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Short Communication

The Use of Corifollitropin Alfa in Combination with a GnRH Analogue as Final Trigger in the Potential High Responders

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Abstract

Background: A great concern exists in using corifollitropin alfa to induce ovarian stimulation in high responders due to the riskof OHSS.In this study, we utilized corifollitropin alfa in patients with the potential of being high responders, in addition to the GnRH analogue triptorelin, as final trigger to induce the oocyte maturation. An intensive luteal support was administered to allow the transfer in the same cycle.

Patients and methods: Between January 2013 and September 2014, 35 patients were stimulated with corifollitropin alfa and underwent in vitro fertilization or intracytoplasmic sperm injection procedures. All women had levels of antimullerian hormone>3 ng/ml and antral follicle count >10 and <20. The patients with polycystic ovarian syndrome were excluded from the study.

Results: The mean number of oocytes collected was 13.95 ± 6.04, the mean number of oocytes inseminated was 5.11 ± 1.66, the mean number of embryos obtained and transferred was 3.13 ±1.61 and 2.11 ± 0.92, respectively. All patients received a fresh embryo transfer,and the luteal phase was intensively supported by triptorelin and progesterone.A part of oocytes (2.47 ± 4.28) and blastocysts (0.39 ± 0.75) was vitrified.The clinical pregnancy was achieved in 15 patients and the ongoing pregnancy in11 women. Cumulative ongoing pregnancy rate, including the pregnancies achieved after thawing of eggs or embryos, was 39.47%. No OHSS were observed.

Conclusions: Corifollitropin alfa plus triptorelin trigger elicits a safe ovarian stimulation in the potential high responderpatients.

Keywords: Corifollitropin; Triptorelin; GnRHa trigger; Intensive luteal support; High responders

Introduction

The long-acting fertility hormone corifollitropin alfa is a recombinant fusion protein composed of thefollicle stimulating hormone (FSH) and the carboxy terminal peptide of the hCG α-subunit [1,2]. This molecule has a two-fold longer half-life than recombinant human FSH and four-fold extended time-interval to peak serum levels [3]. These pharmacokinetic characteristics allow sustained follicle stimulation with the same pharmacodynamic activity as rFSH. Consequently, a single subcutaneous injection of corifollitropin alfa is sufficient to induce and maintain the follicular growth up to a week, replacing seven daily gonadotropin injections during the first week of ovarian stimulation. The main advantage of corifollitropin alfa administration is the improvement of drug compliance, more over both physical and psychological burden associated with IVF treatments drop out [4].

Corifollitropin alfa has been developed in a GnRH antagonist protocol and is usually administered in normal responders [5-7]. The recommended doses are 100 µg for patients with body weight <60 kg and 150 µg for patients with body weight >60 kg [8]. The choice of a GnRH antagonist protocol enables to decrease the risk of ovarian hyper stimulation syndrome (OHSS). Likewise, itallows the option of triggering ovulation with a GnRH analogue which in turn further lowers the risk of OHSS.

In the present study, we decided to use corifollitropin alfa in combination with triptorelin to trigger ovulation in the potential high responder patients, irrespective of the risk of OHSS. A part of oocytes and embryos was frozen, but all patients received a fresh embryo transfer which had been followed by an intensive luteal support with triptorelin 0.1 mg, every other day starting from the day of transfer, for a total dose of five injections.

Patients and Methods

The patients with levels of antimullerian hormone (AMH) >3 ng/ml and antral follicle count (AFC) from 10 to 20 were included in this study. Women with polycystic ovarian syndrome (PCOS), defined by the Thessaloniki ESHRE/ASRM-sponsored PCOS Consensus Workshop Group [9], were excluded from the treatment,as well as the patients with body mass index (BMI) >30 kg/m^{2}and diabetes or thyroid dysfunctions. Severe male factor (criptozoospermia or azoospermia) was an additional exclusion criteria.

Between January 2013 and September 2014, 35 women with a mean age of 35.05 ± 2.86 years were stimulated with corifollitropin alfa (Elonva), 100 µg or 150 µg according to their body weight, the first day of the treatment cycle. Six days later, a GnRH antagonist was administered at a daily dosage of 0.25 mg until the day of ovulation triggering. All patients received triptorelin acetate 0.2 mg (Decapeptyl) as trigger. Ovum pick-up (OPU) was performed 36 hours later, and fertilization was determined by the presence of two pronuclei on the

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first day after insemination.

Luteal phase was supportedby triptorelin 0.1 mg, one injection every other day from the embryo transfer, for a total of five injections. Additionally, 600 mg/day of micronized progesterone (Progeffik 200 mg, 3 cps/die) was started from the day of oocyte retrieval. A quantitative pregnancy test, done by dosing serum β-hCG, was performed 12 days after ovulation triggering with triptorelin and it was repeated 2 days later. In the presence of pregnancy, a transvaginal ultrasound was performed 28–32 days after the embryo transfer and repeated as required. Clinical pregnancy was confirmed if a fetal heartbeat was observed by transvaginal ultrasound.

Results

Characteristics of ovarian stimulation and IVF/ICSI parameters are described in Table 1. Despite the patients included in this study had a high follicular response (14 women had over 15 oocytes retrieved), the ovarian stimulation protocol allowed to obtain a good fertilization rate and top- and good-quality embryos.

