RESEARCH ARTICLE

Effect of Dual Trigger with Follicle Stimulating Hormone and Chorionic Gonadotropin Hormone on Ovulation Rate in Infertile Women received Aromatase Inhibitor Superovulation in Kirkuk City, Iraq

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ABSTRACT

A prospective during the period October 2020 to April 2021, a comparative study was conducted at the Al-Nahrain University's High Institute for Infertility Diagnosis and Assisted Reproductive Technologies (HIIDART). The study's primary goal was to determine whether using a dual trigger (FSH and hCG) could increase the likelihood of achieving pregnancy. The participants in this study totaled one hundred women. Before taking part in the study, each participant signed a written informed consent form that was approved by the Al-Nahrain University's Ethics Committee before participating. A total of one hundred and one women participated in the study, who were chosen from among those who attended the consultant clinic of the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies in New York City. On the day of the IUI An ultrasound scan of the vaginal cavity was performed after 36 to 48 hours of trigger ovulation to confirm ovulation, measure, and evaluate the endometrial pattern, and assess sub endometrial blood flow. FSH, LH, Progesterone, and E2 levels were determined in a blood sample drawn on the same day for hormonal testing. Luteal phase support was initiated on the day of the IUI and continued for two weeks by administering 400 mg of progesterone vaginal suppository daily to the patient. Estimation of Beta human chorionic gonadotropins 14 days after IUI. The distribution of study groups by general characteristics is shown in Table 1. Study patients' age was ranging from 19 to 39 years with a mean of 29.98 years and a standard deviation (SD) of ± 5.3 years. The highest proportion of study patients in all groups was aged between 25–34 years, overweighed, and complained from infertility for less than five years' duration. The comparison in hormonal parameters between study groups at day of IUI is shown in Table 4.5. Mean of FSH level was significantly lower ($p = 0.031$) in group C than that in groups A and B (6.98 versus 9.06 and 9.3 IU/L respectively). Mean of E2 level was significantly higher ($p = 0.001$) in-group A than that in groups B and C (69.62 versus 53.32 and 36.65 pg/mL, respectively). The comparison in percentage of change in hormonal parameters at day of IUI compared to that at day of trigger according pregnancy outcome is shown in table (4.16). No significant differences between women who get pregnant than that in those who didn't, in percentage of change of all other hormonal parameters at day of IUI ($p \geq 0.05$) compared to that at day of trigger.

Keywords: Aromatase inhibitor, Dual trigger, IUI, Ovulation rate.

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INTRODUCTION

Oocyte The hormone HCG can effectively induce oocyte maturation, but it only provides LH-like exposure, implying that the mid-cycle FSH surge observed in the natural cycle is not required for successful oocyte maturation in vitro. When compared to hCG and rLH, GnRHa and kisspeptin have an advantage in that they release FSH at the same time as they exhibit LH-like activity. LH receptor production, nuclear maturation, and cumulus expansion can all be stimulated by follicle-stimulating hormone (FSH) in luteinizing granulosa cells when the hormone is released.[1] In most mammalian species, the surge in FSH and luteinizing hormone (LH) that occurs prior to spontaneous ovulation is known as the luteal phase (LH) To complete oocyte nuclear maturation (meiosis) and initiate follicular rupture, a surge of gonadotropins must be released at the same time. It is frequent practice in IVF cycles to administer hCG injections prior to oocyte retrieval in order to simulate the LH surge and promote final oocyte

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maturation.[2] Several lines of evidence suggest that an increase in FSH near the end of oocyte maturation has biological significance, and this is supported by the literature. In the monkey model, for example, if FSH is administered alone, it can cause oocyte maturation and ovulation to occur in the laboratory. It is important for normal fertilization to have a healthy intrafollicular environment as well as specific FSH concentrations for oocyte recovery and estradiol levels. Ovulation occurs because of the physiologic increase in FSH levels that occurs just before ovulation.[3] In signaling pathways, one possible function of folicle-stimulating hormone is to maintain the open state of the gap junctions between the oocyte and the cumulus cells.[4] According to current evidence, FSH works in concert with other hormones to create the optimal conditions for oocyte maturation and ovulation.[2] If the male factor is mild/moderate, intrauterine insemination is a treatment option that can be used. There have been numerous studies over the years attempting to determine which parameters are limiting to ensuring a successful pregnancy with this assisted reproduction technique based on the semen's quality (female origin, synchronization with ovulation), assessment of follicle rupture (number of IVF cycles per cycle, and the influence of uterine contractions). When properly indicated, intrauterine insemination (IUI) is a less invasive and more affordable alternative to other methods of conception.[5-7] The aim of the study was to determine whether dual trigger (FSH and hCG) can improve the ovulation and pregnancy rate (Figure 1).

