Original Article

Comparison of Triggering Final Oocyte Maturation with Follicle Stimulating Hormone Plus Human Chorionic Gonadotropin, versus Human Chorionic Gonadotropin Alonein Normoresponder Women Undergoing Intracytoplasmic Sperm Injection: A Randomized Clinical Trial

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Abstract

Background: Few studies have so far been done about the role of follicle stimulating hormone (FSH) in final oocyte maturation. However, none of these studies have been performed solely on normoresponder patients. This study aimed to determine whether oocyte maturation, as well as fertilization and pregnancy rates, could be improved in normoresponder women with concomitant FSH and human chorionic gonadotropin (hCG) trigger compared to those with the hCG trigger alone.

Materials and Methods: In this prospective randomized clinical trial, 117 normoresponder women, aged 19-40 years who were candidates for the gonadotropin-releasing hormone (GnRH) antagonist protocol at Avicenna Infertility treatment Center, were enrolled and claasified in two groups. Final oocyte maturation was triggered using 10000 IU of hCG plus 450 IU of FSH in the first group (59 subjects) and 10000 IU of hCG alone in the second group (58 subjects). The primary outcome was clinical pregnancy rate.

Results: Mean age of the patients was 33.21 ± 4.41 years. There was no difference in clinical pregnancy among the two groups (30.9% vs. 25.5%, P=0.525). There was no statistically significant difference in fertilization rate (80.0% vs. 74.1%, P=0.106), implantation rates (18.9% vs. 16.7%, P=0.352), and chemical pregnancy rates (38.2% vs. 32.7%, P=0.550). Oocyte maturation rate (84.2% vs. 73.6%, P<0.001), 2 pronuclei (2PNs) (6.53 ± 2.54 vs. 5.36 ± 2.85, P=0.021) and total embryos (5.85 ± 2.43 vs. 4.91 ± 2.58, P=0.046) were significantly higher in the first group.

Conclusion: Adding FSH to hCG for oocyte triggering, significantly improved oocyte maturation rates and total embryos. While there was no significant difference in the clinical and chemical pregnancy rates, between these two groups (registration number: IRCT20190108042285N1).

Keywords: Fertilization, Follicle Stimulating Hormone, Human Chorionic Gonadotropin, Pregnancy Rate, Triggering Oocyte Maturation

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Introduction

Ovarian and pituitary hormone changes during the midcycle period have been previously studied. Surge of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) precede normal ovulation (1). LH surge plays a crucial role in the last stages of oocyte maturation. The effect of different ovarian stimulation protocols has been reported in several studies (2-4). In practice, the gold standard method to trigger oocytes in the last stages of maturation is human chorionic gonadotropin (hCG), which has been routinely used for decades as a surrogate for LH surge (2, 3). However, ovarian hyperstimulation syndrome (OHSS), due to the prolonged luteotrophic effect of hCG, is an important and potentially fatal complication of hCG triggering (2-5).

Multiple randomized controlled trials (RCTs) have demonstrated the efficacy of gonadotropin-releasing hormone agonists (GnRHa) administration for the final phase of oocyte maturation as an alternative to the classic triggering by hCG (6, 7). GnRHa trigger has been suggested to be beneficial in GnRH antagonist protocols because it has a lower risk of OHSS than the conventional hCG trigger (4, 8). Nevertheless, several recent studies have shown that GnRHa triggering can be associated with corpus luteum dysfunction, decreased pregnancy rate and increased early miscarriage rate (4, 6, 9).

During the natural cycle, ovulation is induced by

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simultaneous rises in LH and FSH (5). Effect of FSH surge in inducing ovulation has not been completely understood yet; however, its roles in stimulating LH receptors on luteinizing granulosa cells (4, 5, 10), resumption of oocyte meiosis (10, 11) and stimulation of plasminogen activator activity for follicular rupture (5) have been reported. In addition, a bolus of FSH can induce ovulation independently in rodents and macaques (5). FSH alone has been reported to induce oocyte maturation and ovulation in the monkey model (10). Similar findings were reported in humans who inadvertently administered a FSH bolus instead of hCG after undergoing *in vitro* fertilization (IVF) (12).

