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Original Research Article

The association of serum progesterone on day of hCG trigger and IVF outcome

Parul Garg*

Department of Reproductive Medicine, Sarvodaya Fertility and IVF Centre, Delhi, India

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***Correspondence:**
Dr. Parul Garg,
E-mail: drparul23@yahoo.co.in

ABSTRACT

Background: A large number of clinical studies have examined the effect of rise in serum progesterone levels on the day of hCG administration in GnRH agonist and antagonist cycle, on pregnancy rates. The mechanisms of this rise in progesterone levels on day of hCG trigger are controversial and also the results of these studies are variable.
Methods: This prospectively observational cohort study was conducted from November 2020 to November 2021 at Sarvodaya IVF centre, Delhi. 279 patients completed an IVF/ICSI-ET cycle during the study period and were included in the final analysis. The standard GnRH antagonist (fixed or variable) and long GnRH agonist COS protocols were used. Participants undergoing COS with all gonadotropins were recruited. The study population was subgrouped into two groups according to P4 level on day of hCG trigger (calculated according to ROC curve): Group A ($p \leq 1.5$ ng/dl, n=140/279, 50.17%) and Group B ($p > 1.5$ ng/dl, n=139/279,49.82%).
Results: The dose of Gonadotropins required, terminal estradiol levels and number of oocytes retrieved were significantly required higher in group B as compared to group A. The percentage of subjects with progesterone rise on the day of hCG trigger were significantly more in agonist protocol (56.1%) as compared to antagonist protocol(43.9%, $p<0.001$). Pregnancy rate was significantly higher in group A (41.4%,58/114) when compared with group B (29.5%,41/139). The clinical pregnancy rate was also significantly more in group A (50/140,35.7%) as compared to group B (34/139,24.5%) ($p=0.041$).
Conclusions: Patients with higher levels of Progesterone (>1.5 ng/ml) on day of hCG trigger is associated with lower pregnancy rate and clinical pregnancy rates.

Keywords: Clinical pregnancy rate, Progesterone rise, hCG trigger

INTRODUCTION

Despite the use of GnRH analogue, subtle increase in serum progesterone levels beyond an arbitrarily defined threshold value have been observed at the end of the follicular phase in COS (Controlled ovarian stimulation) cycles for In vitro fertilization (IVF). Although the frequency of elevated serum progesterone level varies in COS cycles, incidence as high as 35% (5-35%) have been reported in individuals treated with GnRH agonists and 38% (9-38%) in those treated with GnRH antagonists.[1-6]

In natural cycles, there is a small physiological rise in serum progesterone (P4) levels prior to ovulation and it is considered essential for bringing about an increased LH receptor induction on granulosa cells for enhanced LH action. This rise in serum progesterone levels is due to increased responsiveness of granulosa cells to LH. However, the rise seen in stimulated cycles is far more than that in natural cycles, possibly due to higher number of follicles (stimulated by maintained high FSH (Follicle Stimulating Hormone) concentrations by dint of daily FSH injections), will produce and secrete more progesterone

into the ovarian vein than a single follicle in the normal mid-follicular phase, with declining FSH concentrations. In the event of ovarian stimulation-induced multiple-follicle growth, the progesterone output to the periphery will be magnified in accord with the number of follicles and the FSH drive. This is likely to impact upon progesterone concentrations in the periphery and may influence endometrial development. Thus, the three major components to the degree of progesterone secretion from the ovaries will be: (i) the number of follicles (or granulosa cells); (ii) the degree of trophic stimulus (FSH drive to granulosa cells); (iii) the degree of LH drive to theca cells, which encourages conversion of progesterone precursors to androgens and then oestrogen.[6]

The rise in progesterone levels then coupled with high estradiol levels may result in endometrial glandular stromal asynchrony which may commonly be associated with implantation failure due to luteal phase defect while having no influence upon oocyte/embryo development.[7-10]

