed by decreasing FSH activity. The FSH threshold level is reached faster with corifollitropin alfa (approximately 24 hours after injection) than with daily FSH injections where about 3 days of injections are necessary (Fauser et al., 2009).

According to clinical studies and marketing authorization, corifollitropin should preferentially be used for ovarian stimulation in normoresponders (Griesinger, Boostanfar, et al., 2016; Lerman et al., 2017; Pouwer, Farquhar, Kremer, & Marjoribanks, 2016). While corifollitropin should be avoided in high responders according to the high risk of ovarian hyperstimulation syndrome (OHSS) (Griesinger, Verweij, et al., 2016), some trials were conducted in poor responders in order to evaluate if the early rise of FSH and the stable serum FSH levels induced by corifollitropin lead to sustained follicular development and improved ovarian response to stimulation (Polyzos, Camus, Llacer, Pantos, & Tournaye, 2013; Polyzos, DeVos, Corona, et al., 2013; Polyzos, DeVos, Humaidan, et al., 2013). These studies did not provide evidence of improved clinical outcome for poor responders. As some studies reported that the addition of LH (luteinizing hormone) activity to FSH via the use of highly purified human menopausal gonadotropin (hp-HMG) may improve embryo quality and pregnancy rates (Bosch et al., 2011; Dahan, Agdi, Shehata, Son, & Tan, 2014), some trials, such as COMPORT trial, were designed to evaluate the interest of an antagonist protocol with corifollitropin alfa followed by hp-HMG for ovarian stimulation in poor responders (Polyzos, Camus, et al., 2013; Polyzos, DeVos, Corona, et al., 2013). Promising results were recently reported (Drakopoulos et al., 2017). However, the potential interest of adding LH

activity via the use of hp-HMG to long-acting FSH stimulation for follicular development might advocate for initiating this association from the beginning of ovarian stimulation cycle.

The aim of our study was to evaluate the interest of associating corifollitropin alfa and hp-hMG from the beginning of ovarian stimulation in antagonist protocol in poor responders and to compare it with high dose daily rFSH antagonist protocol.

Material and methods

Study population

This retrospective monocentric case-control pilot study was conducted in an University based IVF centre between August 2015 and November 2016. Patients were included after poor ovarian response, defined as fewer than 3 mature follicles (≥ 17 mm) or cycle failure (i.e. cycle cancellation, embryo transfer cancellation or implantation failure) after antagonist protocol and high-dose daily rFSH injections (≥ 300 IU/d). Patients were considered poor responders if they fulfilled the Bologna criteria (Ferraretti et al., 2011). No other inclusion criteria were used. The study has been approved by the local ethical committee and consent has been obtained from patients for the anonymous retrospective use of their clinical data.

Stimulation regimen and ART procedures

The control protocol was a standard antagonist regimen (named A) with daily injections of ≥ 300 IU of FSH (follitropin alfa or beta) (Figure 1(A)). Following poor ovarian response and cycle failure with this high dose rFSH antagonist cycle, all patients underwent another stimulation cycle within 6 months. Ovarian stimulation protocol (named B) consisted of a single subcutaneous injection of 150 μ g corifollitropin alfa (Elonva[®] MSD) on the first stimulation day associated with daily injections of hp-HMG (Menopur[®] Ferring), 75 IU/d during the first 7 days of stimulation followed by 300 IU/d if needed on day 8 and later on until final follicular maturation (Figure 1(B)).