Few studies have been done on role of FSH in final oocyte maturation (5, 10, 13). However, none of the previous studies have been performed solely on normoresponder patients. "Normoresponder" refers to a group of patients who have neither decreased ovarian reserves nor predisposition to hyperstimulation (14). This study aimed to determine whether oocyte maturation, as well as fertilization and pregnancy rates, could be improved in normoresponder women with concomitant FSH and hCG trigger compared to those with the hCG trigger alone.

Materials and Methods

This prospective randomized controlled trial was performed between February 2019 and February 2020. The study was approved by the Ethics Committee of Avicenna Research Institute, Tehran, Iran (IR.ACECR.AVICENNA.REC.1397.016) and registered in the Iranian Registry of Clinical Trials (IRCT20190108042285N1).

This study evaluated women undergoing intracytoplasmic sperm injection (ICSI) treatment at Avicenna Infertility Treatment Center. Written informed consent was obtained from all couples participating in the trial.

Patient population

Women aged 19-40 years who were candidates for GnRH antagonist protocol at an academic centre, enrolled in this study.

Inclusion criteria were day-3 serum FSH levels <11 mIU/ml, two or fewer previous embryo transfer cycles, both ovaries present, absence of uterine abnormalities, antral follicle count (AFC) >5 on the third day of cycle, and anti-mullerian hormone (AMH) level >1 ng/ml. In this study, only normoresponding women were included, i.e. women who had 6-20 follicles >10 mm on the trigger day.

Exclusion criteria were estradiol (E2) level >3,500 pg/ml and <500 pg/ml on the day of hCG injection, severe male factor infertility, polycystic ovary syndrome (PCOS), undertaking a cycle involving preimplantation genetic diagnosis (PGD) or not having an embryo transfer, due to the freeze-all policy, donor or surrogate cycle, grade 3 and 4 endometriosis, contraindications to ovulation stimulation, important systemic diseases, such as hepatic failure and renal failure. Patients also were excluded if they were unable to give informed consent.

Ovarian stimulation

Ovarian stimulation was done using recombinant FSH (Cinnal-f, CinnaGen, Iran) from cycle day 3. The initial gonadotropin dose was based on the patient age, body mass index (BMI), AFC, and AMH level.

Transvaginal ultrasound was performed every 2 to 3 days from the sixth day of stimulation to measure the follicular diameter. The GnRH antagonist (Cetrotide, Serono International S.A., Switzerland) was administered (0.25 mg/day) when the dominant follicles reached ≥14 mm in diameter.

All patients were triggered when at least three follicles measured 18 mm or more in the transvaginal ultrasound. The patients were randomly classified in two groups using a computer-generated random number table with six blocks on the day of trigger. The random allocation and participants' assignment were done by an independent nurse who was not involved in the study or patient care.

All physicians, research coordinators and clinic personnel were blinded. The study coordinator who was not blinded prepared the appropriate study medication syringe, which IVF in-cycle nurses administered. The triggers administered were 10000 IU of hCG (Pregnyl, Netherlands) (10) plus 450 IU of FSH in the first group and 10000 IU of hCG alone in the second group. FSH and hCG were injected with two separate syringes, so participants and IVF in-cycle nurses were not blind.

Oocyte retrieval was done under ultrasound guidance, 36 hours after trigger administration for all subjects, using a Cook (Sydney, Australia) catheter. Retrieved oocytes were fertilized by ICSI. Oocyte maturation was evaluated after cumulus cell stripping, and 18 hours after aseessement of sperm injection fertilization. One to three good-quality embryos were transferred 72 hours after oocyte retrieval (15). Pregnancy was assessed by blood β-hCG test 14 days after transfer. Transvaginal ultrasound was performed 2-3 weeks after a positive β-hCG test to evaluate pregnancy sac and fetal heart rate.

Outcomes

The primary outcome was clinical pregnancy. Clinical pregnancy was defined as detection of a fetal heartbeat by transvaginal ultrasound scan. Secondary outcomes included oocyte maturation rate, ICSI fertilization rate, implantation rate and a chemical pregnancy.

