ORIGINAL RESEARCH ARTICLE

Comparative Study of Dual Trigger vs hCG Trigger in Intrauterine Insemination Cycles

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Abstract

Aim: The aim of this study was to assess if follicle-stimulating hormone (FSH) surge induced by gonadotropin-releasing hormone agonist (GnRHa), when given in addition to human chorionic gonadotropin (hCG) for triggering ovulation in intrauterine insemination (IUI) cycles, was beneficial and resulted in higher pregnancy rates.

Background: Gonadotropin-releasing hormone agonist (GnRHa), when given as an ovulation trigger, causes a surge of both FSH and luteinizing hormone (LH) due to its "flare" effect mimicking the midcycle surge of gonadotropins in a natural cycle. The role of midcycle FSH surge in humans is not completely understood. But when GnRHa alone is used as an ovulation trigger, it causes luteolysis and luteal phase defect due to its shorter duration of action. In IUI cycles, GnRHa can be combined with hCG, which is responsible for only LH surge, and compared with cycles in which hCG alone is used as a trigger to analyze the impact of midcycle FSH on clinical pregnancy rates.

Materials and methods: A total of 60 IUI cycles were analyzed that were divided into two groups. Group I received hCG alone and group II received hCG + GnRHa for ovulation trigger. In both groups stimulation protocol used was letrozole, which started from day 2 of the cycle for 5 days, and recombinant FSH (rFSH) from day 7. Follicular monitoring was done using two-dimensional (2D) ultrasound and color Doppler. Once follicles and endometrium attained functional maturity, an ovulation trigger was given. In group I, recombinant hCG and in group II, triptorelin acetate (0.2 mg) along with recombinant hCG was given. In both groups, IUI was done 34–36 hours after the trigger; luteal support was given with 800 mg micronized vaginal progesterone per day. Clinical pregnancy rates were compared in both groups.

Results: There was a difference in pregnancy rates between the hCG group (26.7%) and GnRHa + hCG group (40%).

Conclusion: It was concluded that though there was a difference in pregnancy rates in both groups, the difference was not statistically significant due to the small patient cohort ($p = 0.273$).

Keywords: Dual trigger, Follicle stimulating hormone surge, Gonadotropin-releasing hormone agonist, Human chorionic gonadotropin, Intrauterine insemination, Ovulation trigger.

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Introduction

Ovulation is the most crucial step for conception in a menstrual cycle, and triggering ovulation is the most important step in the artificial reproductive therapy (ART) cycle for successful conception and ongoing pregnancy. As inadequate endogenous LH surge is a very common phenomenon in gonadotropin cycles triggering ovulation is considered a mandatory step in these cycles.

Human chorionic gonadotropin (hCG) has been traditionally used as a surrogate LH surge in ART cycles because of the degree of homology between these two hormones, but following physiology, in a natural cycle, the midcycle surge consists of LH and FSH surge from the pituitary gland.

Gonadotropin-releasing hormone agonist (GnRHa) causes "flare" effect with a resultant surge of LH and FSH mimicking natural midcycle LH surge; thus, a bolus of GnRHa can "trigger" ovulation.[1] While the role of FSH is not completely elucidated in humans; there are animal and human cell studies suggesting the role of FSH in oocyte

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maturation and resumption of meiosis,[2,3] also in function of oocyte cumulus complex and facilitation of its detachment from the follicular wall,[4] and generation of LH receptors on granulosa cells.[5] Thus, there may be advantages to an ovulation trigger which can result in a surge of both LH and FSH. In spite of these advantages, an agonist trigger, due to its short duration of action, resulted in luteal phase defects.

To counter this, Shapiro et al. first described the concept of a dual trigger, that is, a combination of GnRHa and a low dose of hCG with the aim of aiding final oocyte maturation and sustained luteal support.[6] This approach was subsequently corroborated by Griffin et al.[7] More recently, Castillo et al.[8] also reported the successful use of a dual trigger using GnRHa and low-dose hCG in a patient showing repetitive immature oocytes and empty follicle syndrome with the agonist-only trigger.

