Original Article

The Impact of Progesterone Level on Day of hCG Injection in IVF Cycles on Clinical Pregnancy Rate

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Abstract

Background: Premature progesterone rise (PPR) has long been implicated as contributing to implantation failure. Despite the use of gonadotropin-releasing hormone (GnRH) analogues, subtle increases in serum progesterone (P_4) levels beyond a threshold progesterone concentration were observed on the day of trigger in controlled ovarian hyperstimulation cycles. **Aims:** The purpose of the study was to evaluate the incidence of PPR on the day of trigger in conventional IVF/ICSI cycles and its impact on clinical pregnancy rate. **Settings and Design:** A total of 235 patients undergoing conventional IVF/IVF–ICSI by fresh embryo transfer cycles from January 2016 to December 2016 at the infertility unit of a tertiary care hospital were prospectively analyzed. **Material and Methods:** Patients included in the study were subjected to GnRH agonist long/antagonist protocol. Ovulation induction was given with rFSH and/or HMG in both the protocols. The cutoff for defining PPR was $P_4 \geq 1.5$ ng/ml, and an analysis of the role of P_4 on clinical pregnancy rate was performed. Statistical analysis was performed with the Statistical Package for the Social Sciences trial version 23.0 software for Windows and Primer software. **Results and Conclusion:** The overall clinical pregnancy rate per embryo transfer was 30.6%. The clinical pregnancy rate in the patients with $P_4 < 1.5$ ng/ml was significantly higher than those with elevated levels, $P_4 \geq 1.5$ ng/ml (33.3% vs. 12.9%; $P = 0.037$). Premature progesterone elevation in ART cycles is possibly associated with lower clinical pregnancy rates.

Keywords: *Clinical pregnancy rate, controlled ovarian hyperstimulation, premature progesterone rise*

Introduction

The role of progesterone is to favor implantation in an estrogen-primed endometrium in normal as well as in induced cycles. Serum progesterone (P_4) concentrations are low, <1.5 ng/ml, during the normal early follicular phase of ovulatory cycles but tend to increase gradually 12–24 h before the onset of luteinizing hormone (LH) surge.[1] The source of progesterone in the early follicular phase is of adrenal origin. However, in the late follicular phase, progesterone mainly accumulates from the growing follicles and sometimes due to the premature luteinization (PL) of the leading follicle owing to premature LH surge.[2]

Premature progesterone rise (PPR) is defined as a rise in serum progesterone concentrations toward the end of the follicular phase or on the day of trigger above a threshold concentration, which is usually arbitrarily defined.[3,4] Although this pre-hCG progesterone increase has been referred to as "premature luteinization," the term is misleading given that the increased levels of P_4 also occur in the presence of gonadotropin-releasing hormone (GnRH) analogues, that is, with normal serum LH concentrations.[5] The high follicular phase progesterone concentrations have long been implicated as contributing to implantation failure by causing embryo–endometrial asynchrony.[6,7]

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In the pre-GnRH analogue era, PL was usually defined as an elevation of serum progesterone levels >1.5 ng/ml, with LH surge before the completion of follicular growth or serum estradiol (E_2) reached 200 pg/ml,[8] with a reported incidence of 14% in natural cycles. Multifollicular development in IVF cycles involving gonadotropins led to the supraphysiological levels of E_2, which could trigger an endogenous LH surge prematurely even before the leading follicle attained an appropriate size, resulting in early follicle rupture and, subsequently, an increased number of cancelled cycles. With the use of chemical or hormonal ovulation induction in the management of infertility, the incidence has been variously quoted as 13–71%.[9] Despite the abolition of LH surge with GnRH analogues, the occurrence of PPR without any documented increase in LH levels is seen in approximately 12–52%.[5]

The pathogenesis of PPR in controlled ovarian hyperstimulation (COH) cycles is still poorly understood. Several hypotheses have been proposed as follows: (i) increased LH receptor sensitivity due to higher cumulative exposure to estradiol in conjunction with FSH;[3,10] (ii) incomplete pituitary suppression by GnRH may result in some LH secretion sufficient to stimulate granulosa cells to produce progesterone despite not being enough to trigger ovulation;[11] (iii) the disruption of certain signaling pathways in the oocyte granulosa cell regulatory loop.[12]

