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Original Research Article

Prediction of efficacy of gonadotropin releasing hormone agonist trigger for final oocyte maturation through post-trigger 12-hour luteinizing hormone, follicle stimulating hormone and progesterone levels in COS: a prospective study

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ABSTRACT

Background: Circulating levels of luteinizing hormone (LH), follicle stimulating hormone (FSH) and progesterone (P4) in serum after administration of gonadotropin releasing hormone agonist (GnRHa) trigger for final oocyte maturation are found to be predictive of oocyte maturity. This prospective study was conducted at a tertiary care centre to evaluate relationship between serum LH, FSH and P4 levels at 12-h post-trigger and oocyte maturity rate and to predict which hormone has maximum sensitivity and specificity for appropriate oocyte maturation.
Methods: Women at risk of ovarian hyper-stimulation syndrome who underwent either autologous or donor IVF cycle treated with flexible GnRH antagonist protocol were taken as participants of the study. GnRHa as trigger for final oocyte maturation was given. After 12 hours of agonist trigger, blood sample was drawn to assess LH, FSH and P4 levels in serum. Continuous variables were expressed as mean±SD. Independent sample t test was used for continuous variables which were normally distributed and Mann-Whitney U test for data not normally distributed. Main outcome measures were number of oocytes retrieved, oocyte maturity rate, fertilization rate, cleavage rate and grade of embryos.
Results: There was a statistically significant reduction in number of retrieved oocytes, maturity rate, fertilization rate and grade 1 embryos with a concentration of serum LH and P4 less than the cut off value ($p < 0.05$).
Conclusions: Serum LH and P4 level less than the cut off value at 12-hour post-trigger with GnRHa is associated with a dramatically less oocyte maturity rate and fertilization rate.

Keywords: Gonadotropin releasing hormone agonist, Oocyte maturation, Ovarian hyper-stimulation syndrome, Post-trigger LH level, Post-trigger progesterone level

INTRODUCTION

Ovarian hyper stimulation syndrome (OHSS) is a life-threatening iatrogenic complication characterized by hemo-concentration, hemodynamic instability and hypoxia.[1] Incidence has dramatically increased over past three decades due to increased use of ovulation induction drugs and assisted reproduction techniques. OHSS may result in significant morbidity, psychological distress and rarely mortality. Mild OHSS has no adverse consequences but severe OHSS is associated with higher morbidity.[2]

HCG binds to LH receptor causing follicular maturation, luteinization and ovulation. It has 6-7 times increased biological activity with half life persisting upto 5-6 days.[3]

Pertaining to greater affinity to LH receptors ,it has prolonged luteotropic effect increasing risk of development of OHSS in hyper-responders.

Huge discovery of agonist by Andrew Shally and Guillemin led to its usage in field of ovulation by Nakano et al with synthetic GnRH infusion.[4] GnRHa trigger is associated with lesser size and number of corpora lutea and decreased expression of steroidogenic enzymes. The use of GnRHa for inducing oocyte maturation in individualized ovarian stimulation cycles utilizing GnRH antagonist for pituitary suppression has proved to be a very effective measure in prevention of risk of OHSS.[5] GnRHa trigger has been a tremendous revolutionary tool in history of development of assisted reproductive technology leading to a new era of administering it as a sole method in having OHSS-free clinic.[6] This concept came from the short half-life of endogenous luteinizing hormone surge which results in early luteolysis of corpus luteum.[7] Optimal modified luteal phase support after GnRH agonist trigger is utmost important in such cases as there may be impaired endometrial receptivity because of defective corpus luteal function.[8] There has been a concern regarding effectiveness of agonist trigger in maximizing the retrieval rate and yield of mature oocytes along with avoidance of empty follicle syndrome.[9] Subsequent rise of serum LH and progesterone after agonist trigger indicates effective endogenous flare .This is an indirect measure to show oocyte maturation if hormone surge has crossed a particular threshold of serum concentration.[10]

The study has tried to decipher and evaluate the magnitude of endogenous LH surge and progesterone rise after agonist trigger and its predictive potential in measuring total number of oocytes retrieved and maturity rate.

METHODS

Study design and participants

This prospective interventional study was conducted in a tertiary care center. 400 patients predicted as hyper-responders based on ovarian reserve tests undergoing IVF in an antagonist protocol between April 2017 and May 2018 were recruited for the study. At the time of allocation, informed written consent was taken. Study was approved by the Institutional Review Board and Ethics Committee.