Though the main reason for using an agonist as an alternative trigger was to prevent ovarian hyperstimulation syndrome (OHSS), but in patients undergoing ovulation induction with gonadotropins and IUI,[9] the number of developed follicles is limited. A potential benefit to employing the use of GnRHa trigger for IUI cycles, therefore, is to induce a more physiologic type of gonadotropin surge involving the flare effect of FSH and LH from the pituitary.[10]

The study attempts to analyze if the FSH surge induced by GnRHa, when given in addition to hCG, is beneficial and convertible to higher pregnancy rates in IUI cycles.

Materials and Methods

Study Design

A retrospective, comparative, observational study was conducted between August and November 2021. Ethical clearance was taken from Institutional Ethical Committee.

Study Methodology

A total of 60 women were recruited into the study. Inclusion criteria were infertile women aged 20–37 years, body mass index (BMI) between 22–28 kg/m^2, and diagnosed with either unexplained/dysovulatory/grade I or II endometriosis/mild male factor infertility. Exclusion criteria were age >37 years and <20 years, bilateral tubal block, severe male factor infertility, grade III and IV endometriosis, fresh rupture noted on the preovulatory scan, perifollicular pressure support ventilation (PSV) >20 cm/s on the preovulatory scan, poor ovarian reserve with antral follicle count (AFC) <4 on baseline scan and patients with other endocrinological abnormalities affecting ovulation.

Study Technique

A total of 60 IUI cycles were analyzed. They were divided into two groups, 30 in group I, who received the hCG trigger, and 30 in group II, who received the hCG + GnRHa trigger for ovulation. In both groups stimulation protocol used was letrozole (letoval 2.5 mg/day), starting from day 2 of the cycle for 5 days, and rFSH (Follisurge, Intas) from day 7. The dose of gonadotropin was decided based on baseline ultrasound on day 2 of the cycle using an ultrasound ovarian scoring system described by Nagori et al.[11] The parameters for scoring used were; age, BMI, AFC, ovarian volume, stromal respiratory index (RI), and stromal PSV was used (Tables 1 and 2). The ultrasound features that demanded higher doses indicated poor response and were therefore given a lower score, and ultrasound features that required lower doses indicated better response and were given a higher score.[11]

In both groups, the transvaginal scan was performed with a transvaginal volume probe of 5–9 MHz on Voluson E10 BT20 (GE Medical Systems Kretztechnik GmbH, Zipf, Austria). A 2D and color Doppler parameters were used for monitoring follicular and endometrial growth. Follicular monitoring was started from day 7 of the cycle, the presence of a dominant follicle was confirmed, and gonadotropins were started. At least one dominant follicle (larger than 10 mm) or one mature follicle (18 mm in diameter) in each/either ovary or an increase in endometrial thickness to 5 mm was considered an adequate response. In patients with an adequate response, stimulation with the same dose was continued till at least one follicle reached a diameter of 18 mm. The diameter of the follicle was taken as a mean of three orthogonal diameters measured in two orthogonal sections. The next scan was done on the day when the size of the follicle was expected to be 16–17 mm, considering the growth rate of the follicle to be 1–2 mm/day. Once the follicle reached 16–17 mm, color Doppler and pulse Doppler

Table 2: Starting dose of gonadotropin for IUI cycle according to baseline score

Score	*Starting dose of rFSH in IU*
25	25
20–24	37.5
15–20	75
10–15	112.5
06–10	150