SUBJECTS, METHODS AND MATERIALS

The High Institute for Infertility Diagnosis and Assisted Reproductive Technologies at Al-Nahrain University conducted a prospective comparative study from October 2020 to April 2021, which was published in the journal Fertility and Sterility. The participants in this study totaled one hundred women. Before taking part in the study, each participant signed a written informed consent form that was approved by the Al-Nahrain University's Ethics Committee before participating. A total of one hundred and one women participated in the study, who were chosen from among those who attended the consultant clinic of the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies in New York City.

Inclusion Criteria

- Age of women was (18–39) years old.
- BMI 18.5–30 Kg/m^2.
- AMH≥1.1 ng/mL.
- Patency of the fallopian tubes.
- Mild male factor infertility
- No endocrinopathy
- No anatomical or pathological problem in the uterus

Exclusion Criteria

- Moderate and sever endometriosis
- Sever male factor infertility
- Ovarian cyst
- Bilateral tubal obstructions
- Acute genital tract infection in either parents
- Any medical diseases contra indicating to the pregnancy.

Methods

All women in the study subjected to:

1. Full history taking, include obstetrical and gynecological history, details about history of infertility, previous miscarriage.
2. Complete general examination, complete gynecological examination.
3. Infertility workup including hormonal assay in CD3 and vaginal ultrasound examination, tubal patency evaluation by hysterosalpingogram or laparoscopy.
4. The husband also subjected to a full history and seminal fluid analysis, the seminal fluid analysis was assessed according to WHO 2010
5. The women in the study have received aromatase inhibiter (Gynotril 2.5 mg) tablet, was given orally twice daily 12 hours apart from day 3 for 5 days.
6. At CD3 hormonal assay (FSH, LH, Progesterone, prolactin, E2, AMH) was done, assessment of antral follicle counts and endometrial thickness by ultra sound
7. From day 9 serial ultrasound was done every two days till detection of at least one mature follicle with ≥17 mm diameter.
8. At day of trigger all patient sends again for hormonal study LH, FSH, E2, Progesterone. Another assessment for sub endometrial blood flow, endometrial pattern. According to the type of triggering, patients were classified in to 3 groups:

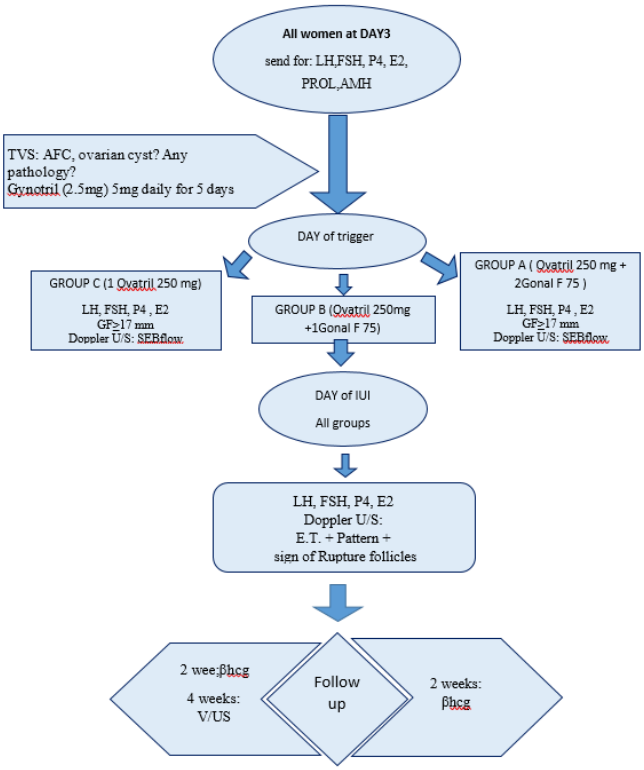

Figure 1: Study design

- Group A: study group, women were received dual trigger by injection of (ovitrelle 250 mg plus FSH 150 IU Gonal f).
- Group B: study group women were received dual trigger by injection of (ovitrelle 250 mg plus FSH 75 IU gonal f) at day of trigger.
- Group C: women were received ovitrelle 250 mg only.

At day of IUI After 36–48 hours of trigger ovulation vaginal ultrasound was done to confirming ovulation, measurement and evaluation of endometrial pattern, sub endometrial blood flow. Blood sample was collected at same day for hormonal assay of FSH, LH, Progesterone, E2. Luteal phase support started from day of IUI for two weeks by giving the patient progesterone vaginal suppository 400 mg daily. Estimation of Beta human chorionic gonadotropins 14 days after IUI.

Query Addition: is it Week or Weeks?