Sample size

Incidence of mild OHSS in high risk groups that is hyper-responders undergoing IVF has been calculated as around 20-30% based on previous studies. It was hypothesized that GnRH agonist trigger will lead to an 80% decline in the incidence of OHSS. Based on significance level of 0.05 and 95% power, it was anticipated that with a fallout rate of about 10%, sample size of at least 100 patients need to be recruited over two year period. Finally we analysed 400 cases after strict allocation according to inclusion criteria and excluding drop outs.

Inclusion criteria

- Age 21-35 years
- Normal early follicular phase serum FSH concentration (<10.0 IU/L)
- Body mass index (BMI) >18 and <30 kg/m^2
- Woman with antral follicle count of more than/equal to 15 or AMH ≥3.5ng/ml
- Presence of both ovaries
- Stimulation by GnRH antagonist protocol
- Willingness to participate in the study.

Exclusion criteria

- Chronic diseases like overt hypothyroidism and hyperthyroidism, kidney or liver failure, late-onset adrenal hyperplasia and diabetes
- Severe endometriosis
- Severe male factor infertility
- Multiple fibroids
- Previous IVF treatment failure
- Patients with hypogonadotrophic hypogonadism
- Uterine abnormalities.

Statistical analysis

Descriptive statistics were presented as mean and standard deviation for continuous variables. Frequencies and proportions were deciphered for categorical variables. Independent sample t test was used for continuous variables which were normally distributed and Mann-Whitney U test for data not normally distributed. Chi-square test or Fisher's exact test was used for categorical variables where appropriate. Odds ratio (OR) with 95% confidence intervals (CIs) was calculated. For post-hoc analysis one-way ANOVA test and Bonferroni test were used. In addition, receiver operating characteristic curve was used. All tests were two-sided with p-value taken less than 0.05 as statistically significant.

Ovarian stimulation and monitoring

Prior to starting ovarian stimulation, psychological counselling was done. Baseline scan by trans-vaginal ultrasound (Voluson P6) using a 4 - 6 MHz vaginal probe was performed and follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and anti-mullerian hormone (AMH) were done on day 2/3 of menstrual cycle to recruit the patient depending on inclusion criteria variables. Controlled ovarian stimulation (COS) was started thereafter with either recombinant Follicle stimulating hormone (R-FSH), (Gonal F, Merck) with or without human menopausal gonadotropin (hMG; Menopur). Starting dose was

calculated based on age, BMI, AFC, AMH and baseline FSH level ranging between 112.5-200 IU daily for four days.[11] Monitoring was done with ultrasound and serum E2, LH and P4 measurements to adjust dose of gonadotropins accordingly. Antagonist (Cetrotide, Merck) 0.25 mg subcutaneously (flexible antagonist protocol) was added when leading follicle was ≥13-14 mm in diameter and/or serum E2 > 350-400 pg/mL, continued until trigger day. Patient was given triptorelin acetate (Decapeptyl) trigger 0.2 mg subcutaneously at night when criteria of atleast 3 follicles ≥17 mm as mean diameter met. Next morning after 8-12 hours post injection, serum FSH, LH and P4 values were measured and assessed to ensure efficacy and adequacy of trigger in inducing LH surge and final oocyte maturation. Trans-vaginal oocyte retrieval was performed 34-36 hours post trigger under intravenous sedation with single lumen oocyte retrieval needle (Swemed, vitrolife).

No other interventions were done for prevention of OHSS. Number of oocytes retrieved and number of mature oocytes (maturity rate) was calculated. Intra-cytoplasmic sperm injection (ICSI) was done for all cases irrespective of associated male factor as a standard operating protocol. Fertilization was assessed 18 hours after ICSI and confirmed by presence of two pronuclei. Embryos were graded as per Istanbul consensus.

For cleavage-stage embryos: Grade 1 (G1) (good): <10% fragmentation, stage-specific cell size, and no multi-nucleation. Grade 2 (G2) (fair): 10%–25% fragmentation, stage-specific cell size for majority of cells, and no evidence of multi-nucleation. Grade 3 (G3) (poor): severe fragmentation (>25%), cell size not stage specific, and with evidence of multi-nucleation. Grade 1 and 2 embryos were taken as top-quality embryos which were frozen as a standard operating protocol. Embryos of grade 3 if formed were discarded after taking written informed consent from the commissioning couple.

Assessment of hormones via immunoassay

Electro-chemi-luminescent automated immunoassay system (Roche Cobas e411) was used to measure serum levels of all hormones.