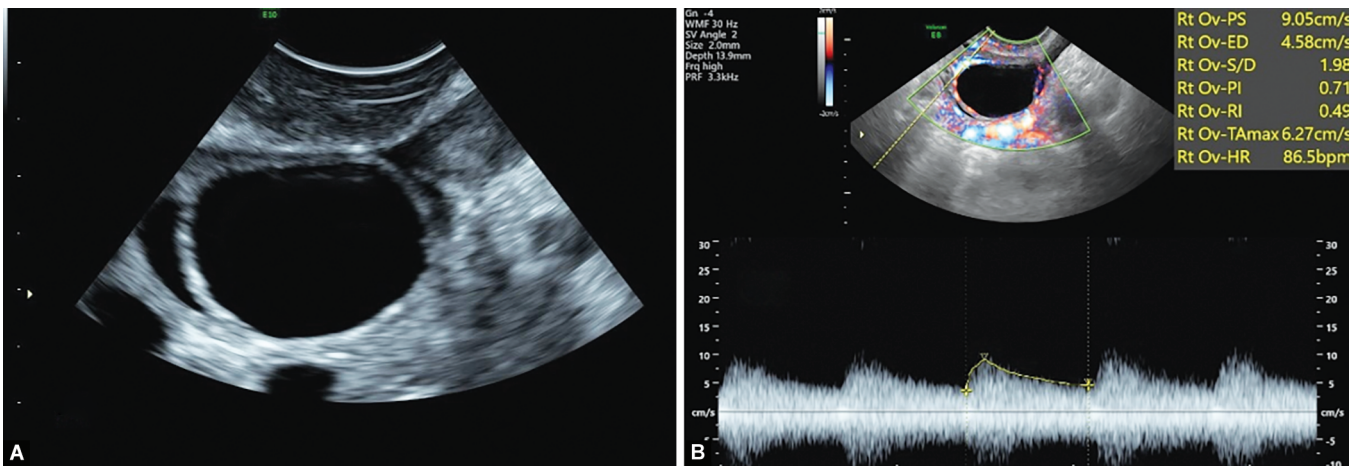
Table 1: Baseline ultrasound scoring for starting dose of gonadotropins on day 2 scan

Score	*1*	*2*	*3*	*4*	*5*
Age	>40	35–40	30–35	25–30	<25
BMI	>30	30–28	28–25	25–22	<22
AFC	<5	5–10	10–15	15–20	>20
Ovarian volume	<3	3–5	5–7	7–10	>10
Stromal RI	>0.75	0.75–0.65	0.65–0.55	0.55–0.45	<0.45
Stromal PSV	<3	3–5	5–7	7–10	>10

