RESEARCH ARTICLE

The Role of Progesterone/Estradiol (P4/E2) Ratio in Predicting Assisted Reproductive Technology (ART) Outcome in Agonist Cycles with Elevated Progesterone Levels on Trigger Day: A Prospective Study

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Abstract

Aim: Progesterone (P4) rise on the day of the trigger is often regarded as a poor prognostic factor in assisted reproductive technology (ART) cycles. We aimed to identify the utility of the progesterone/estradiol (P4/E2) ratio as a predictor of pregnancy outcome in the subgroup of patients with P4 elevation.

Materials and methods: We conducted a prospective study on women with normal basal hormonal parameters who underwent ART utilizing the long downregulation protocol. Serum P4 and E2 were assayed on the day of the trigger. The role of P4 elevation and the role of the P4/E2 ratio in those with elevated P4 were analyzed with respect to ART outcome using the *t*-test and Mann–Whitney *U* test. Receiver operating characteristic (ROC) curve analysis was done to identify a cutoff value of the P4/E2 ratio below which a good prognosis could be predicted.

Results: We included 422 patients. The pregnancy rate was 42.4%. Elevated P4 > 1.5 ng/mL was seen in 20.4%. The P4/E2 ratio was higher in nonpregnant patients when compared to pregnant patients and was statistically significant (0.56 ± 0.81 vs 0.4 ± 0.61 and $p = 0.001$). The cutoff value for P4/E2 ratio by ROC curve analysis was 0.463, with a negative predictive value of 69.6%. Those with elevated P4 > 1.5 ng/mL and P4/E2 ratio >0.463 had a significantly lower pregnancy rate than those with normal (<1.5 ng/mL) P4 levels (45.4% vs 32%, and $p = 0.03$).

Conclusion: Progesterone/estradiol (P4/E2) assay on the day of human chorionic gonadotropin (HCG) assumes significance in predicting pregnancy outcomes in patients undergoing ART, especially those with elevated P4 levels. If the P4 level is high on the day of HCG, it is better to see P4/E2 ratio before the routine cancellation of the transfer.

Clinical significance: The clinical practice of freezing all the embryos in those with elevated P4 on the day of the trigger could be restricted to only those with elevated P4/E2 ratio also.

Keywords: Assisted reproductive technology, Clinical pregnancy, Progesterone elevation, Progesterone/estradiol ratio.

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Introduction

Progesterone (P4) level rise in the last part of the follicular phase is often considered a poor prognostic factor in predicting pregnancy outcomes in assisted reproduction cycles involving gonadotropin-releasing hormone (GnRH) agonists,[1,2] as well as GnRH antagonist molecules.[3,4] The underlying mechanism may be that elevated P4 levels on the trigger day might be leading to advanced endometrial maturation on a histological level[5,6] and also changes in endometrial gene expression,[6,7] which lead to implantation failure.

Large prospective studies such as the Merit study[8] and retrospective cohorts[9] report cases of decreased pregnancy rates related to increasing levels of trigger day P4, particularly when a cutoff value of 1.5 ng/mL is taken.

In a controlled stimulated cycle, high P4 in the late follicular phase need not always result in implantation failure. Clinical pregnancies are reported in many cycles with elevated P4 levels too. So, it may be prudent to identify a subgroup of patients who might have high chances of conception even if the P4 levels are raised.

Premature luteinization (PL), often described as a rise of serum P4 on the day of the final trigger, can be seen in upto 5–30% of assisted conception [*in vitro* fertilization (IVF)] cycles.[10,11] Its pathogenesis and impact on pregnancy outcomes are still poorly understood. Considering the fact that the increased number of follicles in stimulated cycles contributes to increased

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P4 levels, it can be argued that the ovarian response should also be taken into account rather than taking serum P4 only when considering the reasons for "PL." Another concept of P4/E2 ratio was described by Younis et al.[12] to define PL. They took a P4/E2 ratio of >1 to define PL and observed that a P4/E2 ratio of >1 showed a compromise in a clinical pregnancy (CPR). Although P4/E2 ratio has been proposed as a predictive marker for pregnancy rates, the available data show varying results. Many studies also have calculated a cutoff value for P4/E2 ratios by ROC analysis that might prove detrimental to the positive pregnancy outcome.[13,14]

A retrospective study[15] involving mixed stimulation protocols had shown that the adverse effect of elevated P4 was mainly limited to those with elevated P4/E2 ratio also. They recommended going for a practice of elective freezing of all the embryos in cases with elevated P4 of >1.5 ng/mL and a P4/E2 ratio of >1. Hence, we thought of studying prospectively to know the utility of the P4/E2 ratio as a predictive factor of pregnancy outcome. We also planned to determine the importance and the role of the P4/E2 ratio in the subgroup of patients who have elevated P4.