A large number of clinical studies have examined the effect of rise in serum progesterone levels on the day of hCG administration in GnRH agonist and antagonist cycle, on pregnancy rates.The mechanisms of this rise in progesterone levels on day of hCG trigger are controversial and also the results of these studies are variable. Possible explanations for the discrepancies in the findings are the use of retrospective study design, the use of different protocols of controlled ovarian stimulation, and different cutoff levels for P4 at the time of data analysis. Some studies imprecisely define references for elevated serum P4 levels, and there is variation in the statistical methods used to estimate specific circulating P4 limit values and in the precision of P4measurements that use different immunoassays. Most investigators have agreed upon a cumulative deleterious effect on pregnancy rates as a result of this supra-physiological rise in progesterone in the late follicular phase.[11-20]

In this report, we present a prospective, noninterventional, observational, single centre cohort study aimed to evaluate the association between serum progesterone levels on day of hCG administration and pregnancy outcome in patients undergoing in vitro fertilization with COS using agonist and antagonist protocol as well as in cycles using drugs such as rFSH/LH versus only recombinant FSH (rFSH) and rFSH versus hMG (human Menopausal Gonadotropin) cycles.

Aims and objectives

To establish the level of serum progesterone on day of hCG administration above which it can affect the IVF outcome. To further establish the incidence of serum progesterone rise in an agonist and antagonist cycle as well as in cycles using cycles using drugs such as rFSH/LH versus only recombinant FSH (rFSH) and rFSH versus hMG cycles.

METHODS

This prospectively observational cohort study was conducted from November 2020 to November 2021 at Sarvodaya IVF Centre, Pitampura. Three hundred and fifty two infertile couples treated by IVF/ICSI-ET (In vitro fertlization/ intracytoplasmic sperm injection-embryo transfer) meeting the inclusion criteria were included in the study. Participants undergoing COS with all gonadotropins; recombinant or urinary FSH/urinary hMG or recombinant LH were recruited. The progesterone levels were obtained at three time points: Day 2 or 3 of IVF cycles, the day 6 of stimulation in long agonist as well as multiple dose antagonist protocol, the morning of hCG trigger.

The standard GnRH antagonist (fixed or variable) and long GnRH agonist COS protocols were used for all patients. The written informed consent was taken from all couples before recruiting the patients in the study.

Inclusion criteria

All women registered for IVF or IVF-ICSI using an agonist or antagonist protocol.

Exclusion criteria

Day 2 progesterone level greater than 2 ng/ml. Age greater than 37 years. ≥2 previous failed IVF cycles. Unclipped hydrosalpinx, intramural fibroid ≥4 cm, localized adenomyosis (>4 cm) or diffuse adenomyosis. Patient on DHEA (Dehydroepiandrosterone acetate) at the time of starting stimulation. Donor recipient cycles.

Cancellation criteria

Poor responders (≤3 oocytes retrieved). Endometrium ≤6 mm on day of oocyte retrieval. Embryos with poor morphology on day 2,3 and 5. Embryo transfer not done.

Outcome measures

Primary outcome measure

Pregnancy rate.

Secondary outcome measures

Clinical pregnancy rate. Pregnancy loss rate. Ectopic pregnancy rate. Incidence of serum progesterone rise in various protocols. Incidence of serum progesterone rise with cycles using drugs such as hMG/LH versus only recombinant FSH or urinary FSH cycles.

Pregnancy rate

Number of patients with serum beta hCG> 20mIU/ml on day 14 after OCR divided by the total number of cycles.

Clinical pregnancy rate

The number of clinical pregnancies expressed per 100 completed cycles.

Pregnancy loss

Miscarriage upto 12 weeks.

Ectopic pregnancy

A pregnancy in which implantation takes place outside the uterine cavity.[21]

Hormonal assay

The blood samples were drawn at three designated time points. The blood were collected aseptically, allowed to clot as soon as possible. No additives or preservatives were required to maintain integrity of the sample. The sample was analysed for progesterone with liaison progesterone assay which is a chemiluminescent immunoassay to be used with liaison analyzer, for quantitative determination of progesterone in human serum.