Before enrollment, each couple underwent assessment for infertility, by Careful history and physical examination, age of female, partner. duration and type of infertility, details of menstrual history, previous pregnancies and miscarriages, illnesses, smoking, drugs, surgery, infertility investigations and/ or treatments including previous IUI and/or IVF. It is also important to ask about sexual history including coital frequency and any history of contraception. Written informed consent was obtained from each patient. At (cycle day 3, (day 11–14)), a base line reading of FSH, LH, E_2, progesterone, AMH and prolactin, blood sample was taken from all women was done as a part of the work up. In addition, a test of the thyroid gland (TSH), as a screening of thyroid function.

RESULTS

The distribution of study groups by general characteristics is shown in Table 1. Study patients' age was ranging from 19 to 39 years with a mean of 29.98 years and a standard deviation (SD) of ± 5.3 years. The highest proportion of study patients in all groups was aged between 25–34 years, overweighed, and complained from infertility for less than five years' duration.

The comparison in clinical and ruptured follicle between study groups at day of IUI is shown in Table 2 and 3. Mean of FSH level was significantly lower (p = 0.031) in group C than that in groups A and B (6.98 versus 9.06 and 9.3 IU/L, respectively). Mean of E2 level was significantly higher (p = 0.001) in-group A than that in groups B and C (69.62 versus 53.32 and 36.65 pg/mL, respectively).

In all study groups, most of the follicles were ruptured and no significant differences detected (p= 0.668) between study groups.

The comparison between study groups by pregnancy outcome is shown in Table 4. No statistically significant association was detected (p =0.645) between pregnancy outcome and treatment options (study groups).

The comparison in percentage of change in hormonal parameters at day of IUI compared to that at day of trigger according pregnancy outcome is shown in Table 5. No significant differences between women who get pregnant than that in those who didn't in percentage of change of all other hormonal parameters at day of IUI (p ≥ 0.05) compared to that at day of trigger.

DISCUSSION

Many studies have concluded that there are several lines of evidence that the surge in FSH that occurs in conjunction with the LH midcycle surge in the natural menstrual cycle may be

Table 1: Distribution of study groups according to general characteristics

	Study group			
Variable	*A (%) n= 35*	*B (%) n= 37*	*C (%) n= 29*	*Total (%) n= 101*
Age (Year)				
< 25	8 (22.9)	7 (18.9)	8 (27.6)	23 (22.8)
25–34	15 (42.9)	23 (62.2)	17 (58.6)	55 (54.5)
≥ 35	12 (34.3)	7 (18.9)	4 (13.8)	23 (22.8)
BMI Level				
Normal	10 (28.6)	9 (24.3)	9 (31.0)	28 (27.7)
Overweight	25 (71.4)	28 (75.7)	20 (69.0)	73 (72.3)
Type of infertility				
Primary	21 (60.0)	16 (55.2)	13 (44.8)	50 (49.5)
Secondary	14 (40.0)	21 (60.0)	16 (55.2)	51 (50.5)
Duration of infertility (Year)				
< 5	25 (71.4)	26 (70.3)	25 (86.2)	76 (75.2)
5–9	7 (20.0)	7 (18.9)	4 (13.8)	18 (17.8)
≥ 10	3 (8.6)	4 (10.8)	0 (0)	7 (6.9)

Table 2: Comparison between study groups in clinical parameters at day of IUI

Clinical parameter at day of IUI	*Study group*			
	A Mean ± SD	*B Mean ± SD*	*C Mean ± SD*	*p-value*
LH (IU/L)	19.96 ± 11.1	24.65 ± 11.5	22.01 ± 12.4	0.24
FSH (IU/L)	9.06 ± 3.7	9.3 ± 4.3	6.98 ± 3.02	0.031
Progesterone (ng/mL)	1.78 ± 1.4	1.87 ± 1.7	2.14 ± 1.6	0.655
E2 (pg/mL)	69.62 ± 45.0	53.32 ± 33.1	36.65 ± 24.0	0.001

Table 3: Number of ruptured follicle in study groups

	Study group			
Follicle	*A (%) n= 35*	*B (%) n= 37*	*C (%) n= 29*	*p-value*
Ruptured	33 (94.29)	34 (91.89)	25 (86.21)	0.51
Not ruptured	2 (57.71)	3 (8.11)	4 (13.79)	

Table 4: Comparison between study groups by pregnancy outcome

	Pregnancy outcome		
Study group	*Pregnant (%) n= 25*	*Not pregnant (%) n= 76*	*p-value*
A (n:35)	9 (25.71)	26 (74.29)	
B (n:37)	8 (21.6)	29 (78.4)	0.87
C (n:29)	6 (20.67)	23 (79.31)	

Table 5: Comparison in percentage of change in hormonal parameters at day of IUI compared to that at day of trigger according pregnancy outcome.