Outcome

Primary outcome was maturity rate. Secondary outcome was number of oocytes retrieved, fertilization rate, cleavage rate and quality of embryos. Oocyte maturity was defined as the ratio of MII oocytes to the total number of cumulus oocyte complexes retrieved. Fertilization rate was defined as the ratio of normal fertilized oocytes (2PNs) to the number of MII oocytes. Cleavage rate was defined as the ratio of number of cleavage stage embryos on day 2 to the number of fertilized oocytes.

It was hypothesized that rise in LH > 45IU/L and P4 > 13.05 ng/ml from our ROC curve post triggering may help in prediction of maturity rate, fertilization rate, cleavage rate and grade of embryos.

RESULTS

Participant flow

The participant flow is shown in Figure 1. 411 patients were screened for the study, after proper allocation 402 patients underwent IVF stimulation cycles with antagonist protocol. 2 patients had empty follicle syndrome and thus were excluded from analysis.

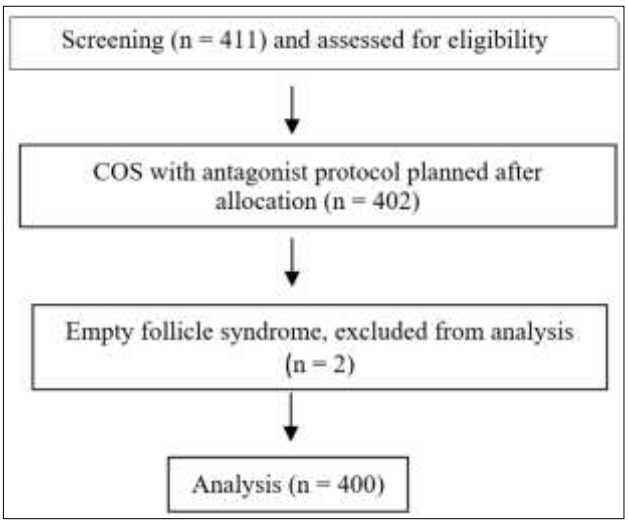

Figure 1: Participant flow.

Table 1: Baseline and stimulation characteristics.

Variable	Mean±SD
Age (years)	28.27±3.883
BMI (kg/m^2)	24.36±4.176
TSH (mu/l)	2.70±1.219
PRL (ng/ml)	15.32±6.377
Homocysteine (mmol/l)	11.10±5.623
HBA1C (%)	5.45±0.459
AMH (ng/ml)	5.28±3.366
FSH (IU/L)	5.57±1.415
LH (IU/L)	7.47±4.537
AFC (n)	24.10±6.952
Peak E2 (pg/ml)	4902.64±2104.912
Peak LH (IU/L)	3.31±2.275
Peak P4 (ng/ml)	1.44±0.977
OOCYTE (n)	18.87±7.216
MII (n)	13.64±5.410
Yield (%)	73±13.4
Post 12-hour FSH (IU/L)	24.14±11.794
Post 12-hour LH (IU/L)	45.53±20.555
Post 12-hour P4 (IU/L)	13.05±6.590

Baseline and stimulation cycle characteristics

Baseline, routine and stimulation cycle characteristics of 400 cases (275 autologous and 125 donor cycles) are given in Table 1.

The relationship between FSH, progesterone and LH level at 12-h post-trigger and number of oocytes, maturity rate, fertilization rate, cleavage rate and grade of embryos is depicted in Table 2. None of the study patient developed OHSS. Data from 400 cycles were plotted on locally weighted scatter plot smoothing (LOESS) curve to determine association between maturity rate and post trigger LH values and predict cut off value for optimal number of mature oocytes and maturity rate as shown in Figure 2. Increased sensitivity and specificity is shown when all three parameters that is post-trigger FSH, LH and progesterone values are combined together and assessed for outcome (Figure 3 and Table 3). We made a receiver operating characteristics (ROC) curve and found area under curve for post-trigger LH, FSH and P4 was 0.685, 0.573 and 0.617 respectively. Statistics of the study showed that serum LH concentration of 45.5 IU/L and progesterone concentration of 13.05 ng/ml represents critical threshold level below which there may be a negative impact on oocyte yield, maturity, fertilization, cleavage and grade of embryos. Thus, finding the optimum levels of LH and progesterone can be used for prediction of number of retrieved oocytes, maturity rate and fertilization rate.

Table 2: For post 12-hour FSH, P4 and LH values.