Materials and Methods

This was a prospective observational study conducted in the reproductive medicine department of a referral center (level 3 care center) from June 2016 to May 2017. Those couples with a female partner aged <40 years, with normal body mass index and normal day 3 hormone levels, were included. Ethical committee approval was obtained for the study and appropriate informed consent was taken.

It was observed from a previous study[15] that the success rate in the group with a P4 level of >1.5 ng/mL and P4/E2 of >1 was 15%, and the group with P4 of <1.5 was 43%. By taking this ratio into consideration, the sample size required in both the groups (those with P4/E2 ratio of <1 and >1) was 32. Type I error (α) fixed at 5%. And the type II error (β) was fixed at 20% so that the power is 80%. To ensure 32 cases in each group after considering dropouts, we had to get around 75 cases of patients with high P4 levels. The proportion of patients with high P4 among those undergoing ART was 18 % at our center and a sample of 75 could be achieved by taking a whole sample of 420 ART cycles.

In all the recruited patients, detailed history with respect to nature, duration, etiology of infertility, previous surgeries, and treatments were noted. The mode of ART done was intracytoplasmic sperm injection (ICSI) for all the participants. Couples underwent basic investigations like basal transvaginal ultrasound (TVS), basal hormonal assays-serum E2, P4, follicle-stimulating hormone (FSH), thyroid stimulating hormone, prolactin, luteinizing hormone (LH), glycosylated hemoglobin on day 2/3 as part of routine tests of the institution for ART cycles. They were called in 3rd week, around the 21st day of the menstrual cycle. On that day, TVS using an 8 MHz transvaginal probe (GE Logiq Pro 5 ultrasound machine) was performed. Then, the female partner was put on long luteal phase hypothalamic-pituitary-ovarian axis down-regulation (long agonistic protocol) with gonadotropin-releasing hormone agonist, leuprolide acetate 0.5 mg [injection (Inj.) lupride, Inca-Sun Pharmaceuticals Industries Ltd. India] subcutaneously daily or leuprolide depot 3.75 mg intramuscular (Inj. leuprodex depot, Bharat serums & vaccines Ltd. India). The couple was then asked to report on day 2/3 of the next menstrual cycle and on that day female partner underwent a TVS assessment to ensure good suppression.

Controlled ovarian stimulation was achieved with daily injections of Gonadotropins [human menopausal gonadotropin (IVF M, LG life sciences, Korea)/recombinant FSH (Recagon, NV Organon, Netherlands)]. Couples were advised to report after 7 or 8 days to evaluate response to gonadotropins (serum E2 estimation, ultrasonographic assessment of follicular growth). Along with the above parameters, serum P4 and serum LH levels were also measured. Exogenous gonadotropins, along with leupride acetate, were continued till at least two or three follicles attained the size of 17–18 mm. The final trigger was done using 10000 IU of HCG Inj. (Inj. Ovunal SC, Intas Pharmaceuticals Ltd. India).

Serum E2, P4, and LH levels were obtained on the final trigger day. These values were the basic data for the primary outcome of the study. All blood samples were analyzed using a cobas 411 analyzer (Roche diagnostics GmBH, Mannheim, Germany). Serum P4 was analyzed using electrochemiluminescence immunoassay catalog number—12145383160, using a cobas 411 analyzer, the lower limit of detection being 0.3 ng/mL. P4/E2 ratio was obtained by the formula [P4 (ng/mL) × 1000]/E2 (pg/mL)].

After 36 hours of HCG injection, ultrasound-guided oocyte retrieval was done transvaginally under intravenous anesthesia (using propofol or ketamine). Sperms were obtained from the husband through masturbation, or cryopreserved sperms were used. In the case of azoospermia, sperm was retrieved surgically (PESA, TESA, Micro TESE), or donor sperm was used, and then ICSI was carried out.

