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Dual FSH and HCG Triggering Increases Clinical Pregnancy Rate in IUI for Unexplained Infertility: A Randomized Controlled Trial

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Abstract

Objectives: Despite advancements in the assisted reproduction technology (ART), the proportion of unexplained infertility is 30% among infertile couples. This study aimed to explore the pregnancy proportions in women with primary unexplained infertility who were given follicle-stimulating hormone (FSH) along with the human chorionic gonadotropin (hCG) trigger compared with those who were only given the hCG trigger.

Materials and Methods: In this randomized controlled trial, the women eligible for intrauterine insemination (IUI) were investigated between April 1, 2022 and April 1, 2023 at Al-Zahra referral academic center. To this end, a total of 130 women were primarily screened and then 50 ones were excluded from the study based on the pre-defined inclusion criteria. Therefore, the final study population consisted of 80 eligible women with primary unexplained infertility, who were randomly assigned to the intervention group (n=40) and control group (n=40). The patients in the intervention group received two ampules (75 IU) of FSH in addition to two ampoules (5000 IU) of hCG, while the patients in the control group only received hCG. Both groups underwent IUI 34-36 hours after the hCG triggering. The biochemical and clinical pregnancy rates were evaluated as primary outcomes.

Results: No significant differences were observed between the baseline and clinical characteristics, including endometrial thickness and the number of follicles before intervention ($P>0.05$). However, the clinical pregnancy rate was higher in the dual FSH and hCG group (40.0%, 16/40) than that in the hCG group (20.0%, 8/40) ($P=0.048$). The chemical pregnancy rates were 32.5% (13/40) and 37.5% (15/40) for the hCG and dual FSH and hCG groups, respectively. No significant relationships were detected between the biochemical pregnancy and the number of gestational sacs ($P>0.05$).

Conclusions: The dual administration of FSH and hCG for oocytes, compared with the injection of hCG alone, improved the clinical pregnancy. The biochemical pregnancy and live birth rates as well as the number of gestational sacs were not improved significantly.

Keywords: Unexplained infertility, Pregnancy, Assisted reproduction technology, Oocyte

Introduction

The success likelihood of assisted reproduction technology (ART) has been improved over the last decades (1), and the recent advancements in laboratory techniques – the enrichment of ovarian stimulation, in particular – have played important role in this regard (2). However, the proportion of unexplained infertility is 30% among infertile couples worldwide (3). Couples' infertility and women's inability to perceive after a minimum of twelve cycles of unprotected sex or after six cycles in women over 35 years are characterized by unexplained infertility (4).

In vitro fertilization (IVF) and ovarian stimulation with intrauterine insemination (IUI) are two different treatment options to deal with the given condition. To adopt an appropriate treatment strategy, however, several factors including demographic characteristics, treatment efficacy, side effects (e.g., multiple pregnancy), and treatment costs should be considered (5).

The most expensive yet effective strategy to deal with unexplained infertility is to implement one of the ART methods including IVF, with and/or without intracytoplasmic sperm injection. However, in cases where other less expensive treatment methods like drug treatments and IUI have been unsuccessful, IVF may be considered as a more advanced and potentially effective option for addressing infertility (6).

IUI could be performed in a normal cycle in combination with ovarian stimulation by letrozole, gonadotropins, and clomiphene citrate (CC). The purpose of ovarian stimulation in IUI is to increase the number of dominant follicles in each cycle, which leads to a growth in the pregnancy rate.

An oocyte trigger using a combination of hCG and Follicle-stimulating hormone (FSH) has been shown to

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Key Messages

- The dual administration of FSH and hCG can improve clinical pregnancy rates in ART, but may not significantly impact biochemical pregnancy and live birth rates or the number of gestational sacs.

potentially decrease the risk of ovarian hyperstimulation syndrome (OHSS) compared to the traditional trigger method using hCG alone. However, it is important to note that this modification may not necessarily lead to improved pregnancy outcomes or IVF success rates (2,7,8). Previous studies have highlighted the impact of the intrafollicular milieu – FSH meditations, in particular – on estradiol concentrations and oocyte recovery in the normal fertilization (8). This study, therefore, aimed to compare the pregnancy rates in women suffering from primary unexplained infertility who were given FSH plus the human chorionic gonadotropin (hCG) trigger with those who were only given the hCG trigger.

Materials and Methods

Design

In this randomized controlled trial, all women eligible for IUI were investigated between April 1, 2022 and April 1, 2023 at Al-Zahra referral academic center. To this end, a total of 130 patients were initially screened and, then, 50 ones were excluded from the study based on the pre-defined inclusion criteria. Therefore, the final study population consisted of 80 women with primary unexplained infertility. The CONSORT flow diagram is depicted by Figure 1.