Statistical analysis

Sample size calculation

In Sarvodaya Fertility and IVF centre, the pregnancy rate in infertile patients undergoing IVF ranges from 35 – 40%. For the sample size calculation, we expected p=35%, with the precision error of estimation (d)=6%, and alpha=0.05 a sample size of at least 245 cases is needed. But we had taken at least 300 cases to counteract any drop out cases. Sample size was calculated using the formula for study $(Z^2 \times p \times q)/d^2$).

Statistical methods

Statistical testing was conducted with the statistical package for the social science system version Statistical package for social sciences (SPSS) 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analysed using either the chi square test or Fisher's exact test. A receiver operating characteristics (ROC) analysis was calculated to determine optimal cut-off values for (mention those variables name). The area under the curve and its 95% CI. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

RESULTS

In our study, 352 patients were recruited.279 patients completed an IVF/ICSI-ET cycle during the study period and were included in the final analysis. 73 patients did not meet the final inclusion criteria because they either had poor response (n=11) or endometrial thickness on the day of oocyte retrieval was ≤6 mm (n=4) or the embryos were poor morphology (n=14) or they did not undergo immediate ET because of suspected ovarian hyperstimulation syndrome (n=42). Two patients did not undergo ET due to fever with URI (upper respiratory tract infection) on the day of transfer. The protocols used in patients were either agonist (n=116) or antagonist (163). 30 patients out of 279 took rLH in addition to rFSH for gonadotropin stimulation and 24 patients took only hMG for gonadotropin stimulation and rest (225) took only rFSH.

Table 1: The demographic variables of patients in the two subgroups.

Variables	P4 (ng/dl) on day of hCG trigger						P value
	≤1.5 (n=140), Group A			>1.5 (n=139), Group B			
	Mean±SD	Min - Max	Median (IQR)	Mean±SD	Min - Max	Median (IQR)	
Age (years)	30.64±3.35	22-36	30.5 (28-33)	30.53±3.17	22-36	31.0 (28-33)	0.777
BMI (kg/m2)	25.87±3.78	17.3-37.9	25 (23-28.75)	26.26±5.54	16-67.7	25.6 (23.2-28.3)	0.494
Duration of infertility (years. months)	4.45±2.57	1-16	4 (3-6)	5.00±2.60	1-13	5 (3-6)	0.070
AMH (pmol/l)	30.55±18.71	4.6-119.0	24.95 (18.23-39.90)	34.28±23.12	5.7-131.5	28 (20-41)	0.240
Total dose of Gonadotropins required (IU)	1499.0±751.97	300-3725	1500 (875-2079)	2068±727.28	1050-4750	1935 (1500-2500)	<0.001

Continued.

Variables	P4 (ng/dl) on day of hCG trigger						P value
	≤1.5 (n=140), Group A			>1.5 (n=139), Group B			
	Mean±SD	Min - Max	Median (IQR)	Mean±SD	Min - Max	Median (IQR)	
Duration of stimulation (days)	8.59±1.54	6-13	8 (7.25-9)	8.50±1.33	6-13	8 (8-9)	0.863
Terminal serum E2(pg/ml)	1421.59±618.72	480-3715	1339 (901.25-1826)	1608.77±670.13	330-3406	2545 (1043-3962)	0.017
Number of oocytes retrieved	12.40±4.24	6-32	11 (10-15)	14.32±4.28	7-26	14 (11-17)	<0.001
Endometrial thickness on day of OCR (mm)	9.44±1.64	6.3-14.0	9.15 (8.30-10.58)	9.56±1.65	6.1-14.4	9.30 (8.40-10.60)	0.526
Number of embryos transferred	2.10±0.69	1-3	2 (2-3)	2.17±0.72	1-4	2 (2-3)	0.451

Table 2: The comparison between the two groups according to protocol.

Agonist/antagonist protocol	P4 (ng/dl) on day of hCG trigger				P value
	≤1.5 (n=140), Group A		>1.5 (n=139), Group B		
	Frequency	%	Frequency	%	
Agonist (n=116)	38	27.1%	78	56.1%	<0.001
Antagonist (n=163)	102	72.9%	61	43.9%	
Total	140	100%	139	100%	

Table 3: The comparison between two groups according to type of Gonadotropins usage.