Embryo transfer was done under ultrasound guidance and we transferred day 2 or 3 (cleavage stage) embryos of good quality. Luteal phase support was started with natural micronized P4 (Inj. Hald 100 mg IM, Intas Pharmaceuticals Ltd. India or Crinone vaginal gel 8%, Merck Serono). After 15 days of embryo transfer, serum beta HCG levels were estimated (using electrochemiluminescence) and a value of 50 mIU/mL was taken as the cutoff of the positive cycle. Pregnancy location and viability were confirmed by ultrasonography one month after the transfer of embryos. The presence of any intrauterine gestational sac at this time defined the CPR, which was taken as the principal parameter of primary and secondary outcome variables. Follow-up was done till 12 weeks of pregnancy to identify the first-trimester outcome.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software (SPSS 21.0). Continuous data were summarized as mean with standard deviation (SD) or median with Inter quartile range. Categorical variables were summarized as frequencies with percentages and were analyzed using the Chi-squared test. Comparison of the continuous variable was done by using the independent sample *t*-test or Mann–Whitney *U* test. For all tests, a *p*-value was considered statistically significant if it was <0.05. The ROC curve was used to test whether there exists a cutoff level for the P4/E2 ratio in predicting the outcome of the ICSI cycles.

Results

The number of patients who participated in the study was 422. The study population had a mean age of 31.8 ± 4.38 years and a mean infertility duration of 6.7 ± 3.69 years, with 65.4% having primary infertility. The CPR rate was 42.4% (Table 1). The comparison between pregnant and nonpregnant groups showed statistically significant differences in age, HCG day P4, endometrial thickness, and quality of the embryo. The details are summarized in Table 2.

Around 20.4% of the study population had HCG day P4 >1.5 ng/mL. The value of HCG day P4/E2 ratio varied from 0.007 to 9.038 with a mean value of 0.49 ± 0.77. The comparison of IVF outcome with HCG day P4/E2 ratio showed that there were higher mean levels of HCG day P4/E2 in the nonpregnant group and the difference was statistically significant (0.56 ± 0.81 vs 0.4 ± 0.61 and $p = 0.001$). For the purpose of analyzing HCG day P4/E2 as a predictor for pregnancy outcome, a ROC curve analysis was performed (Fig. 1). The area under the curve (AUC) was only 0.595 (95% confidence interval 0.54–0.65), suggesting HCG day P4/E2 would not predict pregnancy. In an effort to maximize sensitivity, we arrived at a value of P4/E2 at 0.463 as a cutoff (from the ROC curve) with a sensitivity of 80% and specificity of 32.9%. The predictive values (positive and negative) were 46.9% and 69.6%, respectively.

There were a total of 115 patients whose HCG day P4/E2 ratio was >0.463 and the pregnancy rate in this group was 30.4%. There were 307 patients whose HCG P4/E2 ratio was <0.463 and the pregnancy rate in this group was 46.9%. The pregnancy rate among those with HCG P4/E2 of >0.463 is significantly lower than those with HCG P4/E2 of <0.463 ($p = 0.002$) (Table 3).

Subgroup analysis of HCG day P4/E2 cutoff of 0.463 was done within the cycles in those who had high P4 (>1.5 ng/mL). Subgroups were not analyzed in the group with P4 < 1.5, as the pregnancy rates in this group (45.4%) were comparable to our overall IVF pregnancy outcome (42.4%). Out of 85 cycles with P4 > 1.5 ng/mL, 10 cycles had a P4/E2 ratio of <0.463, of which there were two clinical pregnancies and 75 cycles had a P4/E2 ratio of >0.463, of which 24 had clinical pregnancies. When compared to the P4 < 1.5 ng/mL group, there was a statistically significant reduction in CPR in the group with high P4 (>1.5 ng/mL) and P4/E2 ratio of >0.463 (Table 4).

Discussion

We attempted to identify the correlation between P4/E2 ratio on the day of trigger (HCG) and CPR in ICSI cycles. We also aimed to arrive

Table 1: Distribution of variables in the study population

Parameter	*Distribution*
Age (years)	31.8 ± 4.38
Duration of infertility (years)	6.7 ± 3.69
Basal FSH (IU/L)	3.88 ± 2.16
E2 on the day of trigger (pg/mL)	2606.8 ± 1123
P4 on the day of trigger (ng/mL)	0.99 ± 0.91
Total number of oocytes	15.6 ± 10.17
Total number of M II oocytes	10.79 ± 6.61
Number of grade I embryos	5.63 ± 4.33
CPR	179/422 (42.4%)

E2, estradiol; FSH, follicle-stimulating hormone; M II, metaphase II; P4, progesterone