Participants and eligibility

All eligible women aged 18-38 years and were with unexplained infertility, normal profile of follicular hormonal including LH, FSH, TSH, and prolactin, normal pelvis and uterus evaluated by hysterosalpingography and/or laparoscopy and adequate sinogram, and normal sperm profile determined based on WHO criteria (9). The exclusion criteria were the explained infertility, endometriosis, irregular menstrual cycles, abnormal sperm analysis, polycystic ovary syndrome and/or ovarian cysts, previous IUI, endocrinologic maladies, lost cycles caused by no or poor response to ovarian stimulation, liver or kidney diseases and/or systemic pregnancy-related disease, as well as medication-related hypersensitivity.

Interventions

The intervention group in this study consisted of the women with primary unexplained infertility who received a combination of two ampoules of 5000 IU hCG and 2 ampoules of 75 IU FSH to stimulate follicle growth and enhance the chances of pregnancy. The IUI trigger was performed 34-46 hours after the administration of these hormones. The control group, on the other hand,

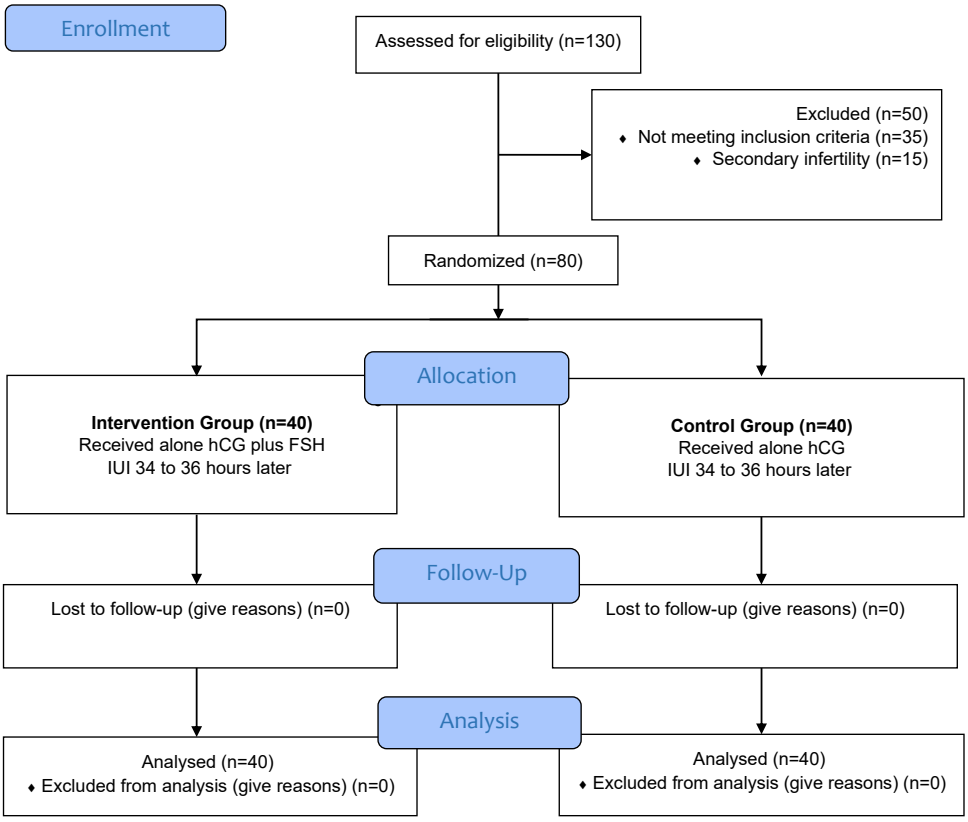

Figure 1. CONSORT Flow Diagram of the Study.

only received two ampoules of hCG (5000 IU) injected simultaneously by following the period and methods similar to those followed in the intervention group.

Sample Size

A pilot study with 50 primary infertility patients was conducted to calculate the appropriate sample size, out of who 20 patients received dual administration of FSH and hCG while 30 ones received hCG alone for oocyte triggering. The clinical pregnancy rates were 40% in the dual administration group and 25% in the hCG alone group. Then the odds ratio (OR) of clinical pregnancy between the two groups was determined based on the pilot study results in order to estimate the effect size (ES) and standard deviation for the sample size calculation. The ES was calculated as the difference in the log odds of the clinical pregnancy between two groups, and the standard deviation was estimated as the square root of the sum of variances of the clinical pregnancy's log odds in each group. Then the results from these estimates were used to conduct a power analysis with a power of 0.8 (beta=0.2) and an alpha level of 0.05. Considering a 5% compensation for potential loss to follow-up cases, a sample size of 40 cases in each group was determined large enough to detect a significant difference between the dual administration and hCG alone groups in terms of the clinical pregnancy rates. Therefore, a total of 80 primary infertility patients were selected for this study, with 40 patients in each group. The selection of these patients was based on the power analysis, taking into account the effect size and standard deviation estimated by the pilot study.

