Original Article

To Compare the Effect of GnRH Agonist versus Human Chorionic Gonadotropin (HCG) Trigger on Clinical Pregnancy Rate in Intrauterine Insemination Cycle

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Abstract

Context: Gonadotropin-releasing hormone (GnRH) agonist trigger mimics the natural surge more closely with both luteinizing hormone (LH) and follicle-stimulating hormone surge. The present study attempts to find whether this apparent physiological advantage translates into the better pregnancy rate. **Aims:** To compare the effect of GnRH agonist versus human chorionic gonadotropin (hCG) trigger on the clinical pregnancy rate (CPR) in infertile women undergoing intrauterine insemination (IUI) with oral ovulogens. **Settings and Design:** Retrospective analysis at a tertiary care *in vitro* fertilization center. **Materials and Methods:** The records of 280 infertile women, who underwent IUI with oral ovulogens were analyzed. Women who received 0.2 mg triptorelin (GnRH agonist (GnRHa)) as trigger were categorised in Group A (n = 129) and those who received 10,000 IU urinary hCG in Group B (n = 151). The outcome in terms of CPR was studied. **Statistical Analysis Used:** The quantitative variables were compared using the independent t-test/Mann–Whitney test. The qualitative variables were compared using the Chi-square test. $P < 0.05$ was considered statistically significant. **Results:** There was a trend toward better CPR in Group A (21/129 – 16.28%) than in Group B (16/151 – 10.60%), although the difference was not found to be statistically significant (P – 0.162). **Conclusions:** There was a trend toward better CPR with the use of GnRH agonist trigger in IUI cycles with oral ovulogens in comparison to hCG trigger, although the difference was not found to be statistically significant. Further randomized controlled trials are needed to confirm these findings.

Keywords: *Gonadotropin-releasing hormone agonist, human chorionic gonadotropin, intrauterine insemination, ovulation trigger*

Introduction

In a natural cycle when the level of oestradiol secreted from emerging follicle cross a certain threshold, it exerts a positive feedback on hyptothalamic-pituitary axis. Pituitary then releases significant amounts of luteinizing hormone (LH) (and follicle-stimulating hormone, [FSH] as well) leading to final oocyte maturation and release. Since mid-1970s, exogenous human chorionic gonadotropin (hCG) has been used as an ovulation trigger for final oocyte maturation both in intrauterine insemination (IUI) and *in vitro* fertilization (IVF) cycles because hCG acts as a surrogate for LH hence mimicking the preovulatory LH surge. Its use has been associated with higher incidence of ovarian hyperstimulation syndrome (OHSS), particularly in cases with multiple follicle development. As early as in

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1973, Nakano *et al*. illustrated that ovulation in human could be induced by infusion of 600 μg of GnRH agonist for 6 h and then followed by single dose 400 μg subcutaneously.[1] GnRH agonist as an ovulation trigger has been very well investigated in IVF cycles since its use has been shown to decrease the incidence of OHSS remarkably.[2-6]

GnRH agonist trigger mimics the natural preovulation surge more closely due to internal FSH surge as well. FSH surge in a natural cycle is supposed to help in resumption of meiosis, further expansion of cumulus cells surrounding the oocyte and stimulates hyaluronic acid synthesis by oocyte cumulus cell complex for final release of oocyte.[7-11]

Lamb *et al*. in a randomised trial demonstrated that addition of FSH bolus along with hCG trigger significantly improves fertilization rate signifying better oocyte competence.[12] Similarly, GnRHa trigger combined with hCG trigger has been shown to improve cytoplasmic maturity of oocytes with better fertilization rates.[13,14] Use of GnRHa trigger may be associated with better maturity and quality of oocytes due to internal FSH surge along with LH.

The side effect of using GnRHa as ovulation trigger observed in IVF cycles is luteal phase defect due to less sustained LH release from pituitary to support corpus luteum. Mean serum LH and FSH levels are elevated for 34 h after GnRH agonist administration. In contrast, mean serum hCG levels are elevated for approximately 6 days after the administration of hCG, and serum FSH levels do not change.[15] In IVF cycles, studies have demonstrated that with GnRHa trigger, clinical pregnancy rates (CPR) is less due to the luteal phase defect.[6,16-19] Sufficiency of the luteal phase is dependent upon tonic LH release from pituitary to support corpus luteum in the postovulatory phase.[20,21] With multiple follicle development due to hyper oestrogenic environment, the pituitary gets suppressed and tonic release of LH is affected leading to early luteolysis in such situation.[22] Hence, the question arises that in infertile women with only few follicles undergoing IUI with oral ovulogens, will the luteal phase be affected due to choice of trigger? Hypothetically, luteal phase should be normal, if the number of follicles is not too many. Hence, in cases of IUI, GnRHa may be proposed as an ovulation trigger with better mimicking of natural surge without affecting the luteal phase with the hope of better oocyte maturity hence better pregnancy chances.

