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Original Article

Impact of progesterone (on hCG day)/oocyte ratio on pregnancy outcome in long agonist non donor fresh IVF/ICSI cycles

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ABSTRACT

Objective: To assess the role of progesterone (P) on [human chorionic gonadotropin (hCG) day]/oocyte ratio rather than a single cut-off value of serum P on hCG day to predict *in vitro* fertilization (IVF) outcomes.
Materials and Methods: A Retrospective, single center, cohort study in 687 infertile women undergoing fresh IVF/intracytoplasmic sperm injection (ICSI) treatment with long agonist protocol. The data was categorized into three groups according to serum P levels (Group A < 1.0, Group B: 1.0–1.5, Group C ≥ 1.5) and two groups on the basis of P/oocyte ratio (Group A ≤ 0.15; Group B > 0.15) determined using receiver operating characteristic (ROC). For comparing categorical data, χ^2/Fishers exact test was carried out as appropriate. ROC analysis was performed to determine cut-off value for P and P/oocyte, which may discriminate between pregnancy and nonpregnancy.
Results: The mean age of participants was 31.6 ± 3.7 years and overall pregnancy rate was 26.1%. Elevation of both serum P levels and P/oocyte ratio was found to significantly reduce the pregnancy potential in IVF without affecting fertilization and cleavage rates. The detrimental cut-off value for P and P/oocyte was found to be >1.0 ng/mL (sensitivity 56%; specificity 52%) and >0.15 (sensitivity 62%; specificity 61%) respectively. Pregnancy rate (35.3%) among the patients having ≤0.15 P/oocyte ratio was significantly higher ($p < 0.001$) compared with 18.8% observed among the patients having value >0.15.
Conclusion: P/oocyte ratio may be considered as a valuable tool to predict IVF outcomes when compared with serum P levels alone, but more evidence from randomized studies is required.
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Introduction

The effect of elevated serum progesterone (P) on day of human chorionic gonadotropin (hCG) administration on *in vitro* fertilization (IVF) outcome is still a matter of debate. It has been shown in a large number of studies that elevated serum P has a deleterious effect on pregnancy outcome of IVF cycles [1–6], while other studies have denied such an association [7–9]. The mechanism of this elevation of serum P on hCG day is still not clear. However, a number of factors influencing the serum P concentration have been found. The number of follicles and follicular stimulating hormone (FSH) drive have been found to be positively associated with raised P levels [10]. It has also been reported that the level of P elevation varies with type of ovarian response [11].

Different cut-off values of serum P levels that would be considered as detrimental for pregnancy outcome in IVF have been proposed in a number of studies. Considering the relationship between serum P and follicle number, it would be better to use ratio of serum P on hCG day to the number of oocytes retrieved (P/oocyte ratio) rather than a single cut-off value of P to predict pregnancy outcome in IVF. The number of studies evaluating P/oocyte ratio as a tool for prediction of pregnancy outcome are very limited. Thus, we tried to investigate the relationship between serum P on day of hCG administration and P/oocyte ratio with the pregnancy outcome in gonadotropin releasing hormone (GnRH) long agonist protocol in nondonor fresh IVF/intracytoplasmic sperm injection (ICSI) cycles in this study.

Materials and methods

This was a single-center retrospective cohort study of patients undergoing IVF/ICSI treatment from January 2012 to July 2014 at the assisted reproductive technology center of the All India Institute of Medical Sciences, New Delhi. Complete data of 687 women

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who underwent nondonor fresh IVF/ICSI cycles with long agonist protocol was reviewed. Exclusion criteria were as follows: age > 40 years, antimullerian hormone < 1.0 ng/mL, and frozen embryo transfer (FET) cycles. The main outcome measure was the effect of serum P and P/oocyte ratio on pregnancy outcome.

Stimulation protocol

Patients underwent controlled ovarian hyperstimulation (COH) with use of a GnRH agonist long protocol. The pituitary down-regulation was achieved by subcutaneous injection of 1 mg of leuprolide acetate daily from the midluteal phase of the preceding cycle. Ovarian stimulation was done with 150–300 IU recombinant FSH follitropin alpha (Gonal F, Merck Serono, Darmstadt, Germany) subcutaneously and dose adjusted according to the response. Recombinant chorionic gonadotropin alpha (250 mg; Ovitrelle, Merck Biopharma, Darmstadt, Germany) was given to trigger ovulation when at least two to three leading follicles reached a mean diameter of 18 mm. Serum P and E_2 levels were measured on the day of hCG administration by the chemiluminescent immunoassay using the Access 2 immunoassay system (Beckman Coulter, California, United States). Endometrial thickness was also recorded on transvaginal ultrasound. Oocyte pickup was done 36 hours after hCG administration. Oocytes were cultured in G-IVF plus media (Vitrolife, Sweden) containing 10% of human serum albumin with gentamicin as an antibacterial agent and inseminated with motile sperm prepared by the two-layer Percoll gradient method. Fertilization was defined as oocytes with two pronuclei 16–20 hours after insemination. Embryos were transferred to G-IVF plus media and were classified by blastomere equalization and cytoplasmic fragment. Day 3 or Day 5 embryo transfer was done depending upon the number of embryos and excess good-quality embryos were cryopreserved for subsequent FET cycles. An ongoing pregnancy was defined as a pregnancy test done after 14 days of embryo transfer with a positive heartbeat by ultrasound at 6 weeks of gestation.