Randomization and Blinding

The eligible women were allocated into two groups, namely the control and intervention groups. The randomization process was conducted to ensure an unbiased allocation of the participants. A software-generated random number table was used to generate the random allocation sequence, and all subjects were assigned unique codes during the study to maintain the allocation concealment, which was only known by the statistical consultant and was not disclosed to the study team or participants. To reduce the potential impact of confounding factors, moreover, the stratification and blocking factors were involved in the randomization process. These factors were determined based on the relevant participant characteristics. The reason behind the incorporation of stratification and blocking factors was to ensure an even distribution of these characteristics among the study groups, thereby minimizing potential biases. Overall, the randomization procedure was carefully designed and implemented to ensure the validity and reliability of the study's findings. Our study was non-blinded since both ovulation induction of the patients and IUI were performed by the same clinical team at the hospital and because it was not feasible to implement a blinding study.

Measurements

First, a vaginal ultrasound was performed to control and check the condition of the ovaries and uterus. Participants in both the intervention and control groups were instructed to take one to two tablets of letrozole daily from the 3rd to 5th days of menstruation. Additionally, one ampoule of 75 IU Cinnal-F(r-FSH) was administered per day on cycle days 6, 8, and 10, with the dosage tailored based on the individual's age and ovarian condition.

Following a transvaginal ultrasound on the 11th to 12th day of the menstrual cycle to assess ovarian response to the medication, participants in both the intervention and control groups received two ampoules of hCG 5000 IU to trigger egg release. This was done after confirming the ovarian condition and ensuring the presence of at least one mature follicle larger than 18 mm and a suitable endometrium thickness of 6.5-7 mm.

However, the intervention group received two 75 IU Cinnal-F(r-FSH) plus two ampoules of hCG 5000 IU. IUI was performed as usual for both groups 34 to 36 hours later, and then outcomes were assessed. All procedures and administrations were performed by an experienced gynecologist.

Outcomes

The success of our intervention was assessed using both biochemical and clinical pregnancy rates as primary outcomes, while the gestational sacs, incidence of OHSS, live birth rate, abortion, and anomalies were assessed as secondary outcomes.

Statistical Analysis

Data normality was evaluated using skewedness and kurtosis, and the association between paramedic qualitative variables and the study groups was examined using independent t-test; when normality was not established, the Mann-Whitney U test was performed. Chi-square test was carried out to evaluate an association between the categorical or qualitative variables and the study groups. The significant level in all tests was set at <0.05, and SPSS version 22 was used to conduct all analyses.

Results

A total of 80 women with primary unexplained infertility (40 subjects in each group) were included and analyzed in the study (Figure 1).

Table 1 presents the baseline characteristics of the participants allocated to the study groups. Initially, there were no significant differences in demographic factors such as age, BMI, educational level, duration of marriage, and infertility status ($P > 0.05$). However, there were statistically significant variances in employment status and family history of infertility between the groups ($P < 0.05$).

Table 2 presents the comparison between intervention and control groups regarding the study outcomes. According to this Table, the two study groups were not

different in terms of sperm motility, morphology, and count ($P>0.05$). The clinical pregnancy proportion was 22.5% (9/40) in hCG group versus 35.0% (15/40) in dual FSH and hCG group. There was a borderline significant difference between intervention group (i.e., Dual hCG/FSH) and control group (i.e., hCG) regarding the clinical pregnancy, and a dual hCG/FSH increased the likelihood of clinical pregnancy ($P=0.051$). Likewise, a significant relationship was found between the groups concerning the day of hCG injection ($P=0.0.001$).

Biochemical pregnancy rate was 30.0% (12/40) in hCG group, while it was 37.5% (15/40) in dual FSH and hCG group. Likewise, the live birth and abortion rates were 22.5% (9/40) vs. 35% (14/40) ($P=0.329$) and 7.5% (3/40) vs. 2.5% (1/40; ($P=0.305$) in the control and intervention groups, respectively. Anomalies percentages were 5% (2/40) and 0.0% in the control and intervention groups, respectively ($P=0.152$). However, no significant relationships were found for the biochemical pregnancy, endometrial thickness, and number of follicles ($P>0.05$).