Oestrogen pre-treatment was used in both regimens. Daily administration of GnRH antagonist (gonadotrophin releasing hormone) from cycle day 6 was used to prevent premature LH surge. Ovulation triggering was performed with the administration of 250 μ g of rhCG (Ovitrelle[®] Merck-Serono) as soon as at least 3 follicles of ≥ 17 mm diameter were observed by transvaginal ultrasound. Oocyte retrieval was performed 36 hours later. Cycles were cancelled when

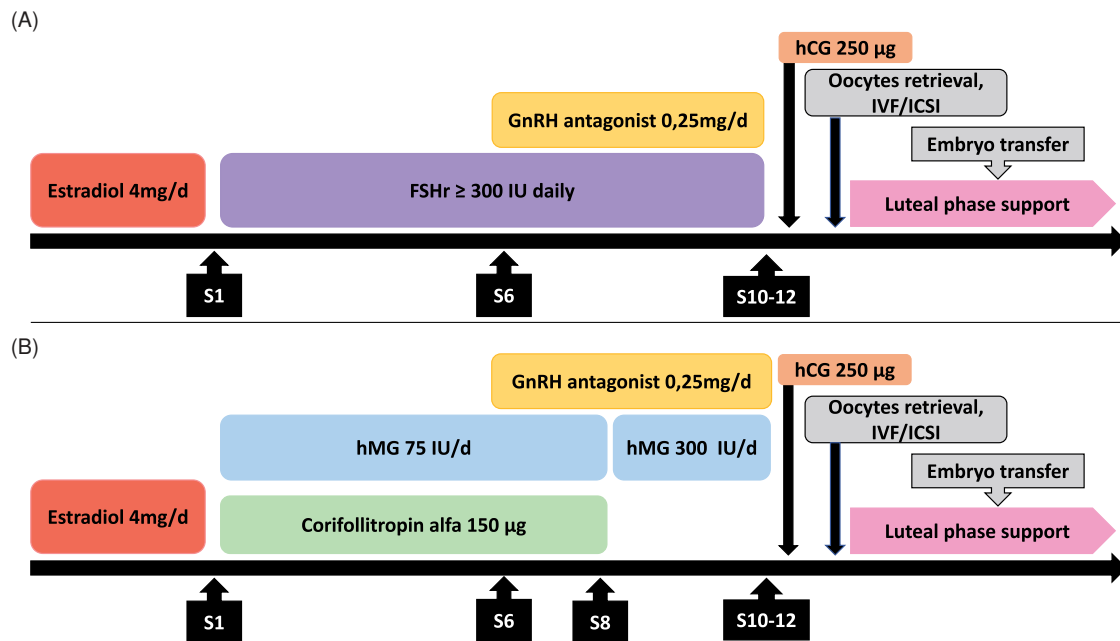


Figure 1. Graphical illustration of the two regimens of the study: (1A) standard antagonist regimen with daily injections of ≥ 300 IU of FSH (follitropin alfa or beta); (1B) novel regimen studied consisting in a single subcutaneous injection of 150 μ g corifollitropin alfa (Elonva[®], MSD) on the first stimulation day (S1) associated with daily injections of hp-HMG (Menopur[®], Ferring), 75 IU/d during the first seven days of stimulation followed by 300 IU/d if needed on day 8 and later on until final follicular maturation. (S: stimulation day).

only 1 or 2 follicles were observed. Rescue intrauterine insemination (IUI) was proposed if tubal patency and sperm parameters were compatible. Embryo quality was evaluated daily according to The Istanbul consensus workshop on embryo assessment (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). Embryo transfer was always performed on day 5 or 6, with one or two blastocysts transferred. Luteal support was given using vaginal progesterone tablets (Utrogestan[®] Besins International) 200 mg \times 2 daily for 2 weeks from the day of oocytes retrieval. A pregnancy test was performed 11 days after the embryo transfer. Clinical pregnancy was defined as the presence of an intrauterine gestational sac with fetal heart activity at 6–8 weeks of gestation, confirmed by ultrasound examination.

Main outcomes

The primary endpoint was the number of mature oocytes retrieved and the secondary outcomes were stimulation cancellation rate and embryo transfer rate per initiated cycle. The total number of oocytes retrieved (i.e. mature + immature), blastocysts obtained and cryopreserved were also compared between both cycles for each patient. Clinical pregnancy rate was calculated after corifollitropin hp-HMG

stimulation cycle, but could obviously not be compared with previous high dose rFSH cycle as all patients were included after failing to get pregnant.