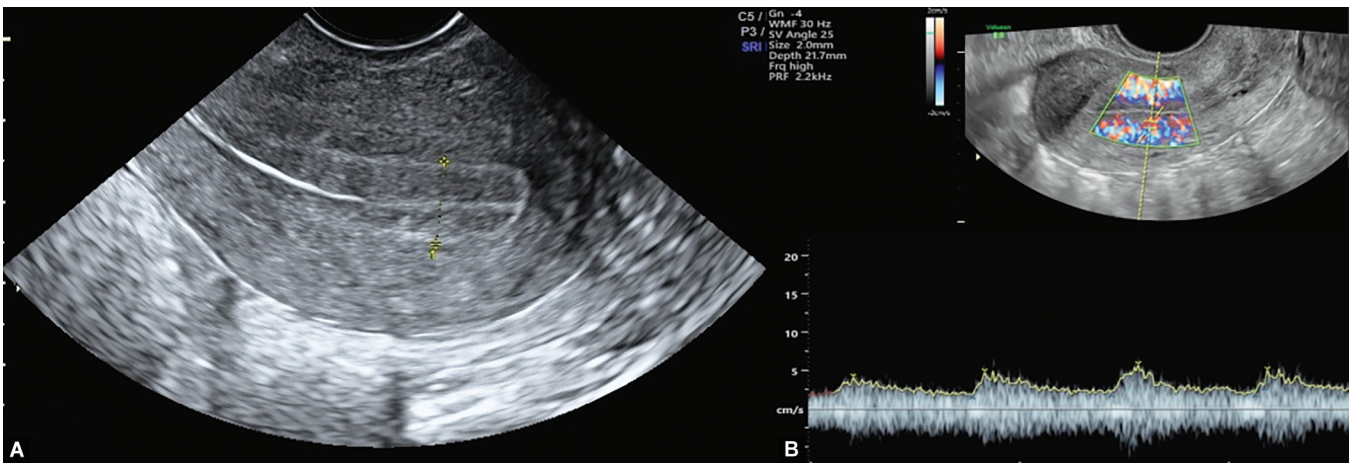
parameters were used for the assessment of the functional maturity of the follicle with perifollicular spectral Doppler parameters (Fig. 1). When three-fourths of the follicular circumference was covered by blood vessels, and at least one of the vessels showed RI < 0.48 and PSV > 10 cm/second, the follicle was considered to be mature for ovulation trigger. Endometrial thickness was assessed when the follicle was 18 mm in diameter or larger. Endometrial thickness was measured from the outer margin of the echogenic outer margin to the outer margin of the echogenic outer margin of the endometrium, not including the hypoechoic endometrial-myometrial junction. Endometrium that is at least 7 mm thick and shows blood vessels reaching zone 3 or zone 4 with RI < 0.6 is considered an endometrium with good implantation potential (Fig. 2). Before triggering ovulation, uterine artery Doppler was also done in each patient and it was confirmed that uterine artery perfusion index (PI) was <3.2 (Fig. 3). In group I, injection of r-HUCOG HP 6500 IU (rhCG) was given subcutaneously. Group II patients received an injection of triptorelin acetate 0.2 mg (GnRHa) subcutaneously, and an injection of r-HUCOG HP 6500IU subcutaneously. Single IUI was done 34–36 hours after the trigger. A fresh semen sample was collected on the day of IUI. Semen preparation was done by the density gradient method. Luteal support was given with micronized progesterone 400 mg Bd, vaginally started on the next day of IUI in both groups.

A luteal scan was done on day 8 after IUI for confirmation of corpus luteum and corpus luteal adequacy. The parameters assessed on the luteal scan were corpus luteal RI, PI, PSV, spiral artery RI and PSV, and uterine artery PI, RI, and PSV. Corpus luteum Doppler parameters were considered normal when corpus luteal RI was between 0.35 and 0.50; PI was 0.7 and 0.8, PSV was 10 and 15 cm/second, and uterine artery PI was 2 and 2.5. The morphology of the endometrium was assessed, and secretory changes in the endometrium were confirmed. Spiral artery spectral Doppler parameter in an adequate luteal phase was RI between 0.48 and 0.52.

A urine pregnancy test was done after 14 days of IUI. Ultrasound for confirmation of clinical pregnancy was done after 2 weeks of the positive urine pregnancy test. Clinical pregnancy was confirmed with the presence of a gestational sac on ultrasound. Biochemical and clinical pregnancy rates were compared in both groups.



Figs 1A and B: (A) B-mode ultrasound image of the mature follicle; (B) Spectral representation of blood flow in the follicle



Figs 2A and B: (A) B-mode ultrasound image of the endometrium; (B) Spectral representation of blood flow in zone 3 of the endometrium

Results

There was no significant difference in the groups in terms of age, BMI, and duration of infertility (Table 3).

There was no significant difference in mean baseline score by day 2 ultrasound in the hCG group (20 ± 1.050) and in the hCG + GnRHa trigger group (19.6 ± 1.812). The starting dose of gonadotropin in both groups was a minimum of 37.5 international unit (IU) and a maximum of 75 IU. Duration of stimulation, total gonadotropin dose, and the average number of dominant follicles were comparable in both groups (Table 3).

The pregnancy rates measured by the presence of gestational sac were 26.7% in the hCG group compared to 40% in the hCG + GnRHa group (Fig. 4). The *p*-value for positive pregnancy outcome was found to be 0.273, indicating the difference in outcome was not statistically significant.