Oocyte maturation rate was defined by the number of metaphase II (MII) oocytes divided by the number of oocytes retrieved. ICSI fertilization was defined as the proportion of injected oocytes with 2 pronuclei (2PN) the day after injection. Implantation rate was defined as the number of gestational sacs observed by transvaginal ultrasound divided by the total number of transferred embryos. Rate of good-quality embryos was defined as the ratio of embryos with good quality to the number of 2PNs. Good-quality cleavage stage embryos were defined as having a cell number between 7 and 10 with <10% of the volume of the embryo occupied

by cell fragmentation based on a modified Veeck's grading system. Chemical pregnancy was defined as positive hCG but an absence of gestational sac by ultrasound detection14 days after embryo transfer (5, 16, 17).

The patient age, BMI, duration of infertility (years), type and cause of infertility were collected. Serum E2, AMH, FSH and total FSH levels, as well as the number of total embryos and transferred embryos, in addition to number of follicles counted on trigger day were also recorded.

Statistical analysis

The sample size was calculated regarding the 95% confidence level, power of 85%, the least significant difference of 0.08 and the prevalence of 50% final oocyte maturation in the group receiving FSH plus hCG. Therefore, 50 patients were required in each group.

The SPSS (Ver. 20; SPSS Inc, Chicago. IL, USA) statistical software was used for data analysis. The Student's t test was performed to compare continuous variables. The Chi-square test was performed to compare categorical variables. Statistical significance was defined as a two-tailed P<0.05.

Results

A total of 156 infertile women were initially enrolled in this study. Of them, 39 women were excluded; finally, 117 subjects were included on the day of oocyte trigger and classified in two groups (Fig.1).

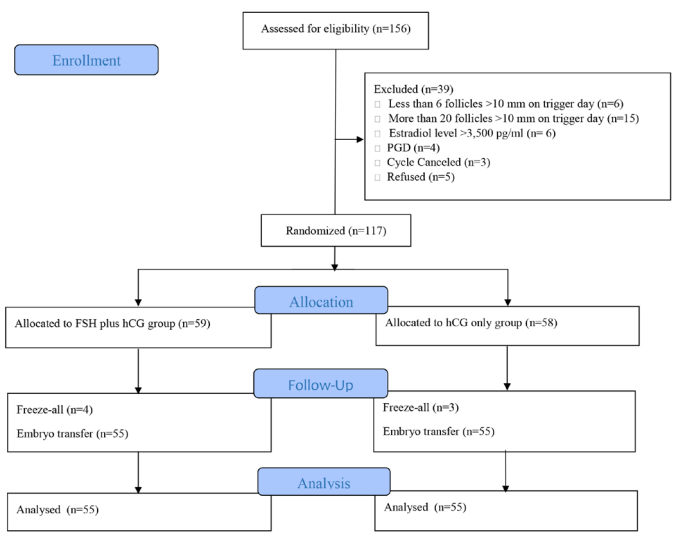

Fig.1: Consort flow diagram. PGD; Preimplantation genetic diagnosis, FSH; Follicle stimulating hormone, and hCG; Human chorionic gonadotropin

Among participants, 59 women received hCG plus FSH, and 58 women only received hCG. Four subjects in the FSH plus hCG group and three subjects in the hCG only group wanted to use the freeze-all procedure for future embryo transfer. Finally, fresh embryo transfer was done in 110 cases, and pregnancy results were compared between 55 women in the first group and 55 women in the second group. There was no loss follow-up evaluation.

The demographic characteristics of the both groups are shown in Table 1. There was no difference in baseline demographic characteristics among the two groups. Cycle characteristics are reported in Table 2. There was also no difference in cycle characteristics, such as total FSH dose, serum E2 on the trigger day, mean number of stimulation days, number of total follicles on the trigger day, number of embryos transferred and number of good-quality embryos. Nevertheless, the number of 2PNs and total embryos were significantly higher in the FSH plus hCG group compared to the other group.