Statistical analysis

Statistical analysis was performed with Graph Pad Prism software (La Jolla, CA, USA). Continuous variables were compared with Student's paired *T*-test and Chi² Mac-Nemar's test when appropriate. Statistical significance was set at $p < 0.05$.

Results

A total of 65 poor ovarian responders successively undergoing high-dose rFSH (protocol A) and Corifollitropin alfa + hMG (protocol B) protocols were included in the analysis. Patients' main demographic characteristics are presented in Table 1.

As each patient was on her own control within a 6-month time period, demographic characteristics were strictly comparable between the two groups A and B. The mean time interval between the 2 cycles was 4.8 ± 3.7 months. ICSI was performed in 66% of the cycles, standard IVF was used for the remaining cycles.

Clinical and biological outcomes are presented in Table 2. The number of mature oocytes was not statistically different between the 2 groups. Cycle

cancellation rate for insufficient ovarian response to COS was significantly lower in group B than in group A. No cancellation for excessive ovarian response occurred and no case of OHSS was observed with both groups. Only 1 out of 65 patients in group B had premature progesterone elevation (>1.5 ng/ml) on hCG day, leading to a 'freeze all' cycle, versus 3 in group A. Fertilization rate was significantly higher in ICSI in group B than in group A, whereas the difference did not reach statistical significance in standard IVF. Although the number of cleaved embryos was significantly higher in group B than in group A, the total number of blastocysts obtained was not significantly different between both groups. However, embryo transfer rate per started cycle was significantly higher in group B (69%) than in group A (38.5%).

Concerning reproductive outcomes, the pregnancy rate (confirmed by positive hCG test) was 27.7% per started cycle, 31% per oocyte retrieval and 45% per embryo transfer in group B. The clinical pregnancy rate was 21.5% per started cycle, 24.1% per oocyte

retrieval and 35% per embryo transfer. Among the 14 clinical pregnancies, 12 live births occurred at the time of the study, 1 patient unfortunately had to have a therapeutic abortion because of fetal abnormalities (spina bifida), and 1 miscarriage was reported. Two pregnancies were also reported after frozen embryo transfer: one achieved in a live birth and the other one unfortunately ended with an early miscarriage. Considering these results, the new protocol provided a live birth rate of 18.5% and a cumulative live birth rate of 20% at the time of the study.

Discussion

To our knowledge, the present study is the first to compare the efficiency of corifollitropin alfa in association with hp-HMG from the beginning of the stimulation, to a classic daily administration of high dose rFSH in antagonist protocols in poor ovarian responders. We found that there was no statistically significant difference between the two regimens in terms of mature oocytes retrieved. This agrees with previously reported studies comparing corifollitropin alfa and rFSH in various types of COS protocols (Kolibianakis et al., 2015; Polyzos et al., 2015; Salgueiro, Rolim, Moura, Machado, & Haddad, 2016; Souza et al., 2017). This is also in agreement with the very recently reported results of the COMPORT trial, presented during last ESHRE meeting in Geneva in July 2017, which showed that the addition of hp-HMG to corifollitropin alfa from the outset of the ovarian stimulation did not significantly impact the number of mature oocytes retrieved (Abstracts of the 33rd Annual Meeting of the European Society of Human Reproduction and Embryology, 2017). However, we report here that the association of corifollitropin alfa with hp-HMG from the beginning of the stimulation significantly improves

Table 1. Demographic and fertility characteristics of the 65 patients.

Age (years): mean \pm SD	34.26 \pm 4.4
BMI (kg/m ²): mean \pm SD	23.8 \pm 4.4
Previous COS cycles: mean \pm SD	2.06 \pm 1.3
AFC: mean \pm SD	10.6 \pm 4.4
AMH level (ng/ml): mean \pm SD	1.5 \pm 0.9
Infertility characteristics: <i>n</i> (%)	
Primary	48 (74)
Secondary	17 (26)
Smoking: <i>n</i> (%)	
Current	9 (13.8)
Past	22 (33.8)
Non smoker	34 (52.4)
ICSI use: <i>n</i> (%)	43 (66)

Results are presented as proportion or mean \pm standard deviation (SD); BMI body mass index; COS controlled ovarian stimulation; AFC antral follicle count; AMH anti Mullerian hormone; IVF in vitro fertilization; ICSI intra cytoplasmic sperm injection.