However, the most plausible explanation is that it is a consequence of FSH dose and ovarian response and not a LH-driven event. A high FSH-only stimulation recruits a large number of growing follicles leading to an increased ovarian steroidogenic activity and progesterone production. Without an LH drive to theca cells, progesterone will not be further metabolized and will find its way to the circulation.[13,14]

A progesterone rise during the late follicular phase has been considered a negative predictive factor for clinical outcome in both GnRH agonist[8,15] and antagonist protocols.[3,6] The underlying mechanism may be that high P_4 levels on the day of hCG trigger induce advanced endometrial histological maturation[16,17] and differential endometrial gene expression,[17,18] which lead to implantation failure. No association has, however, been reported between progesterone elevation and fertilization rates or oocyte/embryo quality.[19,20]

Data from large prospective studies such as the Merit study[21] and huge retrospective cohorts[14] support that pregnancy rates are inversely related to progesterone levels on the day of trigger, especially when a threshold of 1.5 ng/ml is adopted. This threshold cannot be considered arbitrary, because it signifies the transition from follicular to luteal phase in the natural cycle.[1]

A premature P_4 rise, however, does not uniformly imply failed implantation, because there are still clinical pregnancies reported with high P_4 levels. Hence, there is a need to identify a subgroup of patients who have a good chance of conception in spite of elevated P_4 levels.[22]

Direct clinical significance and influence on the pregnancy rates of increased follicular phase progesterone values have been addressed, but conclusions are not unanimous. Although some postulate an adverse effect on ART outcome,[2,23] others state that there is no significant effect on implantation and clinical pregnancy rates.[5,24] The objective of this study was to investigate the relationship between PPR and implantation, as well as the clinical pregnancy rates in COH cycles.

Material and Methods

The current study was undertaken after approval from the Institutional Ethics Committee and obtaining informed consent from all patients undergoing conventional IVF/ICSI. From 250 patients attending the infertility clinic and recruited in the study, 235 patients were finally evaluated (among the 15 patients not included, the following were observed: in four patients, all embryos were frozen; in five patients, poor quality embryos were obtained; in three patients, no fertilized embryos were noted; and in three patients, embryo transfer was cancelled due to the risk of hyperstimulation). Patients were eligible for inclusion if they (i) were between 21 and 38 years, (ii) had BMI between 18.5 and <30 kg/msq, (iii) had basal (day 3) levels of [E_2] <60 pg/ml and [FSH] <10 IU/ml, (iv) had both ovaries present, (v) had <3 IVF cycles, and (vi) documented normal uterine cavity on hysteroscopy. The key exclusion criteria included the following: (i) the presence of endometriosis grade 3 or 4, (ii) endometrial tuberculosis – patients who were EB-PCR positive, (iii) E_2 level on the day of trigger >6000 pg/ml, and (iv) antral follicle count >15 in baseline scan.

Patients were subjected to agonist long protocol (n = 119) or antagonist protocol (n = 116) depending upon patient-specific characteristics, a history of prior attempts at ART, baseline hormonal profile, and clinician's preference. Baseline (day 3) FSH, LH, estradiol, and AMH levels were recorded, and a transvaginal sonography was performed.

In patients subjected to GnRH agonist long protocol, the GnRH agonist (Inj. Lupride 1 mg s.c. daily, Sun Pharma) was started on day 21 of the preceding cycle. Gonadotropins [rFSH (Inj. Gonal-F, Merck-Serono) or

HMG (Inj. Menogon, Ferring)] were started from day 3 of cycle after complete downregulation (LH <5 mIU/ml, E_2 <60 pg/ml, ET <5 mm, and follicle size <10 mm). In GnRH antagonist protocol, gonadotropins (rFSH/HMG) were started from day 3 (if basal LH <5 mIU/ml and E_2 <60 pg/ml). GnRH antagonist (Inj. Cetrotide 0.25 mg s.c. daily, Merck-Serono) was started from day 6 of stimulation (fixed protocol) and continued till the morning of the day of trigger. The dose of gonadotropin was individualized according to each patient's response to stimulation.