In the present study, we aimed to evaluate CPR in IUI cycles with the use of oral ovulogens combined with ovulation triggering agent as hCG or GnRH agonist.

Aims and objectives

To compare the effectiveness of GnRH agonist versus urinary hCG as an ovulation trigger for final oocyte maturation in IUI cycles and its impact on CPR in patients undergoing IUI cycle with oral ovulogens.

Materials and Methods

Study population

Records of infertile women who underwent IUI in a tertiary care IVF center between January 2019 and January 2020 with oral ovulogens were analyzed.

Type of study

The type of the study was retrospective analysis.

Procedure

The records of infertile women who underwent IUI with oral ovulogens between January 2019 and January 2020 were retrieved and analysed. Ethical committee approval was obtained on 25/05/2021 (No: F.1/IEC/IFS/2021/No.02). At our center, the patients give informed consent whether or not their case data can be utilised for the purpose of education and research. The records analysed were all of patients who had given consent for use of their case data. Since it was a pilot study, sample size was not calculated.

Inclusion criteria

Infertile women of not more than 38 years of age who underwent their IUI with oral ovulogens (either Clomiphene citrate or Letrozole), using husband's sperms were included in the study.

Exclusion criteria

Women with more than 38 years of age.

Women with 2 or more IUI failures earlier.

Donor insemination cycles.

Initiated but cancelled IUI cycles due to any reason.

IUI cycles in which gonadotropins were used either alone or in combination with oral ovulogens.

Women who had a history of rupture of follicles at small size in earlier cycles.

Women who had a history of premenstrual spotting.

Ovarian stimulation

In each IUI cycle, ovarian stimulation had been performed either by Clomiphene citrate or Letrozole starting from day of menstrual cycle for 5 days. Number of follicles, size of follicle at which trigger was given and endometrial response were analysed by the follicular study sheet.

The standard protocol regarding timing of trigger during the study period was to give maturation trigger when the

size of leading follicle reached more than or equal to 18 mm with endometrium more than or equal to 7 mm. In cases where the endometrium was still thin (<7 mm), trigger was not given till the time follicle reached approximately 25–26 mm or urine LH surge became positive, whichever was earlier.

The ovulation trigger used was either 10,000 IU of highly purified urinary hCG intramuscularly or triptorelin 0.2 ml subcutaneously. The record analysis and interaction with the infertility consultants showed that the choice of trigger was alternate and not based on any case characteristics.

IUI had been performed 36–40 h after trigger injection. Luteal phase support (LPS) with oral Dydrogesterone (10 mg) twice daily had been given in all cycles for 17 days following IUI. Records of urine pregnancy test, serum beta hCG test and subsequent follow-up ultrasound for cardiac activity were analyzed for the estimation of CPR.

For the purpose of analysis, women who received GnRH agonist trigger were categorised as belonging to Group A and women who received hCG trigger in Group B.

Outcomes

The primary outcome studied was CPR among both groups. CPR was defined as the presence of intrauterine gestation sac with cardiac activity. The secondary outcome studied was the incidence of OHSS in both groups.

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± standard deviation. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected, then nonparametric test was used.

Statistical tests were applied as follows

1. Quantitative variables were compared using the independent *t* test/Mann–Whitney test (when the data sets were not normally distributed) between the two groups
2. Qualitative variables were compared using the Chi-square test.

$P < 0.05$ was considered statistically significant.

The data were entered in MS Excel Spreadsheet and analysis was done using the Statistical Package for the Social Sciences (SPSS) software version 21.0. IBM SPSS Statistics for Windows, Version 21.00, IBM, Armonk, NY, United States of America. Categorical variables were presented in number and percentage (%).

Results

During the study period, 280 women underwent their first or second IUI with oral ovulogens.

Shows Table 1, baseline characteristics such as age, duration for infertility, indication for IUI, and type of infertility. Both the groups were similar in baseline characteristics.

Table 2 shows stimulation characteristics of treatment cycle. No significant differences were observed in endometrial thickness, type of ovulogen used, no number of follicles, and follicle size at the time of trigger.

Table 3 shows the outcome of IUI cycles-CPR.

In Group A (GnRHa trigger) and in Group B (hCG trigger), CPR was 16.28% (21/129) versus 10.60% (16/151), respectively, which was not found to be statistically significant with $P = 0.162$.

No case of ovarian hyper stimulation was observed in both groups.

