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Should corifollitropin alfa be offered to patients with "genuine" poor response to controlled ovarian hyperstimulation?

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Summary

Objective: To examine whether poor ovarian response (POR) patients during conventional IVF/ intracytoplasmic sperm injection (ICSI) cycle, may benefit from multiple-dose GnRH-antagonist protocol with 150 mg of corifollitropin alfa via a cohort historical study. at a Tertiary, University affiliated Medical Center. *Materials and Methods:* Eighteen POR patients, defined according to the Bologna criteria, who underwent a subsequent 150 mg corifollitropin alfa cycle, within three months of the previous failed conventional IVF/ICSI cycle were included. The elimination of bias in this selection, for the purposes of this study, was achieved by including only a subgroup of "genuine" poor responder patients, those who yielded up to three oocytes following COH with a minimal gonadotropin daily dose of 300 IU. One hundred fifty mg corifollitropin alfa, administered on day 2-3 of the menstrual cycle, followed highly purified human menotropin (HP-hMG) or rFSH + rLH from stimulation day 5-6, within a flexible multiple-dose GnRH-antagonist COH cycle. Pregnancy rate, number of oocytes retrieved, number of embryos transferred, and COH variables were assessed. *Results:* The corifollitropin alfa COH protocol provided a non-significant one more oocyte, with no pregnancies. Considering the equivalence of 150 mg corifollitropin alfa to 2,100 IU of FSH, offering corifollitropin has no cost-effective advantages. *Discussion:* The corifollitropin alfa COH is of no benefit for "genuine" POR and alternative strategies, such as increasing the daily FSH dose or proceeding to egg-donation, should be seriously considered for this population.

Key words: Poor responders; COH; Bologna criteria; Corifollitropin-alfa.

Introduction

Controlled ovarian hyperstimulation (COH) is considered a key factor in the success of in vitro fertilization-embryo transfer (IVF-ET), enabling the recruitment of multiple oocytes and, thereby, multiple, instead of single-ET [1]. However, owing to the extreme variability in ovarian response to COH, in a subgroup of patients, who are collectively referred to as "poor- responders" or "low responders", this method may yield a very small number of follicles, if any [2]. Moreover, until 2011, there was no one single acceptable definition, though the most widely used indicator was a decreased/poor response to COH, which in IVF cycles may be related to the number of oocytes retrieved. The recognition of the controversies surrounding the diagnostic criteria of patients with poor ovarian response (POR) has led to the ESHRE consensus on the definition of 'poor response' to ovarian stimulation for IVF (the Bologna criteria). According to the Bologna criteria, the minimal criteria needed to define POR are the presence of at least two of the following three features (1) Advanced maternal age (≥ 40 years) or any other risk factor for POR, (2) A previous POR (≤ 3 oocytes with a conventional stimulation protocol), and (3) an abnormal ovarian reserve test [3]

Many strategies are offered for the treatment of patients with poor ovarian response (POR) to COH, including the use of gonadotropin-releasing hormone-antagonist (GnRH-ant), reducing or stopping the dose of GnRH-agonist (GnRH-ag), the ultrashort, short and microdose GnRH-ag "flare" protocols), the combined ultrashort GnRH-ag with the multiple GnRH-ant, the administration of letrozole, the modified natural-IVF cycle [2, 4-7, 8] or the use of different type and doses of gonadotropin preparations [9-10]. Nevertheless, no compelling advantage for one stimulation protocol over another has been hitherto established.

Corifollitropin alfa or FSH-CTP, is a long-acting FSH that following a single-dose is able to initiate and maintain follicular growth during the first seven days of COH [11]. It was found to be equally effective compared to daily FSH in women with unexplained subfertility. However, its role in hyper- or poor responders women should be elucidated in further research [11]. Recently, corifollitropin alfa was offered to poor responder patients with promising, comparable results [12-15]. Of notice, in these studies, poor re-

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sponder patients were defined according to the Bologna [12, 13, 15], or a modification of Bologna criterias [14], and the control group received different doses of daily gonadotropins, ranging from 225 IU [15] to 450 [14].