Table 1. Demographic and Baseline Information of Study Population

	hCG Group (Control) (n=40)	Dual hCG/FSH Group (n=40)	*P* Value
Age (y)	31.91±6.19	29.93±5.71	0.148[a]
BMI (kg/m²)	23.95±3.12	24.03±3.95	0.898[a]
Literacy, No. (%)			
Illiterate	2 (5.08%)	0 (0%)	0.206[b]
Preliminary school	5 (7.69%)	4 (9.23%)	
High school diploma	14 (40%)	22 (53.85%)	
University graduate	19 (49.23%)	13 (36.92%)	
Employment state, No. (%)			
Housewife	21 (52.5%)	30 (75.0%)	0.010[b]
Employed	19 (47.5%)	10 (25.0%)	
Family history of infertility, No. (%)			
Yes	9 (22.5%)	3 (7.5%)	0.011[b]
No	31 (77.5%)	33 (92.5%)	
Duration of marriage (y)	5.18±3.0	4.96±2.53	0.652[a]
Duration of infertility (y)	3.57±2.79	2.98±2.11	0.176[a]

[a] Independent t test; [b] Chi-square test.

Table 2. Semen Parameters and IUI Cycle Outcomes in hCG and Dual hCG/FSH Groups

Variables	hCG Group (Control) (n=40)	Dual hCG/FSH Group (n=40)	*P* Value
Total sperm count (×10⁶)	102.73±64.45	89.48±47.56	0.184[a]
Total sperm motility (×10⁶)	87.42±33.51	76.23±29.82	0.056[a]
Sperm with normal morphology (%)	14.16±5.29	15.63±3.95	0.075[a]
Day of hCG injection	13.92±2.05	12.22±1.15	<0.001[a]
Number of follicles (n)	3.13±1.46	2.82±0.53	0.11[b]
Endometrial thickness (mm)	7.04±1.44	6.87±1.03	0.440[a]
Biochemical pregnancy, No. (%)			
Yes	12 (30.%)	15 (37.%)	0.277[c]
No	28 (70.%)	25 (62.%)	
Clinical pregnancy, No. (%)			
Yes	9 (22.%)	14 (35.%)	0.051[c]
No	31 (77.%)	26 (65.%)	
Gestational sacs number (n)	0.32±0.51	0.49±0.55	0.070[a]
OHSS			
Yes	0	0	0.988[d]
No	40	40	
Live birth rate, No. (%)			
Yes	9 (22.%)	14 (35.%)	0.329[c]
No	31 (77.%)	26 (65.%)	
Abortion, No. (%)			
Yes	3 (7.5%)	1 (2.%)	0.305[d]
No	37 (92.5%)	39 (97.%)	
Anomalies, No. (%)			
Yes	2 (5.0)	0 (0.0)	0.152[d]
No	38 (95.0)	40 (100.0)	

[a] Independent t test; [b] Mann-Whitney U test; [c] Chi-square test; [d] Fisher exact test.

The groups were different regarding the number of gestational sacs, but the statistical relation was not significant ($P > 0.05$). Additionally, no OHSS was detected in the participants.

Discussion

The study findings indicated that a dual administration of FSH and hCG for oocyte triggering improved the clinical pregnancy compared to an administration of hCG injection alone. This improvement was obtained by increasing the clinical pregnancy rates (40% vs. 20%). Although the proportion of biochemical pregnancy and live birth rate were higher in the group receiving the dual administration of FSH and hCG, no significant improvement and/or statistical was found.

In a study by Lamb et al, it was determined that an injection of concomitant FSH/hCG trigger improved the developing competence of the oocyte (8), which was in line with our study results and the finding reported by A. Morad. This study demonstrated that an ovulation trigger by a dual injection of hGg and FSH in comparison with hCG alone improved the live birth likelihood as well as the proportion of clinical pregnancy. Likewise, Dashti et al (2) showed that a combination of FSH and hCG to trigger oocyte enhanced the oocyte maturity and fertilization rate, but failed to enhance the implantation and chemical/clinical pregnancy proportions. Additionally, a meta-analysis conducted by Hsia et al (10) found that the use of dual trigger, as opposed to hCG trigger alone, resulted in significant improvements in the number of oocytes retrieved, clinical pregnancy rates, and live birth outcomes in IVF procedures.