Subgroup analysis was carried out to analyse whether the choice of ovulogen made a difference in pregnancy outcome. In both letrozole and clomiphene cycles, there was a trend toward better CPR in Group A in comparison to Group B, although the difference was not statistically significant [Table 4].

Further subgroup analysis was done to determine, whether there was a difference in CPR with these two types of triggers due to different indications for IUI. Again no statistically significant differences were observed [Table 5].

Discussion

This study shows that with GnRH agonist trigger, there is a trend toward higher CPR as compared to hCG trigger in IUI cycles with oral ovulogens, although the difference is not found to be statistically significant.

In IVF cycles prevents, it is now well established that GnRH agonist trigger OHSS, but at the cost of lesser pregnancy rate due to luteal phase defect.[23,24] There are studies to suggest that with GnRH agonist trigger, oocyte quality, and maturity may be better due to more physiological internal LH as well as FSH surge, something which is lacking in hCG triggering.[7-11,25]

In a natural cycle, the corpus luteum is supported by LH secreted regularly from pituitary. However, in cycles with multiple follicles, collective hypersecretion of steroid hormones (both estrogen and progesterone) exerts negative feedback on pituitary leading to cessation of LH secretion from pituitary and early luteolysis. In mildly stimulated IUI cycles where. Furthermore, it may

Table 1: Baseline characteristics

Characteristic	Group A GnRHa trigger (*n*=129), *n* (%)	Group B hCG trigger (*n*=151), *n* (%)	Total (*n*=280), *n* (%)	*P*
Age (years), mean±SD	30.47±4.87	31.19±4.64	30.85±4.75	0.179
Duration of infertility (years), mean±SD	3.12±1.34	2.97±1.68	3.01±1.44	0.15
Indications for IUI				
Mild male factor	21 (16.28)	27 (17.88)	48 (17.14)	0.845
PCOS	31 (24.03)	29 (19.21)	60 (21.43)	0.404
Poor ovarian reserve	25 (19.38)	36 (23.84)	61 (21.79)	0.449
Single blocked tube	13 (10.08)	10 (6.62)	23 (8.21)	0.406
Mild endometriosis	4 (3.10)	2 (1.32)	6 (2.14)	0.419
Unexplained infertility	35 (27.13)	47 (31.13)	82 (29.29)	0.464
Type of infertility				
Primary	94 (72.87)	113 (74.83)	207 (73.93)	0.709
Secondary	35 (27.13)	38 (25.17)	73 (26.07)	

GnRha=Gonadotropin-releasing hormone agonist luteinizing hormone, hCG=Human chorionic gonadotropin, SD=Standard deviation, PCOS=Polycystic ovary syndrome, IUI=Intrauterine insemination

Table 2: Stimulation characterisitics

Stimulation characteristics	Group A GnRHa trigger (*n*=129)	Group B hCG trigger (*n*=151)	Total (*n*=280)	*P*
Ovulogen used, *n* (%)				
Letrozole	98 (75.97)	102 (67.55)	200 (71.43)	0.12
Clomiphene	31 (24.03)	49 (32.45)	80 (28.57)	
Mean endometrial thickness (mm), mean±SD	7.89±0.87	8.25±1.35	8.09±1.17	0.082
Number of follicles, mean±SD	1.29±0.47	1.36±0.55	1.29±0.47	0.359
Mean follicle diameter, mean±SD	19.43±1.44	19.59±1.29	19.52±1.36	0.057

GnRha=Gonadotropin-releasing hormone agonist luteinizing hormone, hCG=Human chorionic gonadotropin, SD=Standard deviation

Table 3: Result

Characteristic	Group A GnRHa (*n*=129), *n* (%)	Group B hCG (*n*=151), *n* (%)	Total (*n*=280), *n* (%)	*P*
CPR	21 (16.28)	16 (10.60)	37 (13.21)	0.162
OHSS	0	0	0	0.499

CPR=Clinical pregnancy rate, GnRha=Gonadotropin-releasing hormone agonist luteinizing hormone, hCG=Human chorionic gonadotropin, OHSS=Ovarian hyperstimulation syndrome

be investigated whether GnRH agonist trigger can lead to better pregnancy rate in IUI cycles by virtue of its being more physiological and leading to both FSH and LH surge. Our study has shown that this hypothesis may have some merits and needs to be confirmed in larger well-designed randomized controlled trials.

In a Randomized controlled trial of 110 infertile women undergoing IUI,[26] the CPR was higher in GnRHa trigger group than in hCG trigger group, but the difference was not statistically significant (26.9% vs. 20.8%, respectively, $P = 0.46$). Furthermore, the incidence of OHSS was not different between the two groups ($P = 0.11$).