Serial monitoring with TVS to determine follicular size hormonal profiling to determine LH, E_2, and progesterone levels was performed on day 8 of stimulation and on the day of trigger. The patients were grouped on the basis of their progesterone levels on the day of hCG trigger, with the cutoff for defining PPR being $P_4 \geq 1.5$ ng/ml. Final oocyte maturation was induced with hCG (Inj. Pubergen/Inj. Sifasi, Serum Institute 10,000 IU i.m.) when at least three follicles of size 17–18 mm were observed in both ovaries. Oocyte retrieval was performed 36 h after hCG. The oocytes retrieved were either inseminated (conventional IVF) or subjected to ICSI as required. Fertilization check was performed on day 1 of insemination/ICSI, and embryos cultured in sequential medium. Embryos were graded according to Veeck's criteria. Two to three embryos of day 3 cleavage stage of grade A/B were transferred under TVS guidance.

The parameters obtained from each cycle were recorded. Statistical analysis was performed with the Statistical Package for the Social Sciences trial version 23.0 software for Windows (SPSS Inc., Chicago, IL, USA) and Primer software. The categorical data were presented as percent (numbers) and were compared among groups using Chi-square test. Groups were compared for quantitative data, which were presented as mean and standard deviation and were compared using Student's *t*-test and ANOVA test. Probability (*P*) value <0.05 was considered statistically significant.

Serum β-hCG levels were recorded 15 days after embryo transfer. Those with positive β-hCG, that is ≥50 mIU/ml, were considered to calculate conception rate. A sonographic confirmation of pregnancy was performed 2 weeks after β-hCG positive. Implantation rate was calculated by dividing the number of gestational sacs by the number of embryos transferred. Clinical pregnancy rate was calculated by the presence of intrauterine gestational sac with fetal cardiac pulsation on TVS performed at 6 weeks of gestation. An analysis of factors affecting the premature P_4 rise and its impact on conception rate, implantation rate, and clinical pregnancy rate was performed.

Results

There was no significant difference in the mean age, BMI, and the duration of infertility among the patients evaluated. A significantly higher number of oocytes were retrieved in the elevated progesterone group; however, there was no significant variation in other stimulation parameters used in this study [Table 1].

The incidence of PPR was found to be higher in the agonist than the antagonist protocol [Table 2].

The factors associated with early rise in P_4 levels were the type and dose (≥2000 IU) of gonadotropins, estrogen levels on the day of hCG trigger (≥2500 pg/ml), and ≥10 follicles of ≥10 mm [Table 3].

Table 1: Demographic profile and stimulation parameters

	P_4 <1.5 ng/ml (*n*=204)	P_4 ≥1.5 ng/ml (*n*=31)	*P*
Mean age (years)	30.4±3.58	30.26±4.19	0.839
Mean BMI (kg/m^2)	25.47±2.87	24.90±2.98	0.31
Mean duration (years)	8.07±4.31	8.03±4.82	0.95
Days of stimulation	9.36±1.72	9.90±1.27	0.094
No. of oocytes retrieved	8.74±4.49	12.29±4.79	<0.001
No. of 2PN embryos	7.21±3.35	8.39±3.39	0.069
No. of embryos transferred	2.51±0.57	2.48±0.63	0.78

Table 2: Association of stimulation protocol with P_4 level on the day of hCG trigger

Stimulation protocol	P_4 <1.5 ng/ml (*n*=204)	P_4 ≥1.5 g/ml (*n*=31)	*P*
GnRH agonist (*n*=119)	98 (82.36%)	21 (17.64%)	0.064
GnRH antagonist (*n*=116)	106 (91.38%)	10 (8.62%)	

Table 3: Factors affecting progesterone levels on the day of trigger

	Type of gonadotropin		
Factor	P_4 <1.5 ng/ml	P_4 ≥1.5 ng/ml	*P*
Type of gonadotropin			
rFSH (*n*=65)	81.54% (53/65)	18.46% (12/65)	0.207
HMG (*n*=88)	93.19% (82/88)	6.81% (06/88)	0.042
rFSH + HMG (*n*=82)	84.19% (69/82)	15.85% (13/82)	0.496
Total dose of gonadotropin (IU)			
<2000 (*n*=121)	91.7% (111/121)	8.3% (10/121)	0.035
≥2000 (*n*=114)	81.6% (93/114)	18.4% (21/114)	
E2 level on the day of trigger (pg/ml)			
<2500 (*n*=126)	92.85% (117/126)	7.14% (9/126)	0.006
≥2500 (*n*=109)	79.81% (87/109)	20.18% (22/109)	
No. of follicles ≥10 mm on the day of hCG trigger			
<10 follicles (*n*=152)	94.07% (143/152)	5.92% (9/152)	0.0001
≥10 follicles (*n*=83)	73.49% (61/83)	26.5% (22/83)	