Discussion

The results of this study, though, showed a difference in terms of pregnancy rates in hCG (26.7%) and hCG + GnRHa (40%) trigger groups; the difference was not found to be statistically significant ($p = 0.273$).

The primary aim of our study was to evaluate the role or utility of midcycle FSH surge in IUI cycles. It's difficult to study the role of FSH surge alone in ART cycles because; the traditional ovulation triggers used in the IUI cycle are either hCG or GnRHa triggers. hCG trigger acts as a surrogate LH only, and the GnRHa trigger alone may not produce sufficient endogenous LH surge and may adversely affect pregnancy rates.

Natural midcycle FSH surge coincides with a more pronounced LH surge, the role of which is well established. Midcycle FSH surge is proven to be vital in animals,[12] but its role in humans is not clear. The FSH surge, as a result of preovulatory progesterone rise, expands and disperses the cumulus cells allowing the oocyte-cumulus cell mass to become free-floating in the antral fluid just before follicular rupture. The follicular fluid after the GnRHa trigger is noted to have significantly higher levels of LH and FSH than those after the hCG trigger due to the combined surge of both gonadotropins.[13] These differences in follicular fluid dynamics may represent a larger difference between the signal required for oocyte maturation vs the signal needed for ovulation; although they are typically two closely related events, they may require slightly different signals.[14]

Humaidan et al. also compared the efficacy of GnRHa with hCG in triggering ovulation in 121 patients undergoing IVF who were given 0.5 mg GnRHa ($n = 55$) or 10000 IU of hCG ($n = 67$). They reported a significantly greater number of oocytes retrieved in the GnRHa group. However, their study revealed lower implantation and clinical pregnancy rates and a higher rate of early pregnancy loss with the use of the GnRHa trigger alone.[15,16]

Table 3: The demographic and treatment characteristics of the patient population in both the groups

Characteristics	*hCG trigger*	*hCG + GnRHa trigger*
Age	31.8 ± 2.8	32.37 ± 3.917
BMI	25.4 ± 2.2	25.567 ± 2.10
Duration of infertility	3.2 ± 1.312	3.5 ± 1.482
Baseline score	20 ± 1.050	19.6 ± 1.812
Starting dose of gonadotropins	67.5 ± 14.157 IU Minimum 37.5 IU Maximum 75 IU	68.33 ± 13 IU Minimum 37.5 IU Maximum 75 IU
A total dose of gonadotropins	417.08 ± 128.38	428.333 ± 126.070
Duration of stimulation	6.4 ± 2.175	6.73 ± 3.3
Number of dominant follicles	1.25 ± 0.585	1.37 ± 0.556

BMI, body mass index; hCG, human chorionic gonadotropin; GnRHa, gonadotropin-releasing hormone agonist; IU, international units

