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Luteal start of exogenous FSH in poor responder women

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Abstract
Purpose To compare the effectiveness of using recFSH commenced in the luteal phase with a long GnRH agonist protocol or in the early follicular phase with a short GnRH agonist protocol, in infertile women designated as poor responders undergoing treatment with assisted reproduction in a prospective, randomized, controlled study.
Materials and methods Forty-two couples undergoing an ICSI cycle of whom female partner diagnosed as poor responder were included in the study. Recombinant FSH was given daily from day 21 of the previous cycle upon initiation of GnRH agonist in the study group. Control group was given FSH on day 2 in a short protocol GnRH agonist regimen. The number of metaphase 2 oocytes was analysed as the main outcome measure; pregnancy rate and clinical pregnancy rate were secondary outcome measures.
Results Patients in the study group had significantly higher number of metaphase 2 oocytes. Although not statistically significantly patients in the study group had higher pregnancy/clinical pregnancy rates, as well.
Conclusion This preliminary study shows that luteal start of recFSH simultaneously with long protocol GnRH agonist in poor responder women produced better results comparing to short protocol GnRH agonist plus high dose FSH regimen.

Keywords FSH · Luteal phase · Long protocol GnRH agonist

Capsule: Luteal administration of recFSH along with GnRHa in poor responder women in an ART cycle increases metaphase 2 oocyte number significantly comparing to GnRHa flare-up protocol

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Introduction

Poor response to exogenous gonadotrophins in assisted reproduction cycles is still a problem waiting to be overcome. Although this situation is regarded to be associated with aging, there are many young cases, as well [1]. Whatever the etiology or the underlying mechanism is the result is low follicular recruitment resulting in low number of oocytes retrieved. In assisted reproduction cycles, exogenous FSH is started with the commencing menstruation to widen the so-called "window" as an effort to increase the number of follicles recruited [2].

Physiologically, the follicular recruitment starts in the late luteal phase of the preceding cycle, while the steroidogenesis of corpus luteum weakens. This is called luteo-follicular shift and that decrease in progesterone synthesis results in diminished negative-feedback on pituitary. FSH starts to rise in a reciprocal manner. This FSH rise recruits some of the follicles undergoing atresia and induce the new cohort for the coming cycle [3]. The most fundamental intervention to increase the follicular cohort might be started in this particular phase of the cycle.

GnRH agonist induced pituitary suppression is an inherent part of controlled ovarian hyperstimulation in assisted reproduction cycles since early 1990s. Long-protocol application of GnRH agonists employs the start of any agonistic drug on day 21 of preceding cycle. In a Cochrane meta-analysis comparing long protocol GnRH

regime to short protocol clearly identified the superiority of long protocol in patients other than poor responders [4]. One of the reasons of this superiority can be starting of GnRH agonist on day 21 of preceding cycle when the follicular recruitment for the next cycle is in process. This aforism is reflected and supported by the increase of the number of oocytes in long protocol cycles.

We hypothesized that augmentation of this FSH rise with exogenous FSH preparations could have an improving effect in poor responder women. In order to test this we conducted the current study in poor responder women.

Materials and methods

We designed a prospective, randomized, controlled study. The inclusion criteria for the study were female factor infertility, baseline FSH level less than 15 IU/l, less than four oocytes in previous ICSI cycle and no other medical condition. We included only the cases which previous controlled ovarian hyperstimulation (COH) was operated by the first author; by this we made sure that previous COH was adequate, but this criteria caused limitation of number of cases. Male factor cases were excluded from the study; this further limited the number of cases but purified the patient cohort. Randomization was done by predetermined application order. Applicants with an odd number were allocated to the study group, while applicants with an even number were allocated to the control group. The reason for selecting this approach was the ease of the method and was the random application of the patients. About 21 patients were randomized to the study group while other 21 patients constituted the control group. All patients signed an informed consent.