		Number of oocytes	Number of MII	Fertilization rate	Cleavage rate	Grade 1 embryos
Correlation coefficient	FSH	0.031	0.080	0.089	0.084	0.136
	P4	0.055	0.086	0.119	0.119	0.100
	LH	0.048	0.248	0.292	0.283	0.296
Significance	FSH	0.534	0.109	0.076	0.094	0.007
	P4	0.268	0.086	0.018	0.017	0.045
	LH	0.337	0.000	0.000	0.000	0.000

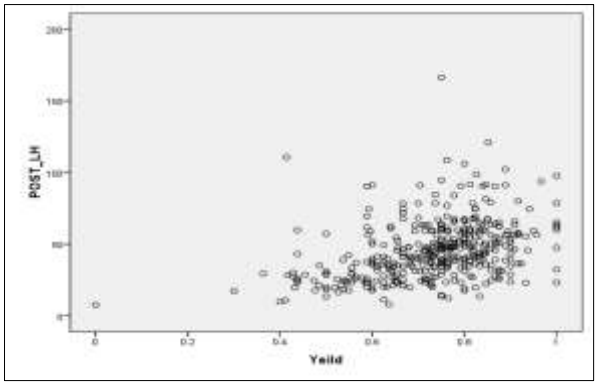

Figure 2: Scatter plot for depiction of relation between post-trigger LH level and yield.

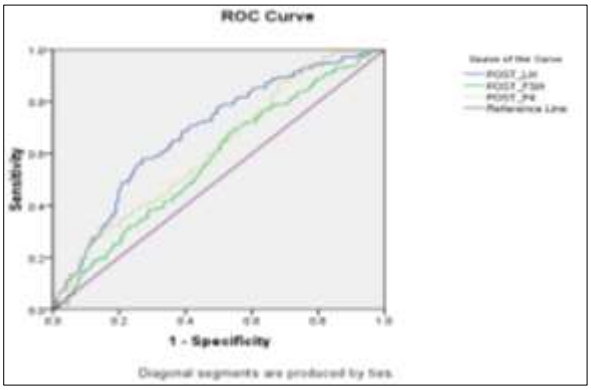

Figure 3: ROC curve.

Table 3: Illustration of area under ROC curve.

Variable	Area under curve	Standard error	p value
Post 12-hour LH	0.685	0.027	0.000
Post 12-hour FSH	0.573	0.029	0.015
Post 12-hour P4	0.617	0.029	0.000

DISCUSSION

Since long time, exogenous HCG is being used to induce final oocyte maturation due to the property of h CG and LH binding to and activating same receptor. Compared to natural cycle/HCG induced LH surge, GnRHa induced LH surge is short-lasting for about 24 hours having short ascending phase of 4 hours and descending phase of 20 hours.[12] Thus there is a shorter flare of LH and FSH as compared to natural cycles. This small duration of peak decreases luteinizing stimulus on the granulosa cells thus limiting production of vascular endothelial growth factor, reducing incidence of OHSS to almost zero.[13] This is till now the most effective strategy which eliminates OHSS incidence in high responders after ovarian stimulation in antagonist IVF cycles in combination with cryopreservation leading to an "OHSS free clinic". It seems to be a perfect tool in tailoring and individualizing stimulation protocols for hyper-responders without

causing any iatrogenic complication making them safe and patient- friendly.[14] GnRHa triggering is also proven to be useful in patients with breast cancer for fertility preservation. Rapid luteolysis and no supra-physiological estradiol and progesterone levels following agonist trigger have been postulated as safe option during fertility preservation. Reddy et al corroborated that GnRHa trigger arm yielded significantly more mature oocytes and higher fertilization rates than the h CG trigger arm and resulted in lower estrogen levels and OHSS rate in breast cancer patients.[15] These findings have also been inferred by other recent studies.

LH concentration above threshold value for approximately 14-27 hours is necessary to resume meiosis and expansion of cumulus cells which leads to final maturation of oocyte both in natural and stimulated cycles. There may be a suboptimal response due to inadequate LH surge for specific magnitude and duration and inadequate FSH surge with suboptimal signalling at level of follicles. Assessing adequacy wit post trigger hormone values aid as counseling tool for the couple for having an approximate idea of maturity of follicles expected before actual procedure and rescuing the cycle.[16]