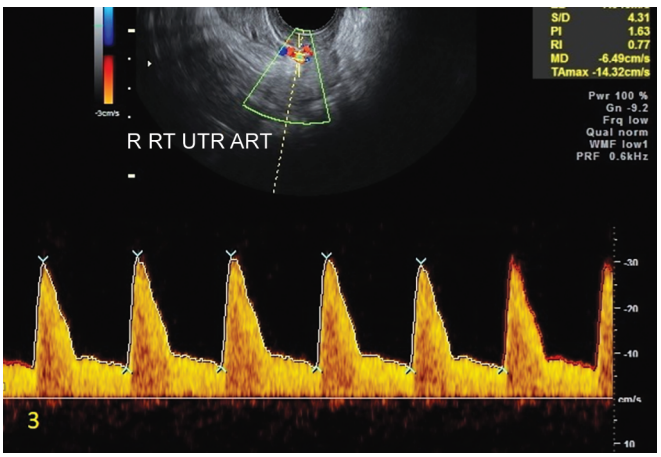


Fig. 3: Spectral representation of uterine artery flow

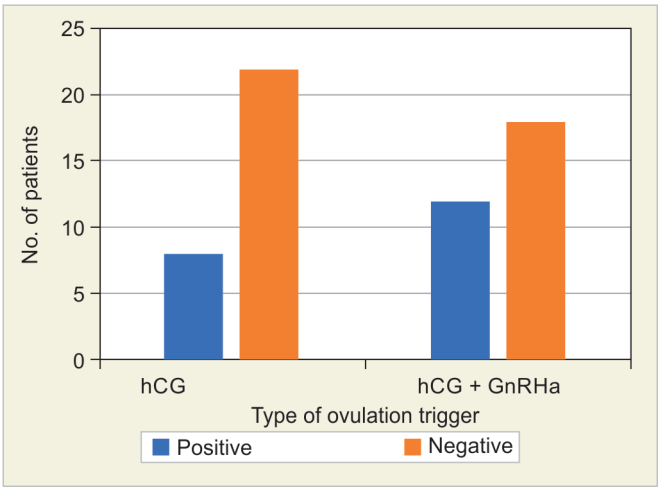


Fig. 4: Pregnancy rates in hCG groups and hCG + GnRHa groups

The duration of LH surge after GnRHa is shorter than the duration of a physiological surge of LH during the natural menstrual cycle. The spontaneous LH surge is defined by a short ascending limb (14 hours), a peak phase (14 hours), and a descending phase (20 hours). The GnRHa-induced LH surge consisted of two phases: a short ascending limb (>4 hours) and a long descending limb (>20 hours).[15,17] This predisposes cycles treated with GnRHa to luteal phase deficiency.

A randomized controlled trial by Minh et al. compared GnRHa and hCG triggers in ovulation induction with IUI in a total of 197 cycles. Women were randomly assigned to either receive the GnRHa trigger (n = 98) or the hCG trigger (n = 99) for the ovulation trigger. There was no difference in ovulation rates in either group. Biochemical and clinical pregnancy rates were higher in the group who received hCG (28.3–23.2%) vs GnRHa (14.3–13.3%) (p = 0.023 and p = 0.096). This study concluded that the use of GnRHa to trigger ovulation in patients undergoing ovulation induction may be considered in patients treated with IUI. But, one of the drawbacks of this study was the inclusion of both gonadotropin-stimulated and natural cycles. Furthermore, serum progesterone values were not measured, and 200 mg vaginal progesterone per day was supplemented, which was proven to be not adequate for luteal support. So, the lesser clinical pregnancy rates in GnRHa may be due to luteal phase defects.

The positive aspects of our study are both groups received the same doses of hCG (6500 IU), and thus endogenous LH surge was not relied upon, and hCG in this dose also acts as an efficient early luteal support. The risk of OHSS is negligible as the average number of dominant follicles obtained was 1.25 ± 0.585 in the hCG group and 1.37 ± 0.556 in the dual group. GnRHa trigger was given for women in the dual group with the aim of studying the effect of midcycle FSH surge on pregnancy outcomes.

The same luteal support was given in both groups to avoid confounding effects of luteal phase defect on pregnancy outcome. Luteal support was given by supplementing 800 mg vaginal progesterone per day in two divided doses. A systematic review and meta-analysis suggest that luteal phase support improved the likelihood of clinical pregnancy and live birth in gonadotropin-stimulated IUI cycles.[18] Twice-a-day doses can achieve a higher concentration of progesterone and reach a steady state within 24–32 hours and maintain a mean concentration above 10 ng/mL.[19]

Conclusion

In conclusion, though there was a difference in pregnancy rates between the hCG group and the GnRHa + hCG group, the difference was not statistically significant due to the small patient cohort. But still, it does initiate the concept of the role of FSH surge in humans, and larger studies may be more conclusive.

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