The study group was given long protocol triptorelin 0.1 mg (Decapeptyl, Ferring, Switzerland), on day 21 of preceding cycle. Along with triptorelin, 150 IU recombinant FSH (Gonal-F, Serono, Switzerland) was given daily from day 21. On the second day of menstruation, triptorelin was halved to 0.05 mg and the recFSH was increased to 450 IU.

The control group was given a flare-up regimen of triptorelin starting on the second day of menstruation. Along with triptorelin, 450 IU recFSH was started. Controlled ovarian hyperstimulation was continued with individualized dosages. When at least two follicles reached 18 mm 0.25 mg recHCG (Ovitrelle, Serono, Switzerland) was given. Oocyte retrievals were performed 34–36 h later. Oocyte and sperm preparations were made in the same center and all ICSI procedures were done by the same technician (ES). The reason for using ICSI was a try to avoid total fertilization failure. All embryo transfers were done under sonographic guidance on the second day due to the low number of transferrable embryos and to the embryo transfer policy in repeated cycles in the country.

Because the women were poor responders the main outcome measure was the number of metaphase 2 oocytes retrieved. Pregnancy rate as defined by a positive pregnancy test on day 14 after embryo transfer and clinical pregnancy rate as defined by the presence of a gestational sac in the fifth week on transvaginal sonography were the secondary outcome measures.

Statistical analysis

To compare the differences between two groups we used Mann–Whitney *U* test and Fisher Exact Test. Analyses were performed using the SPSS 11.0 package (SPSS Inc., USA).

Results

The baseline characteristics of the patients included in the study are given in Table 1. There was no significant difference between the study and the control group.

There were two cancellations in the control group, 19 patients proceeded to oocyte retrieval. The reason for cancellation was low response to gonadotropin treatment on the seventh day of the controlled ovarian hyperstimulation indicated by less than three follicular growth. There was no cancellation in the study group, all 21 patients proceeded to oocyte retrieval. Table 2 summarizes the outcome of the treatment cycles.

Table 1 Baseline characteristics

Characteristic	Study group (n=21	Control group (n=21)	P value[a]
Mean age (years)	36.5	33.1	0.721 (NS)
Mean BMI (kg/m^2)	25.3	24.1	0.689 (NS)
Mean no. of previous cycles	3.2	2.3	0.089 (NS)
Day 3 FSH (IU/L)	8.4	7.1	0.121 (NS)

BMI Body mass index; *NS* not significant
[a] Comparison was made by using Mann–Whitney *U* test

Table 2 Outcomes

Characteristic	Study group (n=21)	Control group (n=21)	P value
Days of FSH (mean)	17 (16.3–17.7)	11 (10.4–11.6)	<0.05[a]
Total recFSH (mean)(IU)	4,140 (3,600–4,580)	2,980 (2,660–3,300)	<0.005[a]
RecFSH dose from day 2 to day hCG (mean9 (IU)	3,040 (2,700–3,340)	2,980 (2,720–3,240)	NS[a]
Mean no. of M2 oocytes	6.8 (5.4–8.2)	3.8 (1.4–6.2)	<0.05[a]
Mean no. of embryos transferred	2.7 (1.5–4.9)	1.9 (1–2.8)	<0.05[a]
Number of pregnancy (Pregnancy rate %)	8 (38)	3 (15)	NS[b]
Number of Clinical pregnancy (CP rate %)	8 (38)	3 (15)	NS[b]

M2 Metaphase 2; *NS* not significant; *CP* clinical pregnancy
[a] Mann–Whitney *U* test
[b] Fisher Exact test

The duration of the treatment and the total dose of recFSH were significantly higher in the study group. The number of metaphase 2 oocytes were higher in the study group. Correspondingly, the number of the embryos transferred was higher in the study group. There were eight pregnancies in the study group (95% confidence interval between 20 and 59%), while there were only three in the control group (95% confidence interval between zero and 32%).