Moreover, a recently published company sponsored randomized clinical trial (PURSUE study) [16], compared the efficacy and safety of a single injection of 150 mg of corifollitropin alfa to daily 300 IU of recombinant FSH for COH in women aged 35 to 42 years. The PURSUE study demonstrated that a single injection of corifollitropin alfa effectively replaced the first seven daily injections of recombinant FSH (300 IU/day), with no differences in vital pregnancy rate and the number of oocytes retrieved.

In the Chaim Sheba Medical Center, since 2014, 150 mg of corifollitropin alfa has been offered to poor responder patients. Prompted by the aforementioned observations, the present authors sought to examine whether POR patients during conventional IVF/ intracytoplasmic sperm injection (ICSI) cycle, may benefit from 150 mg of corifollitropin alfa. Moreover, due to the possible different phenotypes of POR, according to the Bologna criteria, they elected to concentrate on the "genuine" POR patients, defined as those who yielded less than four oocytes in response to conventional COH of at least 300 IU FSH per day. This will aid both fertility specialists' counseling and their patients in adjusting the appropriate treatment strategy for patients with POR.

Materials and Methods

The authors reviewed the computerized files of all consecutive women admitted to their IVF unit, at the Chaim Sheba Medical Center, Israel, during a three-year period. Only poor responder patients during conventional multiple-dose GnRH-antagonist IVF/ICSI cycles, defined according to the Bologna criteria [3], who underwent a subsequent COH, using the multiple-dose GnRH-antagonist protocols with 150 mg of corifollitropin alfa, within three months of the previous *failed* conventional IVF/ICSI cycle, were included. The elimination of bias in this selection, for the purposes of this study, was achieved by including only a subgroup of "genuine" poor responder patients, those who fulfilled two out of three bologna criteria, and also yielded up to three oocytes following COH with a minimal gonadotropin daily dose of 300 IU. The study was approved by our institutional review board (IRB).

In the conventional COH, gonadotropins were started on day 2-3 of the menstrual cycle (corresponding to stimulation day 1) in variable doses (with a minimal daily those of 300 IU), depending on patient age and/or ovarian responsiveness in previous cycles, and further adjusted according to serum E2 levels and vaginal ultrasound measurements of follicular diameter obtained every two or three days. GnRH-antagonist treatment (0.25 mg/day) was begun when a follicle of 13 mm was present.

In the corifollitropin alfa protocol, 150 mg corifollitropin alfa was administered on day 2-3 of the menstrual cycle (corresponding to stimulation day 1). Serum E2 levels and vaginal ultrasound measurements were determined on day 5-6 of stimulation, and if no substantial response was observed, highly purified human menotropin (HP-hMG) or rFSH + rLH >300 IU/ day, were added. GnRH-antagonist treatment (0.25 mg/day) was begun when a follicle of 13 mm was present. In both groups, final oocyte maturation was triggered by 250 mg of recombinant hCG. Routine IVF or ICSI was performed, as appropriate. All patients received luteal support with progesterone.

Embryos classification was based on the individual embryo scoring parameters according to pre-established definitions [17]. While a top quality embryo (TQE) was defined as three or more blastomeres on day 2 and seven or more blastomeres on day 3, equally-sized blastomeres and < 20% fragmentation, poor quality embryos consisted of all the remaining.

Data on patient age and infertility-treatment-related variables were collected from the files. Ovarian stimulation characteristics, cancellation rates, amount of FSH required to COH, number of days with FSH injections, day 5-6 and peak estradiol levels (on the day of hCG administration), number of retrieved oocytes, number of embryos transferred, and fertilization and pregnancy rates were assessed and compared between the previous conventional (conventional roup) and the corifollitropin alfa (corifollitropin group) IVF/ICSI cycles.

Results are presented as means ± standard deviations. Differences in variables were statistically analyzed by Student's paired *t*-test, Fisher's exact test and chi-square test, as appropriate. A p value of less than 0.05 was considered significant.