Table 2. Clinical and biological outcomes with the 2 stimulation protocols.

	Protocol A: FSH $>$ 300 IU/d (<i>n</i> 65 cycles)	Protocol B: Corifollitropin alfa + hMG (<i>n</i> 65 cycles)	<i>p</i> value
Cycle cancellation rate: <i>n</i> (%)	26 (40)	7 (11)	$<$ 0.001
Stimulation duration (days): mean \pm SD	8.89 \pm 1.9	9.7 \pm 1.62	0.05
E2 day of hCG (pg/ml): mean \pm SD	1546 \pm 739.9	1360 \pm 644.5	0.19
Cycles with oocytes retrieval: <i>n</i> (%)	39 (60)	58 (89)	0.003
Total number of oocytes: mean \pm SD	8 \pm 3.22	8.96 \pm 4.49	0.21
Metaphase II oocytes: mean \pm SD	6.39 \pm 3.27	7.09 \pm 3.67	0.35
Fertilization rate in ICSI: % \pm SD	39% \pm 21	57% \pm 27	0.008
Fertilization rate in IVF: % \pm SD	48% \pm 27	65% \pm 28	0.09
Number of cleaved embryos on day 3: mean \pm SD	3.1 \pm 2.3	4.16 \pm 2.5	0.04
Blastocysts obtained: mean \pm SD	1.1 \pm 1.53	1.5 \pm 1.86	0.27
Cycles with embryo transfer: <i>n</i> (%)	15 (38)	40 (69)	0.004
Number of embryos per transfer: mean \pm SD	1.2 \pm 0.41	1.38 \pm 0.48	0.23
Cycles with frozen embryos: <i>n</i> (%)	10 (26)	14 (24)	0.99
Single blastocyst transfer: <i>n</i> (%)	12 (80)	25 (62.5)	0.07

Results are presented as proportion or mean \pm standard deviation (SD). (*n* number; E2 oestradiol; hCG human chorionic gonadotrophin).

ovarian response to COS, as the proportion of cancelled cycle is significantly lower than with rFSH protocol. Although study design did not allow comparing clinical outcome between both regimens, clinical pregnancy rate was promising after corifollitropin alfa + hp-HMG protocol. Very few studies are available in the literature on the interest of corifollitropin alfa in poor responders. While Polyzos, DeVos, Vorona, et al. (2013) reported a 41% positive hCG test per embryo transfer in the pilot study of their COMPORT trial and a 14.3% ongoing pregnancy rate at the end of the trial (Drakopoulos et al., 2017), Kolibianakis et al. (2015) reported a 15.8% positive hCG test with a 7.9% clinical pregnancy rate per patient reaching oocyte retrieval and a 20.7% positive hCG test with a 10.4% clinical pregnancy rate per embryo transfer. The heterogeneity between these studies and ours prevents from drawing firm conclusions, but our preliminary results appear to be promising in poor responders. However, and contrary to the results of Drakopoulos et al. (2017) in the COMPORT trial, we did not find an increased number of frozen embryos with corifollitropin alfa + hp-HMG. Our study population might not be large enough to highlight significant differences.