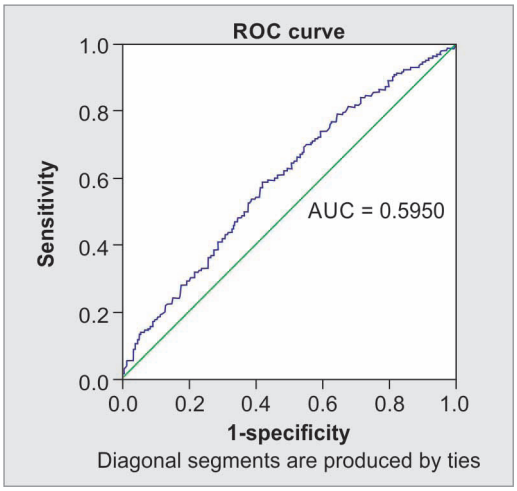

Fig. 1: ROC analysis of HCG day P4/E2 ratio and pregnancy outcome

Table 2: Comparison of variables between pregnant and nonpregnant groups

	Outcome		
Variable	*Pregnant mean ± SD*	*Notpregnant mean ± SD*	*p-value*
Age (years)	30.77 ± 4.06	32.49 ± 4.47	<0.001[a]
Day 2 FSH (IU/L)	4.01 ± 2.2	3.78 ± 2.12	0.297
Day 2 P4 (ng/mL)	0. 65 ± 0.54	0.74 ± 0.95	0.240
Trigger day P4 (ng/mL)	0.84 ± 0.78	1.11 ± 0.97	0.002[a]
Trigger day E2 (pg/mL)	2645.6 ± 1113.4	2578.2 ± 1131.4	0.542
ET (mm)	9.92 ± 1.8	9.4 ± 1.6	0.01[a]
Grade I embryos	6.5 ± 3.62	4.98 ± 4.7	<0.001[a]
Total number of M II oocytes	11.21 ± 6.1	10.5 ± 6.96	0.26

ET, endometrial thickness; E2, estradiol; FSH, follicle stimulating hormone; M II, metaphase II; P, progesterone; [a]significant at 0.05; statistical test used *t*-test for comparing means

Table 3: Comparison of variables with HCG day P4/E2

	HCG day P4/E2 (n = 422)		
Variable	*≤0.463 (n = 307) mean ± SD*	*>0.463 (n = 115) mean ± SD*	*p-value*
Total number of M II oocytes	11.9 ± 6.6	7.9 ± 5.7	< 0.001[a]
Grade I embryo	6.42 ± 4.4	3.5 ± 3.29	< 0.001[a]
Pregnancy rate	144 (46.9%)	35 (30.4%)	0.002[a]

M II, Metaphase II; [a]significant at 0.05; statistical test used Mann–Whitney *U* test

Table 4: CPR rate-subgroup analysis

Group	*Number of patients*	*Clinical pregnancies*	*CPR rate*	*p-value*
P4 ≤ 1.5 ng/mL (group I)	337	153	45.4%	–
P4 > 1.5 ng/mL and P4/E2 ≤ 0.463 (group II)	10	2	20.0%	0.11 (group I vs group II)
P4 >1.5 ng/mL and P4/E2 > 0.463 (group III)	75	24	32.0%	0.03[a] (Group I vs Group III)

P, serum progesterone; P4/E2, progesterone/estradiol ratio; [a]significant at 0.05; statistical tests used Chi-squared test

at a threshold P4/E2 ratio to define cycle outcome and assessed the role of P4/E2 ratio as a predictor in assisted conception cycles in a subset of patients with premature P4 rise. The outcomes were evaluated by comparing CPR with serum P4/E2 ratio and P4 levels on the day of the final HCG trigger.

In our study, those with P4 elevation (>1.5 ng/mL) on the day of the HCG trigger had a significant reduction in CPR. We did a subgroup analysis of the patients with high P4; the group with P4/E2 of >0.463 showed no significant decrease in the pregnancy rate when compared with the group with P4/E2 of <0.463. A similar recent retrospective study[15] found that the CPR in patients with serum P4 of >1.5 ng/mL was reduced than the patients with normal P4 ≤ 1.5 ng/mL and was statistically significant ($p = 0.009$) as in our group. However, the subgroup analysis of those with a high P4 level (>1.5 ng/mL) found that those patients with P4/E2 ratio >1 had a significantly lower pregnancy rate than the patients with P4 of ≤1.5 ng/mL ($p = 0.01$) and those patients with P4/E2 ratio ≤1 had a similar pregnancy rate as the patients with P4 of ≤1.5 ng/mL which is not consistent with our results. Elgindy[13] suggested that an increased P4 level of >1.5 ng/mL and a P4/E2 ratio >0.55 on HCG day were associated with decreased CPR in normo-responder women undergoing long agonist protocol and cleavage stage embryo transfer.