An RCT by Ansaripour et al indicated that a dual FSH and hCG triggering had the potential to significantly improve the oocyte maturation likelihood and total embryos, which was in agreement with our study results. However, they found no significant association between the groups in terms of the biochemical and clinical pregnancy rates (11). Our study also found no significant difference between intervention and control groups after IUI in terms of the chemical pregnancy. As shown in Table 2, however, a significance level of clinical pregnancy was detected in the borderline in the present trial. These inconsistencies may have been due to the differences in the study area, sample size, differential assignment accuracy, and endometrial thickness.

Local FSH is potentially important for oocyte recovery with ART and in vitro maturation in vitro due to the physiological flow of FSH before the ovulation. Therefore, it seems that augmentation FSH could increase the evolving capability of the oocyte (8).

A gonadotropin-releasing hormone (GnRH) agonist has been used in several studies to supplement the supplemental impact of FSH for final oocyte maturation, most of which have been designed to decrease an ovarian hyperstimulation. According to these studies, however, a GnRH-agonist trigger increases both LH and FSH levels in the pituitary (12). Gonen et al reported that the agonist may have provided an additional physiologic flow with significant and advanced serum FSH levels in the GnRH agonist group (27.7 IU/L) 13 hours after the GnRH trigger, while keeping the levels in hCG group at 11 to 12 IU/L (12). This FSH "surge" was parallel to the points perceived in the usual cycle by the time of egg repossession, and FSH levels became normal (11 to 12 IU/L) probably due to the ultimate pituitary suppression by the agonist in the Gonen et al study (8), which was also reported by Fauser et al (13).

In a cohort study by Chung et al in Taiwan, it was demonstrated that an application of low-dose r-FSH and CC not only improved pregnancy rates but had also the potential to prevent the high-order multiple pregnancies rates (14).

FSH and LH are well-known to have a significant and integral impact on folliculogenesis and ovulation. LH is commonly believed to be the primary carrier of final oocyte nuclear maturation and the beginning of follicular rupture; however, there is an ongoing debate over the role of FSH in these procedures (15). Seemingly, the mid-cycle surge of FSH results in the activation of plasminogen, which is followed by the enhancement of LH receptor creation in gram-negative cells, cumulus expansion, and nuclear maturation (16).Other studies have shown that FSH accumulation and cumulus oocyte complex maturation are two separate processes indicative of the follicle competence (17, 18).

Limitations of the Study

Our trial had a few limitations. First, the researchers were not able to determine how interventions were applied since our study was not blinded. Second, the trial and the patient selection process were expensive. However, our study was rigorous in that it enjoyed a suitable randomization and a sufficient sample size.

Conclusions

It was concluded that a dual administration of FSH and hCG, compared to an injection of hCG alone, for oocyte triggering improved the clinical pregnancy rates. However, no significant improvements were observed in the biochemical pregnancy and live birth rates as well as in the number of gestational sacs. Furthermore, no differences were detected between the groups in terms of the abortion and anomalies. To further expand our understanding of the issue at hand, it was recommended that the optimal dosage and timing of FSH and hCG administration for oocyte triggering should be investigated to help optimize the clinical outcome, and the potential effects of the dual administration of FSH and hCG on long-term maternal and neonatal health outcomes should be examined to increase the understanding of this treatment approach. It was found that assessing the scalability, feasibility, and sustainability of implementing the study's findings on a larger scale or

in different contexts was also crucial. It was suggested that further studies should evaluate the effectiveness and practicality of this treatment approach in diverse patient populations, healthcare settings, and regions in order to provide valuable insights into the generalizability of these findings. Finally, it was recommended that the potential impact of this treatment approach on factors such as healthcare costs, patient satisfaction, and environmental sustainability should be explored in order to achieve a more comprehensive evaluation of its overall value.

Authors' Contribution

Conceptualization: Parvin Hakimi, Kobra Hamdi.
Data curation: Mahshid Alborzi, Khadijeh Pouya, Kobra Hamdi.
Investigation: Mahshid Alborzi, Khadijeh Pouya, Reza Asadi maman.
Methodology: Mahshid Alborzi, Khadijeh Pouya.
Project administration: Parvin Hakimi.
Supervision: Parvin Hakimi.
Validation: Parvin Hakimi, Mahshid Alborzi, Kobra Hamdi.
Writing-original draft: Mahshid Alborzi, Khadijeh Pouya, Reza Asadi maman, Amir Fattahi.
Writing-review & editing: Reza Asadi maman, Amir Fattahi, Parvin Hakimi.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The trial was registered in the Iranian Registry of Clinical Trials website (identifier: IRCT20220702055335N2). The study protocol was approved by the ethics committee of Tabriz University of Medical Sciences under number IR.TBZMED.REC.1401.235. Informed consent was obtained from all participants before the study. .

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