Discussion

In the current study, we found that luteal start of exogenous recFSH along with GnRH agonist in poor responder women increases the number of metaphase 2 oocytes available. The power of the study (0.99) indicates the reliability of our finding. Although it was not possible to draw strong conclusions on pregnancy rates (power, 0.65), this definitely was due to the small number of cases in each arm. We included the possible highest number of couples meeting the inclusion criteria applied during the designated time period. And it is obviously not so easy to convince couples craving for a child to participate in any study. Any intervention is perceived as "experimentation" by the couples. Because of these, we did not calculate sample size prior to the study.

FSH treatment duration and the total recFSH used in our study group patients was very significantly higher than those of the control group, resulting in increased cost of the treatment. But this is coming from the nature of the protocol which starts early in the luteal phase. When compared the same criteria starting from day 2 of the menstruation, there is no significant difference.

Previously, FSH commencing in the luteal phase of the ovarian cycle was tested against short protocol by one study in a cohort of 40 poor responder women. FSH treatment was started on day 25 of preceding cycle and GnRH agonist was used in short protocol [5]. There was found no difference in the number of oocytes retrieved which was designated as main outcome measure. They did not take the advantage of additive effect of luteal GnRH agonist flare to luteal FSH treatment. Furthermore, they excluded two patients who used higher dose of FSH instead of 150 IU.

Serum estradiol levels in our study group were significantly higher reflecting the number of recruited oocytes. Rombauts et al did not find any difference in serum estradiol and immunoreactive inhibin levels. Obviously this was because of inadequate number of follicles recruited.

Our study differs from that of Rombauts et al in two significant points: (1) we started to give recFSH earlier (day 21 versus 25), (2) we gave recFSH daily along with long protocol GnRH agonist. The latter might have helped potentiating the effects of FSH and overruling intra-ovarian mechanisms which can be speculated as a co-factor in failure of previous studies.

The first attempt of using luteal FSH in an effort to increase recruited cohort was by Gougeon and Testart [6]. They have given a single hMG injection at various stages of the menstrual cycle. In that study, no difference was found in the percentage of healthy recruitable follicles of ≥2 mm in diameter. This finding was possibly due to either inadequate dosing or inadequate duration or LH part of hMG leading to corpus luteum rescue.

In the study by Gougeon and Testart, granulosa cell mitotic index was found to be doubled by hMG. On the contrary, Rombauts et al. reported that luteal FSH administrated group required 4 more days to reach hCG injection comparing to control group; this finding suggested a slowed granulosa cell mitosis whilst follicular growth functional parameters such as serum estradiol and immunoreactive inhibin levels were not different between two groups. They had no explanation for that slower response. Even though we did not examine neither mitotic index nor immunoreactive inhibin, the estradiol levels and time to hCG from cycle day 2 in the study group suggest increased granulosa cell activity as Gougeon and Testart had reported.

There is possibility of biases inherent with unusual randomization method. But the likelihood of any bias is

very low, because the application order of the couples was not manipulated by us and that served as a natural randomization. Another potential point of debate may be the comparison in our study was not only the prolonged FSH stimulation but also the GnRH agonist regimen. It is not easy to exclude the beneficial effect of the latter. Previous attempts which had demonstrated a poor response were employing a long GnRH agonist protocol; that is why we also changed that for a short protocol in the control group. Because, along with constituting the control group they were also getting their repeat treatment for infertility aiming a child very strongly. Another study to discriminate effects between prolonged FSH and two GnRH agonist regimen is required in the future.

In conclusion, luteal start of recFSH simultaneously with long protocol GnRH agonist in poor responder women produced higher number of metaphase 2 oocytes comparing to short protocol GnRH agonist plus high dose FSH regimen. Although the cost of the treatment is higher it constitutes a new option for desperate cases of poor response. Although not statistically significant, higher pregnancy rate in the study group opens a new avenue worth to pursue. Larger studies are warranted to draw strong conclusions.

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