Results

Eighteen "genuine" poor responder patients (age 41.8 ± 2.2 years) during a conventional IVF/ICSI cycle, who underwent a subsequent corifollitropin alfa cycle, were evaluated.

When comparing the COH variable during the conventional IVF/ICSI cycles preceding the corifollitropin alfa cycle to the corifollitropin alfa cycles, there were no in-between group differences in the duration of stimulation, estradiol level at day 5-6 of stimulation, nor day of hCG administration. The number of days with FSH injections (7.2 + 3.6 *vs.* 10.7 + 2.7, respectively; $p < 0.01$) and the total dose of FSH administered were significantly lower (2,516 + 2,049 *vs.* 4,891 + 2127, respectively; $p < 0.01$) in the corifollitropin alfa-group (Table 1), as compared to the conventional- group. Moreover, the average Δ-dose of FSH used was 2,230 ± 2,723 IU more, in the conventional cycle. However, when adding the equivalent dose of 150 mg corifollitropin alfa (300 IU multiple by 7 days=2,100 IU), to the total FSH dose administered during the corifollitropin alfa cycle, no significant difference was observed between the conventional and corifollitropin-groups (4,891 *vs.* 4,616 IU, respectively).

The endometrial thickness and the number of follicles >14 mm in diameter on day of hCG administration were also comparable (Table 1). Moreover, while a non-significant trend toward a higher number of oocytes retrieved was observed in the corifollitropin alfa-group (2.6 + 2.0 *vs.* 1.4 + 0.8, respectively; $p < 0.055$) (Table 1), as compared to the conventional group, the fertilization rate, the number of top-quality embryos, and the number of embryo transferred were not statistically different.

As expected from the inclusion criteria, no patients conceived following the previous conventional IVF/ICSI cycles. However, none conceived also during the subsequent corifollitropin cycles (Table 1).

Table 1. — *COH variables during the conventional IVF/ICSI cycles and the subsequent corifollitropin alfa cycles.*

	Conventional - COH (1st cycle)	Elonva - COH (2nd cycle)	*p*-value
Number of cycles	19	19	
Age of patients (years)	42.0 ± 2.3	42.1±2.4	< 0.05
Day 3 FSH levels (IU/L)	9.75 ± 2.0		ns
Duration of stimulation (days)	10.7 ± 2.6	11.5 ±3.4	ns
Number of days with FSH injection	10.7 ± 2.6	7.5 ±3.6	< 0.05
Average total dose of FSH used (w/o Elonva) (IU)	4,803 ± 2,102	2573 ±2007	< 0.01
Average total dose of FSH used (considering Elonva) (IU)	4,803	4,673	ns
E2 on stimulation day 5 (pmol/L)	640 ± 826	636 ±373	ns
ΔE2 (day5-day1) (pmol/L)	777 ± 835	500 ±584	ns
E2 on day HCG administration (pmol/L)	2311 ± 1447	2,489 ±1,666	ns
Progesterone on HCG day (nmol/L)	2.1 ± 3.5	1.6 ±0.8	ns
Endometrial thickness on HCG day (mm)	8.8 ± 2.0	9.0 ±2.7	ns
Number of follicle >14mm at HCG day	1.8 ± 1.0	2.7 ±1.6	ns
Mean number of retrieved oocytes	1.5 ± 0.7	2.8 ±2.1	< 0.04
Mean number of 2PN	0.6 ± 0.7	1.7 ±2.0	ns
Fertilization rate (%)	45.4 ± 47.2	47.2 ±42.0	ns
Number of cycle resulting with no oocyte at OPU (% of all cycles)	2 (10.5%)	3 (15.8%)	ns
Number of top-quality embryos	0.5 ± 0.7	0.9 ±1.3	ns
Number of embryo transferred	0.6. ± 0.6	1.2 ±1.2	ns
No. of cycle resulting in embryo transfer (% of all cycles)	10 (52.6%)	12 (63.1%)	ns
Clinical pregnancy rate per cycle. (No. of cases)	0	0	ns