The conception, implantation, and clinical pregnancy rates were significantly reduced in group 2 ($P_4 \geq 1.5$ ng/ml) as compared to group 1 ($P_4 < 1.5$ ng/ml) in the total study population [Table 4].

Discussion

The aim of the current study was to evaluate the role of progesterone levels on the day of hCG trigger in IVF cycles as a predictive tool for clinical pregnancy rate. There was no significant difference among age, BMI, the duration of infertility, and stimulation parameters – days of stimulation, 2PN embryos formed, and number of embryos transferred among the patients evaluated in both groups.

The incidence of PPR irrespective of the type of protocol was 13.19% (31/235). The incidence of PPR was higher among the patients subjected to GnRH agonist protocol with respect to the antagonist protocol [17.64% (21/119) vs. 8.62% (10/116)]. Several studies have supported an increased incidence of PPR 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.[2,14] There was no concomitant rise in LH levels on the day of trigger in association with premature progesterone elevation in our study. In the study by Huang *et al.*,[25] the incidence of PPR was 13.02%. The incidence of PPR in the GnRH agonist subgroup (18%) was significantly higher than in the GnRH antagonist subgroup (9.31%). This was found comparable with our study. In the study by Bosch *et al.*,[3] premature P_4 elevation was noted in 38.3% of the cases. The increased incidence could be attributed to low threshold level ($P_4 \geq 1.2$ ng/ml) to define PPR and the use of isolated rFSH for stimulation.

Table 4: Clinical outcome with respect to progesterone level on the day of hCG trigger

	P_4 <1.5 ng/ml	P_4 ≥1.5 ng/ml	*P*
Conception rate			
Total (*n*=235)	36.3% (74/204)	16.1% (5/31)	0.045
Agonist (*n*=119)	32.7% (32/98)	14.3% (3/21)	0.158
Antagonist (*n*=116)	39.6% (42/106)	20% (2/10)	0.378
Implantation rate			
Total (*n*=235)	15.9% (82/514)	5.8% (5/85)	0.023
Agonist (*n*=119)	14.5% (36/247)	6.7% (4/59)	0.167
Antagonist (*n*=116)	17.2% (46/267)	3.8% (1/26)	0.135
Clinical pregnancy rate			
Total (*n*=235)	33.3% (68/204)	12.9% (4/31)	0.037
Agonist (*n*=119)	29.59% (29/98)	14.29% (3/21)	0.244
Antagonist (*n*=116)	36.79% (39/106)	10% (1/10)	0.175

Conception rate was defined as β-hCG ≥50 mIU/ml. Implantation rate was calculated by dividing the number of gestational sacs by the number of embryos transferred

Among factors implicated to affect PPR were the type of protocol, the type and total dose of gonadotropin given, E_2 levels on the day of trigger, and the number of intermediate follicles recruited.

The incidence of PPR found in patients treated by HMG only, that is 6.81%, was found to be statistically significantly lower in contrast to patients treated by other gonadotropins ($P = 0.042$). Andersen *et al.*[21] concluded that the incidence of elevated progesterone concentrations was higher in rFSH-treated patients than in HMG-treated patients (23% vs. 11%; $P < 0.001$).

The incidence of P_4 elevation on the day of trigger was more in cases in which large doses of gonadotropins had been given (18.4% vs. 8.3%; $P = 0.035$); this was comparable to the observations by Kiliçdag *et al.*[24]

The comparison of progesterone levels with E_2 levels on the day of trigger revealed a higher incidence of PPR in the $E_2 \geq 2500$ IU group (20.18% vs. 7.14%; $P = 0.006$). Bosch *et al.*[14] concluded that estrogen values on the day of hCG trigger were associated with increased progesterone levels ($P < 0.0001$).