Three groups were made according to serum P levels: Group A < 1.0, Group B 1.0–1.5, and Group C ≥ 1.5.

Two groups were made according to P/oocyte ratio as determined by ROC analysis: Group A ≤ 0.15, and Group B > 0.15.

All statistical analysis was carried out using SPSS, IBM version 19 (Armonk, NY: IBM Corp). Data was expressed as mean, standard deviation or frequencies, and percentages. For comparing categorical data, χ^2/Fishers exact test was carried out as appropriate. ROC analysis was performed to determine cut-off value for P and P/oocyte at an approximately equivalent sensitivity and specificity, which may discriminate between pregnancy and nonpregnancy. A value $p < 0.05$ was considered to be statistically significant.

Results

A total of 687 ovarian stimulation cycles were included in the study. Out of these, six cycles needed to be cancelled, as no oocyte could be retrieved. Out of the remaining 681 cycles, 64.9% ($n = 442$) were conventional IVF cycles while 35.0% ($n = 239$) were ICSI cycles. Baseline characteristics such as age, body mass index, FSH, luteinizing hormone (follicular phase), antimullerian hormone, total antral follicle count, total gonadotropin dose, endometrial thickness, E_2, P on day of hCG, and clinical indications for IVF-Embryo transfer (ET) are as presented in Table 1.

The pregnancy outcomes including the number of oocytes retrieved, fertilization rate, cleavage rate, pregnancy rate, P/oocyte ratio, and number of transferred embryos for all of the women are shown in Table 2.

Table 1
Baseline characteristics of patients.

Characteristics	Overall
No. of patients (n)	687
Age (y)	31.6 ± 3.7
BMI (kg/m^2)	25.4 ± 4.0
FSH(follicular phase) (mIU/mL)	6.0 ± 1.9
LH (mIU/mL)	4.2 ± 2.4
AMH (ng/mL)	3.2 ± 1.6
Total AFC	5.9 ± 2.3
Total gonadotropin dose (IU)	3498 ± 1118
Endometrial thickness (on hCG day) (mm)	9.5 ± 1.7
E_2 on hCG day (pg/mL)	3655.5 ± 2391.5
P on hCG day (ng/mL)	1.27 ± 0.8
Clinical indications:	
Tubal factor (%)	42
Endometriosis (%)	9
PCOS (%)	3
DOR (%)	14
Male factor (%)	8
Unexplained (%)	12
Multiple factors (%)	11

AFC = antral follicle count; AMH = antimullerian hormone; BMI = body mass index; DOR = Diminished Ovarian Reserve; FSH = follicular stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone; P = progesterone; PCOS = Polycystic Ovarian Syndrome.

Table 2
Treatment outcome of *in vitro* fertilization/intracytoplasmic sperm injection cycles.

Characteristics	Overall ($n = 681$ cycles)
No. of mature oocytes retrieved	7.2 ± 3.9
P/oocyte ratio	0.24 ± 0.27
Cleavage rate (%)	88.7
No. of embryos transferred	2.8 ± 0.8
Fertilization rate (%)	86.5
Pregnancy rate (%)	26.1

P = progesterone.

We analyzed the correlation between the serum P levels and the fertilization rate, cleavage rate, and pregnancy rate among the three groups made according to serum P levels (Group A ≤ 1.0, Group B 1.0–1.5, Group C ≥ 1.5) as shown in Table 3. It was found that pregnancy rate had a significantly decreasing trend (χ^2 trend in proportion = 11.6; $p = 0.003$) with increasing levels of serum P with no effect on fertilization and cleavage rate.

To determine an optimal detrimental threshold of P levels, ROC analysis was used. The area under curve (AUC) 0.58 (95% confidence interval: 0.53–0.63) was found to be significant ($p = 0.002$). The cut-off value of serum P on hCG day was found to be 1.00 for sensitivity and specificity value of 56% and 52%, respectively (Figure 1).

As the adverse effect of serum P on pregnancy outcome varies according to the type of ovarian response, thus we calculated a cut-off value of P/oocyte ratio to be used as a predictor for IVF outcome rather than P levels alone.

Table 3
Effect of serum progesterone (P) levels on fertilization, cleavage, and pregnancy rate.

Characteristics	Group A ($n = 239$) P ≤ 1.0	Group B ($n = 266$) (P = 1–1.5)	Group C ($n = 176$) P ≥ 1.5	p
Fertilization rate (%)	84.3	84.8	83.8	NS
Cleavage rate (%)	89.8	89.4	88.3	NS
Pregnancy rate (%)	30.8	28.2	16.6	0.003

NS = not significant.

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