In contrast, a recent prospective comparative trial by Le *et al*. in spontaneous ovulation cycle and in human menopausal gonadotrophin stimulated cycles in 197 women concluded that CPR was lower in GnRHa group (23.2% vs. 13. 3%), although the difference was not found to be statistically significant.[27] Here it may be argued that GnRH agonist trigger may not be a suitable choice in IUI cycles where multiple follicles are expected, particularly in gonadotropin-induced cycles.

To analyse whether GnRH trigger works better with a particular type of ovulogen, subgroup analysis of CPR as per different ovulogen used was carried out in our study. This analysis shows that better pregnancy rate with GnRHa trigger was maintained irrespective of type of oral ovulogen used.

On subgroup analysis as per different indications for IUI, overall no significant differences were observed in CPR between Group A and Group B and is not responsible for difference in CPR observed between the Groups A and B.

The strength of our study is analyzing IUI cycles with oral ovulogens and not including gonadotropin cycles.

One of the weakness of our study is that all patients received LPS without the actual evidence that it helps in improving pregnancy rate in IUI cycles mildly stimulated

Table 4: Clinical pregnancy rate according to ovulogen used - subgroup analysis

Drug	Group A (GnRHa)	CPR in Group A, *n* (%)	Group B (HCG)	CPR in Group B, *n* (%)	*P*
Letrozole	98	16 (16.32)	102	11 (10.07)	0.347
Clomiphene	31	5 (16.1)	49	5 (10.2)	0.664

CPR=Clinical pregnancy rate, GnRha=Gonadotropin-releasing hormone agonist luteinizing hormone, hCG=Human chorionic gonadotropin

Table 5: Clinical pregnancy rate according to indication for intrauterine insemination

Factor	Group A GnRha trigger (*n*=129)	CPR in Group A, *n* (%)	Group B hCG trigger (*n*=151)	CPR in Group B, *n* (%)	*P*
Male factor	21	3 (14.29)	27	2 (7.41)	0.641
PCOS	31	10 (32.26)	29	8 (27.59)	0.693
Poor ovarian reserve	25	2 (8)	36	0	0.164
Single blocked tube	13	0	10	1 (10)	0.435
Endometriosis	4	2 (50)	2	0	0.467
Unexplained infertility	35	4 (11.43)	47	5 (13.51)	1

CPR=Clinical pregnancy rate, GnRha=Gonadotropin-releasing hormone agonist luteinizing hormone, hCG=Human chorionic gonadotropin, PCOS=Polycystic ovary syndrome

with oral ovulogens. Limited data exist concerning the need for LPS in oral ovulogen-induced IUI cycles. A randomized controlled trial by Kyrou *et al*. on 468 women undergoing IUI with clomiphene citrate showed no difference in ongoing pregnancy rate-8.7% versus 9.3% in LPS versus no support groups (P = 0.82). The conclusion of their study was that LPS should not be added to IUI cycles mildly stimulated with clomiphene citrate in normoovulatory women.[28] Hill *et al*. in a systematic review and meta-analysis in 2013 concluded that progesterone LPS may be of benefit to patients undergoing ovulation induction with gonadotropins in IUI cycles, while progesterone support did not benefit patients undergoing ovulation induction with Clomiphene citrate, suggesting a potential difference in endogenous luteal phase function depending on the method of ovulation induction.[29] An updated meta-analysis from the same group in 2017 also concluded the same, that progesterone support did not benefit patients undergoing ovulation induction with clomiphene citrate or clomiphene plus gonadotropins.[30] Another meta-analysis by Miralpeix *et al*. also concluded that progesterone LPS did not benefit patients undergoing IUI cycle with clomiphene citrate.[31] It would be interesting to see the comparison of two triggers without any LPS. Since the luteal phase was supported in all cycles, we were also not able to compare the adequacy of luteal phase with the help of serum progesterone levels or by comparing the duration of the luteal phase in both groups. Further studies where the adequacy of luteal phase is compared between the two groups are needed to ascertain or refute whether GnRHa trigger itself is responsible for luteal phase defect. Another weakness of our study is it being retrospective in nature and also not analysing the live birth rate.

Conclusions

Our results suggest that there is a trend toward higher CPR when GnRH agonist is used as an ovulation trigger in comparison to hCG trigger in IUI cycles induced with oral ovulogens, although the difference in CPR was not found to be statistically significant. Further well-designed, randomized controlled trials with a large number of patients are needed to confirm the benefits of GnRH agonist trigger in IUI cycles.

Data availability

The original data is available with the first author i.e. Dr Rashmi Sharma at Origyn Fertility and IVF , NSP , Pitampura, New Delhi. The authors are willing to share it to the journal upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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