Table 2. — *Summary of the patient's IVF cycles.*

Cycle#	COH protocol	Peak E2 (pmol/L)	# of oocytes retrieved	# of 2PN	# of ET
	FSH/hMG				
1	GnRH-antagonist	573	1	1	0
2	GnRH- antagonist	1376	4	3	2
3	Short GnRH-ag	11578	1	1	1
4	GnRH- antagonist	1440	2	1	1
	Corifollitropin alfa				
5	GnRH- antagonist	2004	5	5	3
6	GnRH- antagonist	625	Cancelled: no response		
7	GnRH- antagonist	893	2	1	1

Discussion

In the present cohort historical study of "genuine" POR patients, according to the Bologna criteria, who achieved three or less oocytes following COH with conventional IVF/ICSI, the corifollitropin alfa COH protocol provided a trend toward one more oocyte retrieved, required a significantly lower number of FSH injections (three days), however, with no pregnancies. Moreover, considering the equivalence of 150 mg corifollitropin alfa to 2,100 IU of FSH [16], offering corifollitropin has no cost-effective advantages and an alternative strategy, such as increasing the daily FSH dose [9] or proceeding to egg-donation, would be probably the preferred approach.

The additional oocyte retrieved is probably not a consequence of the addition of corifollitropin alfa, but from the well-known patient's physiological inter-cycle variability in AFC [18]. It was already shown that 10.2-12.5% of patients may switch from low or high to normal response in their subsequent cycles, as was also demonstrated among the present patients. A summary of one of the patient is IVF treatments presented in Table 2. The patient's oocytes yield varied between 1 to 4 and 0 to 5, without and with corifollitropin alfa, respectively, demonstrating the inter-cycle variability, which is unrelated to the use of corifollitropin.

This outcome is in agreement with Polyzos *et al.* [13], who treated poor responder patients, according to the Bologna criteria, with corifollitropin alfa followed by daily fixed dose of 300 IU of HP-hMG, from day 9 of the cycle, in a GnRH antagonist protocol. In this study, no-single pregnancy was achieved in patients who were ≥ 40 years of age [13].

In a different study by Kolibianakis *et al.* [14], they have prospectively compared the use of a single s.c. dose of 150 mg corifollitropin alfa on the first day of ovarian stimulation, followed if necessary, from day 8 onwards, with 450 IU of daily follitropin beta, in poor responder patients, defined as those with previous retrieval of ≤ 4 COCs in a previous IVF cycle. In this group of *non-"genuine"* poor responder patients, by using a higher daily FSH dose (450

IU), they could not demonstrate any statistical differences in the number of COCs retrieved or the probability of live birth between the corifollitropin alfa and the follitropin beta group.

In the present authors' previous observation in this subgroup of "genuine" poor responders, the authors could demonstrate that in their subsequent IVF cycle, using conventional COH, clinical pregnancy was observed in 4% [8]. Moreover, according to a recently published study by the authors' group, the reported live birth rates per cycle for poor responder patients using daily gonadotropin dose of 450 IU resulted in 7.7% [9], figures, in accordance to those of Kolibianakis *et al.* [14], reflecting a reasonable IVF outcome in this frustrating group of "genuine" poor responders.

A limitation of ther present analysis is its retrospective design and the small sample size. However, based on the present patients' selection process, only consecutive patients fulfilling the inclusion criteria were enrolled, which considerably decreases the likelihood of selection bias. In addition, corifollitropin IVF outcomes were compared to the previous COH-IVF of the same patients, this method may eliminate any matching hurdles.

The present authors chose to focus on a specific population among all poor responders (according to Bologna criteria) with three or less oocytes following conventional COH for IVF with high daily dose gonadotropins (> 300 IU), because these patients are the most challenging patients. Since no benefit was demonstrated in this specific subgroup of poor responders, corifollitropin- alfa should not be offered to this subgroup of "genuine" poor responders and the option of a conventional COH-IVF with higher daily FSH dose (450 IU), or egg donation should at this pointbe seriously considered .

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