The proportion of PPR was significantly higher in the cases in which ≥10 follicles of ≥10 mm were observed on TVS (26.5% vs. 5.92%; $P = 0.000$), suggesting the impact of larger follicle cohort on raised progesterone levels. In the study by Kyrou *et al.*,[2] the number of follicles on the day of trigger in the elevated P_4 group was 12.6 ± 5.5, and in the $P_4 \leq 1.5$ ng/ml group, it was 11.1 ± 5.9 ($P < 0.05$). The mean number of oocytes retrieved in patients with PPR (group 2) was significantly higher than group 1 ($P < 0.001$), but a comparable number of 2PN embryos were observed in both groups. This could be attributed to the retrieval of a higher number of immature oocytes with failed fertilization in group 2, finally resulting in a comparable number of 2PN embryos.

PPR on the day of trigger was found to adversely affect conception, implantation, and clinical pregnancy rates.

The conception rate in group 1 was significantly higher than in group 2 (36.3% vs. 16.1%; $P = 0.045$). The conception rates among group 1 and group 2 in agonist (32.7% vs. 14.3%) and antagonist (39.6% vs. 20%) were although more in group 1 and better with antagonist protocol, no statistically significant correlation was found.

Papanikolaou *et al.*[23] concluded that PPR has an adverse effect on conception rates [agonist (48.5% vs. 28.6%);

antagonist (52.9% vs. 23.8%)]. Venetis *et al*.[26] in their meta-analysis, concluded that PPR 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. Because we selected the P_4 level cutoff ≥1.5 ng/ml, conception rates were significantly reduced in group 2.

Implantation rate was adversely affected by the phenomenon of PPR and was found to be significantly lower, 5.8%, in group 2 in contrast to 15.9% in group 1 (P = 0.023). Implantation rate observed in group 1 was more than in group 2 in both the treatment protocols (agonist: 14.5% vs. 6.7% and antagonist protocol: 17.2% vs. 3.8%, respectively). Implantation rate was significantly lower in the group with PPR in the studies by Bosch *et al*.[3] (32.0% vs. 13.8%) and Kiliçdag *et al*.[24] (24.4% vs. 18.1%).

Clinical pregnancy rate observed in the study population was 30.6% (72/235). The clinical pregnancy rate observed was significantly higher in normal P_4 level group than in elevated P_4 level group irrespective of the protocol given [33.3% (68/204) vs. 12.9% (4/31); P = 0.037]. Clinical pregnancy rates in relation to the incidence of PPR were significantly impaired in both agonist (29.59% vs. 14.29%) and antagonist (36.79% vs. 10%) protocols. The incidence of patients attaining clinical pregnancy in antagonist was more than that in agonist in group 1 (36.79% vs. 29.59%) but lesser in group 2 (10% in antagonist vs. 14.29% in agonist, respectively). The cause of lower clinical pregnancy rate in the antagonist protocol in group 2 may be attributed to the smaller proportion of patients in this category (n = 10).

In the study by Mascarenhas *et al*.,[27] P_4 elevation was associated with a significant reduction in clinical pregnancy rate – 44.2% vs. 22.2%; (P = 0.0092). Pregnancy rate observed was significantly lower (54.0% vs. 25.8%) in the prematurely elevated progesterone group in the study by Bosch *et al*.,[3] with the cutoff for PPR being ≥1.2 ng/ml.

Conclusion

We conclude that the measurement of serum progesterone levels in the late follicular phase is important in COH cycles for IVF/ICSI. PPR in stimulated cycles seems to have negative effect on IVF cycle outcome. Elevated progesterone concentrations on the day of trigger likely resulted in embryo–endometrial asynchrony by negatively affecting endometrial receptivity, reducing the probability of implantation. The risk is high in high responders especially with agonist protocol and the use of rFSH. Factors implicated to affect PPR were the type and total dose of gonadotropin given, E_2 levels on the day of trigger, and the number of intermediate follicles recruited.

The results of our study emphasize on the individualization of treatment protocols, ensuring timely and proper monitoring of endocrinological profile during stimulation, and timing the trigger according to the patient's optimal response. Cycle cancellation and embryo freezing if required should be individualized according to the quality and number of embryos, freezing facility, the number of attempts, or the detection of early P_4 rise so as to achieve better success rates in IVF.

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Conflicts of interest

There are no conflicts of interest.

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