Percentage of change at day of IUI compared to that at day of trigger (%)	*Pregnancy Outcome*		
	Pregnant Mean ± SD	*Not pregnant Mean ± SD*	*p-value*
LH	90.26 ± 126.1	99.06 ± 130.5	0.766
FSH	50.02 ± 68.3	73.37 ± 83.0	0.168
Progesterone	506.89 ± 476.9	650.39 ± 741.6	0.267
E2	-64.4 ± 17.1	-71.84 ± 22.5	0.087

important for final oocyte maturation in the final stages of the menstrual cycle.[6] The following chart depicts the distribution of study groups according to general characteristics. The ages of the study participants ranged from 19 to 39 years, with a mean of 29.98 years and a standard deviation (SD) of 5.3 years, respectively. The majority of study participants in all groups were between the ages of 25 and 34 years, were overweight, and had been experiencing infertility for less than five years at the time of enrollment. These findings were close to that reported by Decleer, *et al*.,[7] in a study done earlier showed that, covariates, age, body mass index (BMI), basal hormonal level, the number of days of stimulation as well as the cycle ranking did not demonstrate any differences between the groups compared. In another study, Lamb *et al.*[3] discovered that the mean age of women undergoing ART therapy was 30.36 years, and that the mean BMI was 25.9 kilograms per square meter. In a similar study, Younis *et al.*[8] and Mahajan *et al.*[9] found that the groups did not differ significantly in terms of baseline characteristics such as age, BMI, basal FSH, LH, and AMH levels, and that the etiology of infertility in patients from both groups was the same as in the other. Another study done by Lamb *et al.,*[2] which involved women treated with a long GnRHa protocol, giving an FSH supplementation at the time of hCG trigger and found higher serum FSH levels, but in this study at the time of oocyte retrieval, considered that the higher FSH levels in the serum at the time of oocyte retrieval which is comparable to the higher FSH levels in the serum at the time of IUI in our study, was similar to our findings. The retrieval of a greater total number of follicles as well as a greater number of ruptured follicles has been reported in several studies after triggering with GnRHa as opposed to the conventional triggering with hCG.[9,10] GnRHa's ability to induce the release of both endogenous LH and follicle stimulating hormone (FSH), which more physiologically mimics the natural cycle surge,[12] which it also mimics in our study, may account for this phenomenon. Between the study groups and the conventional group, there was no statistically significant association (p=0.645) in terms of pregnancy outcome. Other researchers[2] have examined reproductive outcomes such as fertilization rate (0.75 0.19 vs 0.68 0.25), implantation rate (14.2 vs 8.5%), clinical pregnancy rates (27.9 vs 15%) and chemical pregnancy rates (32.6 vs 20%), all of which were higher in the FSH group, but not statistically significant (p>0.05) in the FSH group. In addition, he discovered that there was no statistically significant difference in the oocyte recovery rate between the two groups. It is disagreed by Jiao *et al*.[13] who demonstrated that Ovulation trigger with the dual administration of FSH and hCG, compared to hCG alone, significantly increased clinical pregnancy rate and live birth rate in women with unexplained infertility who underwent combined letrozole superovulation and intrauterine insemination treatment. Another study conducted by Kader *et al*.[14] compared patients' previous cycles triggered by hCG to the current cycle. There were no statistically significant differences in the outcomes of the pregnancy. In a manner similar to the trial conducted by Kyrou *et al*.,[15] the researchers discovered that there was no statistically significant difference in pregnancy rates between the GnRHa and hCG trigger groups. In a study conducted by la Cour Poulsen *et al*.,[4] they compared hCG and GnRHa and concluded that GnRHa should not be recommended for routine use as final oocyte maturation trigger in fresh autologous cycles due to the lower live birth and ongoing pregnancy rates observed. Erb *et al*.,[16] showed that, the dual-trigger group had statistically significantly improved rates of implantation, clinical pregnancy, and live birth compared with the control group who received the conventional trigger of hCG alone. Following the findings of Qiu *et al*.[17], the ongoing pregnancy rate (OPR) did not differ between the two groups, and the implantation rates did not differ significantly between the dual trigger group and the hCG trigger group either (21.1% vs 17.1%, respectively) Kim *et al*.[18] reported a 24.7% implantation rate with dual triggering and a 14.9% implantation rate with hCG triggering, with a statistically significant difference between the two groups (p = 0.006) between the two groups. Using a pooled analysis, it was discovered that there was no evidence of any differences in the rate of implantation between groups. Dual trigger FSH/LH can be used to trigger ovulation in a cycle that has been stimulated by aromatase inhibitors or with intrauterine insemination. Further studies to compare the effect of dual trigger fish/lh on pregnancy rate in two groups.

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