The specific pharmacokinetic characteristics of corifollitropin alfa might participate in its apparent clinical interest in poor responders. Indeed, this molecule reaches maximum serum concentration between 25 and 45 hours after injection (Devroey et al., 2009; Fauser et al., 2009). This period is significantly shorter than with daily rFSH injections and leads to a faster and higher exposure of small antral follicles to high and stable FSH serum levels during early follicular phase. A more homogeneous follicular recruitment and a continued growth resulting in a better oocyte yield in women with poor ovarian response could thus be expected (Polyzos, DeVos, Corona, et al., 2013) than with daily injections of high dose FSH, this strategy being reported to be ineffective (Baker, Brown, Luke, Smith, & Ireland, 2015; Dercourt et al., 2016; Haas, Zilberberg, Kedem, Dar, & Orvieto, 2015) or even suspected to be deleterious for oocytes quality (Baart et al., 2007; Sekhon et al., 2017).

The mechanisms underlying poor ovarian response to COS still remain poorly understood. A lack of androgens and/or LH activity has been particularly evoked as one of the main factors affecting granulosa cells' physiology and folliculogenesis, as described in the classic 'two cell-two gonadotropins' theory. The hypothesis that action of LH at the follicular level, increasing androgen production for its later aromatization to oestrogens in a dose-dependent manner, to

restore the follicular fluid and thereby improves oocyte quality, was proposed by the group of Bosch et al. (2011). Based on this physiopathological concept, several studies have evoked the interest of supplementation in LH activity during antagonist protocol, particularly for women older than 35 years old or women with poor ovarian response, who might lack androgen secretion (Bosch, Labarta, Kolibianakis, Rosen, & Meldrum, 2016). However, some authors highlighted the need for an optimal level of LH action on the follicle through which the oocyte achieves adequate maturation and maximal competences (Bosch et al., 2016). Consequently, we chose a relatively low dose of hp-hMG (75 UI/d) in order to enhance follicular maturation and to avoid any deleterious effects on oocyte quality.

Even if the concept is scientifically seducing, some well conducted randomized trials did not find any benefit of adding LH activity in women >35 years old undergoing antagonist protocol (Vuong, Phung, & Ho, 2015) or even agonist protocol (Humaidan et al., 2017). As well, a recent Cochrane review including 36 randomized controlled trials, among which 11 compared GnRH antagonist regimens, concluded that the evidence is insufficient to encourage or discourage stimulation regimens combining rLH and rFSH (Mochtar, Danhof, Ayeleke, Van der Veen, & van Wely, 2017). However, LH substitution was initiated in the mid-follicular phase at the same time as the GnRH antagonist in most studies (König et al., 2013; Younis, Izhaki, & Ben-Ami, 2014). This is the reason why we proposed to evaluate the benefit of such a substitution from the beginning of the stimulation.

According to our results, the addition of hp-HMG to FSH activity for ovarian stimulation does not seem to be at risk of side effects in poor responders. Indeed, only 1 out of 65 patients treated with corifollitropin + hp-HMG had premature progesterone elevation (>1.5 ng/ml) on hCG day, leading to a freeze all cycle, versus 3 with the high dose rFSH protocol. Moreover, no case of OHSS was observed with both groups, as expected in a population of poor responders.

We acknowledge that adding daily hp-HMG injections from the beginning of the stimulation to corifollitropin injection could be considered as a step back in terms of patients' comfort, as it eliminates the main advantages of corifollitropin of lowering the number of injections during stimulation. Although patients have not been specifically questioned about this, we can speculate that adding some daily injections during the first week of stimulation could be acceptable if a significant improvement of the clinical outcome was

confirmed. One-strength of the current study is its case-control design, in which each patient was their own control, our study suffers from the inherent bias of retrospective studies, and these promising results should obviously be confirmed in larger population and in randomized studies. We also acknowledge that our population is limited, exposing to a theoretical risk of bias. However, this work was a pilot study, and was conducted in a specific subgroup of patients.

In conclusion, Corifollitropin alfa remains an interesting and safe therapeutic alternative for ovarian stimulation in poor responders. The addition of hp-HMG to corifollitropin alfa during the whole stimulation seems to improve ovarian response. However, larger randomized trials are necessary to assess the real benefit of this protocol on reproductive outcomes.

Disclosure statement

No potential conflict of interest was reported by the authors.

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