Type of gonadotropins	P4(ng/dl) on day of hCG trigger				P value	hMG versus rFSH	rFSH versus rFSH + LH
	≤1.5 (n=140)		>1.5 (n=139)				
	Frequency	%	Frequency	%			
hMG (n=24)	14	10.0%	10	7.2%	0.493	0.460	0.397
rFSH (n=225)	109	77.9%	116	83.5%			
rFSH+LH(n=30)	17	12.1%	13	9.4%			
Total	140	100%	139	100%			

Table 4: The outcome of study.

Type of gonadotropins	P4(ng/dl) on day of hCG trigger				P value	hMG versus rFSH	rFSH versus rFSH + LH
	≤1.5 (n=140)		>1.5 (n=139)				
	Frequency	%	Frequency	%			
hMG (n=24)	14	10.0%	10	7.2%	0.493	0.460	0.397
rFSH (n=225)	109	77.9%	116	83.5%			
rFSH+LH (n=30)	17	12.1%	13	9.4%			
Total	140	100%	139	100%			

Only the patients with P4 levels <2 ng/dl on day 2/3 of treatment cycles were recruited in the study. P4 levels on day 6 of cycle were not associated with pregnancy outcome.

Using ROC curve on day of oocyte retrieval, Area Under Curve (AUC)=0.537 with 95% confidence interval. The serum progesterone level above which it affects IVF outcome: 1.5 ng/dl.

The study population was subgrouped into two groups according to P4 level on day of hCG trigger (calculated according to ROC curve): Group A (p≤1.5 ng/dl, n=140/279, 50.17%) and Group B (p>1.5 ng/dl, n=139/279, 49.82%).

The demographic variables of patients in the two subgroups are shown in Table 1. The dose of Gonadotropins were significantly required higher in group B as compared to group A (1935 IU versus 1500 IU, p<0.001). The terminal E2 (Estradiol) was significantly higher in group B as compared to group A. (2545 pg/ml versus 1339 pg/ml, p=0.017). The number of oocytes retrieved were significantly more in group B as compared to group B (14 versus 11, p<0.001). The rest of the demographic variables (age, BMI, duration of infertility, AMH levels, Duration of stimulation, endometrial thickness on day of hCG trigger and number of embryo transferred) were same in two groups.

The comparison between two groups according to protocol is shown in Table 2. The percentage of subjects with progesterone rise on the day of hCG trigger were significantly more in agonist protocol (56.1%) as compared to antagonist protocol (43.9%, p<0.001).

The comparison between two groups according to type of Gonadotropins usage is shown in Table 3. There was no association found in the rise of progesterone with usage of rFSH alone vs addition of rLH (p=0.397) for superovulation and also in recombinant gonadotropins (rFSH) versus urinary hMG (p=0.460).

The outcome of study is shown in Table 4. Pregnancy rate was significantly higher in group A (41.4%, 58/114) when compared with group B (29.5%, 41/139). The clinical pregnancy rate was also significantly more in group A (50/140,35.7%) as compared to group B (34/139, 24.5%) (p=0.041). The early pregnancy loss (p=1.000) and ectopic pregnancy (p=1.000) were similar in both groups.

DISCUSSION

This prospective, observational study was performed in 279 IVF/ICSI-ET cycles to establish the level of progesterone on day of hCG administration above which it can affect the IVF outcome and to further establish the incidence of progesterone rise in an agonist and antagonist cycle as in cycles using drugs such as hMG/LH versus only recombinant FSH.

Using ROC curve, a serum progesterone level of 1.5 ng/dl on day of hCG administration was identified as the most appropriate threshold to define detrimental levels of progesterone for the outcome of IVF/ICSI-ET cycles.

There was no significant difference among age, BMI, the duration of infertility, serum AMH levels, endometrial thickness on day of OCR and number of embryo transferred among the patients evaluated in both groups.