GnRHa displaces GnRH antagonists from pituitary receptors and results in a flare in both LH and FSH.[17-18] A time interval of atleast 10-12 hours is necessary between last dose of GnRH antagonist administration and GnRHa trigger to ensure optimal endogenous LH surge as there is competitive inhibition at the receptor site by antagonist.[8] It has been illustrated that when agonist trigger is given, there is a small FSH surge also which promotes LH receptor formation in luteinizing granulosa cells, nuclear maturation and cumulus expansion, thus increasing oocyte competence and mimicking endogenous process. The FSH peak following LH rise is a surrogate surge which involves induction of plasminogen activators for follicular rupture and nuclear maturation. This explains retrieval of more metaphase II oocytes after GnRH agonist trigger versus HCG trigger.[19] It is difficult to predict oocyte yield and maturity rate with a cut off of post-trigger LH value because threshold amplitude of LH surge required to initiate oocyte maturation in natural cycles is still not known.[20]

Studies in rats showed that only 5% of normal LH surge amplitude is needed for it. There is variability in amplitude and length of LH curve also.[21] Trials have shown that in GnRHa triggered cycles, with every unit increase in LH is associated with 13 % increase in odds of clinical pregnancy.[22] Shorter time interval < 4-8 hours will definitely detect higher LH level and lower progesterone value whereas longer post trigger intervals >12-15 hours will result into lower LH and higher progesterone levels. Optimally elevated post-trigger progesterone concentration with borderline LH concentration may still result in successful outcome but reverse is not true.[23]

Temporary or permanent dysfunctions of HPO axis can result in suboptimal flare effect leading to incomplete or deficient oocyte maturation.[24] High responders may have suboptimal response because of self-priming phenomenon of gonadotroph cells in pituitary with supra-physiological levels of estradiol concentration.[25]

Resulting endogenous FSH and LH action on follicular granulosa and theca cells is inadequate due to increased number of intermediate follicles and decreased neo-vascularisation in hyper responders. Patients with GnRH receptor mutations also do not respond appropriately to GnRHa resulting in suboptimal endogenous LH surge.[26] LH measurement has few inherent challenges as inter-subject variations in basal LH and short half life along with intra-subject diurnal variations and fluctuations. While interpreting post-trigger LH and progesterone concentrations, it is important to keep in mind that proper interval time between trigger administration and assay is present as LH is highly time-dependent.

Several authors have concluded relationship between levels of LH, FSH and P4 post 12-hour GnRHa trigger and number of mature oocytes and maturity rate.[27] The study has shown a cut off of 45.5 IU/L for LH and 13.05ng/ml for progesterone. Shapiro et al. deciphered that there is decrease in number of oocytes retrieved, number of mature (MII) oocytes and yield when serum LH levels 12 hours after GnRH agonist trigger was <52 IU/L and huge decrease in yield and maturity when level was < 12IU/L, findings being consistent with the study.[28] Study conducted by Chen et al showed cut off of 30 IU/L for LH levels.[29] Kummer et al. studied patients triggered with GnRH agonist to determine post-trigger LH and progesterone levels (<3.5 ng/ml) for predicting zero oocytes at time of oocyte retrieval.[30]

Meyer et al, studied risk factors such as prolonged use of contraception and LH<1.5 IU/L on trigger day for suboptimal response. He also depicted threshold at 15mIU/mL LH above which all responses were adequate and below which resulted in either very a smaller number of oocytes or empty follicle syndrome. Thus, post-trigger LH and progesterone is helpful in predicting the response and counseling the patients regarding possibility of empty follicle syndrome and approaches to rescue it by triggering with HCG before proceeding directly to retrieval.

It has been illustrated that when agonist trigger is given, there is a small FSH surge also which promotes LH receptor formation in luteinizing granulosa cells, nuclear maturation and cumulus expansion, thus increasing oocyte competence and mimicking endogenous process. The FSH peak following LH rise is a surrogate surge which involves induction of plasminogen activators for follicular rupture and nuclear maturation. This explains retrieval of more metaphase II oocytes after GnRH agonist trigger versus h CG trigger.[19]

CONCLUSION

It is utmost important to determine factors which help in prediction of oocyte yield after GnRHa trigger induced oocyte maturation. Reference values of hormone assessment post 12 hour agonist trigger can be a useful guide to decide on whether to proceed for retrieval or to augment with low dose of HCG to achieve maximum number of mature oocytes. Such reference values may aid all clinicians in deciphering further management and improving IVF outcome.

Strength and limitations of the study includes various points. The study findings can be generalized to all high responders. Assessing the efficacy of the trigger helps in avoiding low oocyte yield and empty follicle syndrome. Till date no study has been done on Indian population for assessing adequacy of GnRHa trigger. Measurement of serum hormones was done between 8 to 12 hours post GnRHa trigger and exact same time could not be maintained. LH peak level might have been missed due to short ascending limb of LH rise of approximately 4 hours after trigger injection.

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