Table 1: Demographics characteristics of both groups

Variables	hCG plus FSH (n=59)	hCG alone (n=58)	P value
Age (Y)	33.14 ± 4.85	33.28 ± 3.95	0.864
BMI (kg/m^2)	25.68 ± 4.63	25.66 ± 3.58	0.980
Type of infertility			0.752
Primary	37 (62.7)	38 (65.5)	
Secondary	22 (37.3)	20 (34.5)	
Cause of infertility	25 (42.4)	27 (46.6)	0.856
Male factors	6 (10.2)	6 (10.3)	
Ovulation dysfunction	5 (8.5)	7 (12.1)	
Tubal problems	12 (20.3)	11 (19.0)	
Mix Unexplained	11 (18.6)	7 (12.1)	
Duration of infertility (Y)	4.45 ± 3.37	4.49 ± 2.23	0.936
AMH (ng/ml)	2.52 ± 1.13	2.44 ± 0.92	0.644
Endometrial thickness (mm)	8.71 ± 1.48	8.61 ± 1.36	0.718
Number of prior ET	0.37 ± 0.67	0.33 ± 0.71	0.759

Data are presented as mean ± SD or n (%). Analyzed using Independent Samples Test and Chi-Square Test. BMI; Body mass index, AMH; Anti-mulerian hormone, ET; Embryo transfer, hCG; Human chorionic gonadotropin, and FSH; Follicle-stimulating hormone.

Table 2: Cycle characteristics

Variables	hCG plus FSH (n=59)	hCG alone (n=58)	P value
FSH on 3rd day	6.82 ± 1.94	6.76 ± 2.19	0.890
Serum estradiol on the day of trigger (pg/ml)	1628.36 ± 506.46	1582.55 ± 567.33	0.646
Number of days of stimulation	9.68 ± 1.32	9.62 ± 1.57	0.831
Total FSH dose (IU)	2065.25 ± 677.03	2046.05 ± 901.31	0.897
Follicles count on the day of trigger	11.88 ± 2.80	11.98 ± 3.16	0.855
Number of MII oocytes	8.32 ± 3.04	7.33 ± 3.15	0.085
Number of 2PNs	6.53 ± 2.54	5.36 ± 2.85	0.021
Number of total embryos	5.85 ± 2.43	4.91 ± 2.58	0.046
Number of embryos transferred*	2.15 ± 0.74	2.07 ± 0.77	0.550
Number of good quality transferred embryos*#	1.40 ± 0.89	1.29 ± 0.90	0.524
Excess count embryos for cryopreservation*	3.58 ± 2.23	2.60 ± 2.45	0.030
Fertilization rate (%)	80.8	74.1	0.106
Oocyte maturation rate (%)	84.2	73.6	<0.001

Data are presented as mean ± SD. Analyzed using Independent Samples Test and Chi-Square Test. *; There were 55 women in each group, #; Good quality embryos were defined as having a cell number between 7 and 10 with <10% of the volume of the embryo, hCG; Human chorionic gonadotropin, FSH; Follicle-stimulating hormone, MII; Metaphase II, and 2PN; 2 pronuclei.

The primary outcome was clinical pregnancy. There was no difference in clinical pregnancies among the two groups (0.31 vs. 0.26, P=0.53). Analysis of the secondary outcomes showed a fertilization rate of 80.8% versus 74.1% (P=0.11), implantation rates of 18.9% versus 16.7% (P=0.35), and chemical pregnancy rates of 38.2% versus 32.7% (P=0.55), in the "FSH plus hCG" and hCG-alone groups, respectively. Additionally, women in FSH plus hCG group had a significantly higher oocyte maturation rate than the hCG alone group (84.2% vs. 73.6%, P<0.001). Pregnancy outcomes are shown in Table 3.

Table 3: Pregnancy outcomes

Variables	hCG plus FSH	hCG alone	P value
Clinical pregnancy rate	17 (30.9)	14 (25.5)	0.525
Chemical pregnancy rate	21 (38.2)	18 (32.7)	0.550
Implantation rate	24 (18.9)	20 (16.7)	0.352

Data are presented as n (%). Analyzed using Chi-Square Test. hCG; Human chorionic gonadotropin and FSH; Follicle-stimulating hormone.

Discussion

The current study showed that co-administration of FSH and hCG for oocyte triggering improved the number of 2PNs, total embryos, excess count embryos for cryopreservation and oo-cyte maturation rate, in comparison with hCG trigger alone. To our knowledge, few randomized clinical trials have been done about the role of FSH in final oocyte maturation (5, 10, 13). However, in this study, only normoresponding women were included.