Our results show that, in this group ofthe potential high responder patients, 15 clinical pregnancies and 11 ongoing pregnancies were achieved per fresh cycle (Table 2). The cumulative ongoing pregnancy rate reached 39.47%, including 4 ongoing pregnancies which were obtained after the transfer of frozen-thawed oocyte (in one patient) and blastocysts (in three patients). Some of the pregnancies have already delivered the birth of a healthy baby. All patients reported good compliance with corifollitropin alfa treatment. The drug was well tolerated by all women, and no patient had suspended the treatment cycle due to the risk of OHSS, as well as no late OHSS occurred.

Discussion

To our knowledge, the results of this study represent the first evidence of corifollitropin alfa administration in the potential high responder women. Our data highlight that the combination of corifollitropin alfa with a GnRH analogue as ovulation trigger can yield a regular number of oocytes and good quality embryos, as well as high pregnancy rates and healthy live births. Furthermore, corifollitropin alfa has a favorable safety profile in this group of patients; neither a cycle was cancelled due to high ovarian response, orlate-onsetOHSS developed.

No. of patients	35
No. of IVF/ICSI cycles	38
No. of patients without further FSH injections	13
Total dose of gonadotropins (IU)	676.61 ± 538.05
Duration of stimulation (days)	9.92 ± 2.20
E2 on trigger day (pg/ml)	2229,61 ± 1092,44
P on trigger day (pg/ml)	1.14 ± 0.49
Endometrial thickness on trigger day (mm)	9.87 ± 2.18
Number of oocytes retrieved	13.95 ± 6.04
Number of MII oocytes	8.97 ± 5.45
Number of inseminated oocytes	5.11 ± 1,66
Number of fertilized oocytes	3.89 ± 1.89
Number of embryo obtained	3.13 ± 1.61
Number of top quality embryos (grade 1)	2.27 ± 0.46
Number of good quality embryos (grade 1 + 2)	2.55 ± 0.52
Number of embryos transferred	2.11 ± 0.92

Table 1: Characteristics of ovarian stimulation (Data are mean ± standard deviation).

Fertilization rate (%)	76.29
Implantation rate (%)	16.25
Clinical pregnancy rate (%)	39.47
Ongoing pregnancy rate (%)	28.97
Cumulative ongoing pregnancy rate (%)	39.47
Number of OHSS	0

The values of clinical and ongoing pregnancy rates had been reported as the ratio of the number of pregnancies and the number of IVF/ICSI cycles.

Table 2: Clinical outcomes in high responder patients.

Interestingly, the choice of this treatment protocol, which excludes any hCG administration, allows to obtain both a luteal benefit and the lowering of the risk of OHSS. This approach offers an attractive new treatment option for patients with the potential high ovarian response. Moreover, this treatment consents to perform fresh embryo transfer leading to the live birth of a healthy child.

The risk of OHSS is the main boundary of IVF treatment cycles. In women with the potential of being high responders, the use of GnRH antagonist protocol can reduce the degree of ovarian stimulation [10]. Likewise, the option of triggering final oocyte maturation with a GnRH agonist,as an alternative to human chorionic gonadotropin (hCG), further lowers an excessive ovarian response [11,12]. Corifollitropin alfa may induce and sustain the follicular growth for an entire week leading to maximal ovarian response; therefore it should not be indicated in women with the potential of being hyper-responders [13]. Although, no higher risk of OHSS has been demonstrated with the use of corifollitropin alfa [14]. To date, all published clinical trials have recruited normal responder patients excluding women with PCOS and high responders [5-8].

The patients included in our study were considered at risk of an excessive ovarian response on the basis of high serum levels of AMH. High basal concentrations of AMH have been associated with hyper-response to gonadotropin stimulation [15]. Moreover, AMH has been identified as one of the best predictor of ovarian response in women undergoing ovarian stimulation with corifollitropin alfa in a GnRH antagonist protocol [16]. There is evidence that the type of gonadotropin may affect certain patients such as women at high risk of hyper-response or with PCOS [15,17].

Our results indicate that the IVF protocol utilized is effective in terms of both clinical procedures and embryological parameters. The number of oocytes retrieved was regular as well as the maturity of the cells and the fertilization rate, suggesting the suitability of ovarian stimulation and ovulation induction. Furthermore, the luteal phase support with triptorelin after GnRHa triggering is not detrimental for IVF outcomes as revealed bypregnancy rates. The use of triptorelin as luteal support allows sustaining constantly small flares of endogenous pituitary gonadotropins which can stimulate and recover the function of corpora lutea [18]. At the same time, the aggressive luteal support with triptorelin appears to have a direct effect on endometrium and embryo by acting on a placental GnRH receptor [19].

In the group of patients included in our study, the choice of an intensive luteal support with progesterone plus triptorelin, instead of estrogens [20] or hCG [21], produced good effects.Our results are in line with previous data which demonstrated that repeated dose of a GnRH agonist during luteal phase recover the luteal phase deficiencyand is compatible with normal implantation and pregnancy evolution [22]. We also observed that three patients achieved pregnancy after the implantation of frozen-thawed blastocyst, and one patient achieved pregnancy after the transfer of vitrified oocytes, enhancing the pregnancy rate per stimulation.

We conclude that the use of corifollitropin alfa in combination with triptorelin as trigger is a safe treatment option in the potential high

responders. It allows both the "freezing all" and the intensive luteal support with progesterone and triptorelin without reducing the clinical outcomes.

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