Moreover, Bosch et al.[16] also showed reduced ongoing pregnancy rates (OPR) in subjects with elevated levels of trigger day P4. Irrespective of the molecule used for downregulation, they identified lower OPRs in those with serum P4 concentration of >1.5 ng/mL. They opined that this elevation had been shown to occur in a considerable number of IVF cycles, and in GnRH agonist cycles, it has been described in 5–35% of cycles. In our study, those with a high P4 of >1.5 ng/mL were 20.1%.

For the purpose of analyzing HCG day P4/E2 as a predictor for pregnancy outcome, we performed a ROC curve analysis. The AUC was only 0.595 (95% confidence interval 0.54–0.65), suggesting HCG day P4/E2 is not a good predictor of pregnancy. In an effort to maximize sensitivity, we arrived at a value of P4/E2 at 0.463 as a cutoff with a sensitivity of 80% and specificity of 32.9%. Similarly, Lee et al.[17] also proposed the clinical utility of the P4/E2 ratio in the prediction of CPR, but they particularly highlighted the low sensitivity and the low positive predictive values of the same, thereby questioning its feasibility. The cutoff for P4/E2 ratio found in our study is similar to that deduced by Shalom-Paz et al.[18] by ROC curve analysis (P4/E2 cutoff of 0.45 with AUC 0.632, sensitivity 65.7%, and specificity 62.7%). Cetinkaya et al.,[19] in their study, proposed a cutoff of P4/E2 of <0.48 in achieving higher CPR and delivery rates, which is relatively similar to our result. However, they evaluated cycles employing antagonist protocol only.

Multiple past studies have shown that elevated P4 levels are associated with poor pregnancy outcomes. Most of these studies state that this is particularly seen in those with elevated P4/E2 ratios only. A policy of elective freezing of all the embryos may be recommended in cases with an elevated P4/E2 ratio of >0.463 in those with elevated P4 of >1.5 ng/mL. In those with P4/E2 ratio of <0.463, pregnancy outcomes can be expected to be similar to those with normal P4 levels (<1.5 ng/mL). Our study results reinforce the view that when the P4 rises prematurely in assisted conception cycles, it can often cause a decrease in CPR. However, it raises concerns regarding the clinical use of the P4/E2 ratio in predicting poor outcomes in the subgroup with elevated P4.

The major strength of our study was the prospective design and uniform protocol used for IVF. However, our study has the limitation that we had a relatively less number of subjects for subgroup analysis. Future studies using a larger sample may be recommended where an adequate number of patients can be subclassified based on ovarian reserve, the response to stimulation, type of stimulation protocol, and also based on cleavage stage embryo vs blastocyst transfer so as to extrapolate the effects of P4/E2 ratio on oocyte quality or endometrial asynchrony. This may further empower this ratio as a powerful tool in a mixture of patients with multiple variables. Furthermore, studies may also be planned for ROC curve analysis to obtain predictive cutoffs for HCG day P4 levels rather than choosing arbitrary levels, as done in our study, which may further enhance the significance of the role of P4/E2 levels.

Conclusion

Progesterone/estradiol (P4/E2) levels on the day of HCG administration may be a prognostic factor for pregnancy outcome in ICSI cycles, as cycles with elevated P4/E2 ratios were associated with lower CPR rates. ROC curve analysis was done and a cutoff level of 0.463 was found for HCG day P4/E2. Analysis showed significantly higher pregnancy rates in ICSI cycles with P4/E2 of <0.463. P4/E2 assay on the day of HCG assumes significance in predicting pregnancy outcomes in patients with raised P4 levels. If the P4 level is high on the day of HCG, it is better to see P4/E2 ratio before the routine cancellation of the transfer. Freezing of all the embryos can be considered for ICSI cycles with P4 elevation >1.5 ng/mL only when associated with P4/E2 of >0.463.

Clinical Significance

The practice of elective freezing of all the embryos in cases with high P4 levels on the day of the final trigger can be modified. This may be limited to a subgroup of those with elevated P4/E2 ratio only, as those with normal P4/E2 ratio can have similar reproductive outcomes to those with normal P4 levels on trigger day.

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