There was significant difference found in total dose of gonadotropins required, terminal serum E2 and number of oocyte retrieved among patients with P4 levels more than 1.5 ng/dl.

The incidence of P4 rise on the day of trigger was more in cases in which large doses of gonadotropins had been given (p<0.001); this was comparable to the observations by Kiliçdag et al.[22]

The comparison of progesterone levels with serum E 2 levels on the day of trigger revealed a higher incidence of P4 rise in the group with higher E2 (>2540 pg/ml, p=0.017). Bosch et al concluded that higher estrogen values on the day of hCG trigger were associated with increased progesterone levels (p<0.0001).[12]

The proportion of high P4 levels was significantly higher in the cases in which >14 oocytes retrieved were observed on TVS (p<0.001).In the study by Kyrou et al the number of follicles on the day of trigger in the elevated P4 group was 12.6 ± 5.5,hence more oocytes and in the P4 ≤1.5 ng/ml group, it was 11.1±5.9 (p<0.05).[23]

The type of protocol also implicated to affect serum progesterone levels.

The incidence of high serum P4 was higher among the patients subjected to GnRH agonist protocol with respect to the antagonist protocol (56.1% versus 84.39%, p<0.001). Several studies have supported an increased incidence of high P4 levels in the long protocol; more number of days of stimulation due to the suppression of the hypothalamo–pituitary–ovarian axis, a higher dose of gonadotropins, more number of intermediate follicles, and higher estrogen levels observed on the day of trigger may be plausible explanations favoring the same.[12,23]

High serum P4 levels on the day of trigger was found to adversely affect pregnancy rate and clinical pregnancy rates.

The pregnancy rate in group A was significantly higher than in group B (41.4% versus 29.5%; p=0.037). Venetis et al in their meta-analysis, concluded that high P4 on day of hCG trigger diminishes the probability of achieving pregnancy in women undergoing fresh IVF cycles, even at concentrations in the range of 0.8-1.1 ng/ml, and conception rates are further reduced when the progesterone concentration reaches 1.2-1.4 ng/ml or higher.[25] Because we selected the P4 level cutoff >1.5 ng/ml, conception rates were significantly reduced in group B.

The clinical pregnancy rate observed was significantly higher in normal P4 level group than in elevated P4 level group irrespective of the protocol given (33.7% versus 24.5%; p=0.041). In the study by Mascarenhas et al P4 elevation was associated with a significant reduction in clinical pregnancy rate- 44.2% versus 22.2%;

(p=0.0092).[26] Pregnancy rate observed was significantly lower (54.0% versus 25.8%) in the prematurely elevated progesterone group in the study by Bosch et al with the cutoff for P4 being ≥1.2 ng/ml.[27]

The advantage of identifying a P4 threshold beyond which pregnancy outcomes may be affected can aid in the practitioner's ability to counsel the patient. Using a time on day of hCG trigger, (when many studies have been done) we further emphasized that a P4 level of >1.5 ng/dl may be predictive of significantly poorer pregnancy and clinical pregnancy rates. The negative effect of an elevated P4 at the time of hCG trigger appears to be limited to the endometrium, as no effect on oocyte maturation or fertilization rate was detected; this has been corroborated by previous studies in donor recipient IVF cycles as well as in frozen embryo cycles.[7-10] Therefore, a simple solution may be cryopreserving embryos when P4 levels exceed this threshold. Thus, the P4 level on the day of hCG trigger may help to stratify which patients may benefit from embryo cryopreservation in lieu of a fresh ET.

CONCLUSION

We conclude that the measurement of serum progesterone levels in the late follicular phase is important in COS cycles for IVF/ICSI. High P4 in stimulated cycles seems to have negative effect on IVF cycle outcome and it helps to stratify which patients may benefit from embryo cryopreservation in lieu of a fresh ET. Elevated progesterone concentrations on the day of trigger likely resulted in embryo–endometrial asynchrony by negatively affecting endometrial receptivity, reducing the probability of implantation.

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