In a case report, 36 hours before oocyte retrieval, FSH bolus was administered instead of the standard 10,000 IU hCG. This was the first human report of FSH administration during oocyte trigger. The given random dose was more than four times (2100 IU) of what was administered in the present study (450 IU). In this case report, the maturity rate was 90% when recombinant human FSH was administered, and there were no adverse outcomes. By Italian legislation, only three oocytes were injected by ICSI, and all three underwent normal fertilization and cleavage, consequently giving rised to three good quality embryos (12).

The first randomized clinical trial to evaluate whether co-administration of FSH bolus at the time of hCG trigger could improve developmental competence of the oocyte was performed by Lamb et al. (10). Oocytes were triggered by injecting either 450 IU FSH or normal saline as a placebo at the time of hCG administration. They found that fertilization proportion (2PN/oocytes collected) and oocyte recovery rate were significantly improved in the FSH group compared to the placebo group. Similar to the current study, there was no statistically significant difference in clinical pregnancy rate, implantation rate and live birth or ongoing pregnancy rate. Although the oocyte maturation rate was not assessed, the IVF fertilization rate was significantly higher in the intervention group. Similarly, we found that FSH plus hCG women group had significantly higher oocyte maturation rate than the hCG alone group.

In another study performed by Qiu et al. (1), all patients received standard long GnRHa protocol for IVF/ICSI and hCG 6000-10 000 IU to trigger oocyte maturation. Then, subjects received a urinary FSH bolus (450 IU) or placebo, at the time of the hCG trigger, respectively. They did not find any statistically significant improvement in clinical pregnancy rate, good-quality embryos rate and the implantation rate in FSH co-trigger group. In another study, the experimental group subjects received 5000 IU hCG plus 450 IU FSH for final oocyte maturation and contril group subjects received 5000 IU hCG at the time of the oocyte triggering. Similar to our findings, MII oocyte, 2PNs and total embryos were significantly higher in the experimental group compared to the control group, respectively. Additionally, fertilization rate, implantation rate, clinical and chemical pregnancy rates were higher in the experimental group, while these differences were not statistically significant (13).

Juneau et al. (18) pursued to determine whether adding an FSH bolus (450 IU) administered at the time of hCG trigger could improve IVF cycle outcomes in a retrospective cohort. They included 874 cycles in the study, demonstrating no improvement in the number of oocytes retrieved or oocyte maturation, fertilization or blastulation rates with the administration of an FSH bolus at the time of hCG trigger.

The specific role of the FSH surge is not well understood yet; however, FSH has been shown to stimulate LH receptors on luteinizing granulosa cells (4, 5, 10). Recently, due to the availability of pure recombinant human FSH, studies have shown ability of FSH to supplement the midcycle LH surge. In general, FSH is known to promote oocyte cumulus expansion and oocyte nuclear maturation (10, 11, 19).

There are some limitations in this study. Firstly, the sample size was relatively small. Secondly, placebo was not used in the control group. Prominently, further studies are required to optimize this triggering strategy with regards to concentration, sample size, etc., to provide significantly higher pregnancy percentages.

Conclusion

Our results demonstrated that adding 450 IU FSH to 10000 IU hCG for oocyte triggering in normoresponder patients significantly improved oocyte maturation rates and the number of total embryos. Also, fertilization rate, implantation rate as well as clinical and chemical pregnancy rates were higher in the FSH plus hCG group, While there were no significant differences between the two groups.

Although further studies with different concentrations and larger sample sizes are needed to optimize this triggering strategy, these findings suggested that addition of the FSH trigger is an option to further improve assisted reproductive technology (ART) success.

Acknowledegements

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Authors' Contributions

S.A., N.T., M.R.S., A.M.A.; Contributed to conception and design. S.A., N.T.; Contributed to all experimental works, data and statistical analyses, as well as interpretation of data, and was responsible for overall supervision. N.T.; Drafted the manuscript, revised it by S.A., M.R.S., A.M.A. All authors performed editing and approved the final version of this manuscript for submission. They also participated in the finalization of the manuscript and approved the final draft.

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