



Original Article

Correlation Between Luteal Phase Serum Progesterone Levels and Pregnancy Outcome in Frozen Embryo Transfer Cycles: A Prospective Cohort Study

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Received: 25 July, 2024

Accepted: 16 September, 2024

Published: 12 November 2024

DOI
10.25259/FSR_27_2024

Quick Response Code



ABSTRACT

Objectives: To study the correlation between luteal phase serum progesterone (P_4) levels and pregnancy outcome in frozen embryo transfer (FET) cycles and to find out the cut-off level of luteal phase serum P_4 which favours successful pregnancy outcome in FET cycles.

Material and Methods: This prospective cohort study included 100 women undergoing hormone replacement therapy (HRT)-FET cycle at Akanksha IVF Centre from December 2023 to June 2024, fulfilling the inclusion and exclusion criteria. Serum P_4 levels were measured for all the patients in the luteal phase (days 21–23) after FET with intramuscular P_4 as luteal phase support. Pregnancy outcome was assessed in terms of implantation rate, biochemical pregnancy rate, clinical pregnancy rate (CPR), first-trimester miscarriage rate and ongoing pregnancy rate.

Results: The most favourable pregnancy outcomes were observed at serum P_4 levels 25.1–35 ng/mL. A statistically significant association was seen between the luteal phase serum P_4 levels and implantation rate (36.08%), biochemical pregnancy rate (4%), CPR (52%) and ongoing pregnancy rate (42%). According to the receiver operating characteristic (ROC) curve analysis, the optimal cut-off value for favourable outcomes was determined to be 22.3 ng/mL. However, the analysis also indicated that the luteal phase serum P_4 levels did not reliably predict clinical or ongoing pregnancy.

Conclusion: Larger studies are needed to establish a threshold level of serum P_4 in the luteal phase that can differentiate between successful and unsuccessful implantation. However, it is still uncertain whether the issue of unsuccessful implantation can be resolved once it is detected on days 21–23 of the HRT-FET cycle.

Keywords: Luteal phase, progesterone, frozen embryo transfer, cryopreserved embryo transfer, pregnancy outcome

INTRODUCTION

The progesterone (P_4) secretion by the corpus luteum following ovulation plays a vital role in orchestrating the necessary changes in the endometrium for successful implantation and a positive pregnancy outcome. P_4 has a regulatory effect on key ultrastructural features of the secretory phase endometrium, such as giant mitochondria, glycogen accumulations in subnuclear regions, pinopodes and the nucleolar channel system, all of which facilitate the process of implantation.^[1] Additionally, it is believed to support implantation by stimulating the immune system to generate non-inflammatory T-helper-2 cytokines.^[2,3]

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In the presence of optimum levels of P_4 , CD56 cells are known to produce a substance known as P_4 -induced blocking factor (PIBF), which is believed to possess anti-abortive properties.^[4] Furthermore, P_4 plays an important role in enhancing nitric oxide production, which, in turn, promotes improved blood circulation and oxygen supply to the endometrium.^[5]

Luteal phase defect (LPD) is commonly observed in most of the assisted reproductive technology (ART) cycles, which often necessitates the supplementation of additional P_4 . The causes of LPD have been associated with various factors, such as the removal of granulosa cells during oocyte retrieval, extended pituitary suppression due to agonist administration in gonadotropin-releasing hormone (GnRH) agonist cycles or elevated levels of serum estradiol and P_4 that inhibit endogenous luteinising hormone release via negative feedback mechanisms at the hypothalamic-pituitary-ovarian axis.^[6-8] As a result, there is a consensus within the medical community regarding the requirement for P_4 supplementation during the luteal phase of all stimulated ART cycles.^[9,10]

The significance of P_4 in the context of implantation and early pregnancy is undeniable, and it's reasonable to consider that LPD could potentially contribute to unsuccessful implantation and early pregnancy loss (EPL) during ART cycles.^[11,12] Research indicates that in fresh in vitro fertilisation-embryo transfer (IVF-ET) cycles, where conceptions occur, there is a more rapid increase in P_4 levels and higher luteal phase P_4 levels compared to cycles without conception.^[13]

However, achieving optimal pregnancy rates in frozen embryo transfer (FET) cycles hinges on adequate luteal phase support (LPS), primarily through exogenous P_4 administration.^[14] Literature is scarce regarding luteal phase serum P_4 levels in FET cycles, in which there is no endogenous production of P_4 due to the absence of ovulation and, in turn, the corpus luteum.^[15]

Endogenous production of P_4 during pregnancy may begin around week 6, coinciding with the uteroplacental shift.^[16] Therefore, in artificial cycles, serum P_4 levels during the mid-to-late luteal phase transition might solely rely on the dosage of exogenous P_4 administered to the patient.^[17]

A specific threshold for luteal phase serum P_4 that may affect the outcomes of hormone replacement therapy (HRT)-FET cycles has also not been established till now. Thus, we conducted a study to find a correlation between luteal phase serum P_4 levels and pregnancy outcome in FET cycles and the cut-off level of luteal phase serum P_4 which favours successful pregnancy outcome.

MATERIAL AND METHODS

Ethics

Ethical clearance was given by the Independent Ethical Committee, Indian Fertility Society via an Approval Letter F.1/IEC/IFS/2023/No.14 dated 20.12.2023.

Study design

This prospective cohort study included 100 women undergoing the HRT-FET cycle at Akanksha IVF Centre from December 2023 to June 2024, fulfilling the inclusion and exclusion criteria.

Inclusion criteria

Patients diagnosed with either primary or secondary infertility, aged 21–40 years, having a BMI (body mass index) of $<30 \text{ kg/m}^2$ with a normal endocrinological profile and normal uterus on 2D (two-dimensional) ultrasonography, undergoing HRT-FET of a good quality embryo (grade A cleavage stage embryo or blastocyst) at our centre were included in this study.

Exclusion criteria

Patients with a history of recurrent implantation failure, having any uterine defects like Asherman's Syndrome or any space-occupying lesions in the uterus like fibroids or adenomyosis were excluded from the study.

Methodology

Endometrial preparation for HRT-FET was done by sequential incremental administration of oral estradiol valerate (Tab Progynova® 2 mg, Bayer Zydus Pharma Pvt Ltd, India) + transdermal 17β estradiol gel (Estogel, Intas Pharmaceuticals Ltd, India) until endometrial thickness was $\geq 8 \text{ mm}$, followed by estradiol combined with injectable intramuscular P_4 (Injection Uterone 100 mg, Jagsonpal Pharmaceuticals Ltd, India) as LPS. FET was done on P+3/P+5 per day, depending upon the stage of the embryo that was transferred. Serum P_4 was measured 3 days after blastocyst transfer or 5 days after cleavage stage transfer, corresponding to the luteal phase of the cycle (days 21–23). The serum P_4 test was conducted for all patients at the same laboratory using electrochemiluminescence immunoassay (ECLIA) to ensure consistent results. The test was performed in the morning, at least 10–12 hours after the last injection. Urine pregnancy test or serum Beta-human chorionic gonadotropin (hCG) levels were checked 14 days after FET. In case of a positive pregnancy test, patients were followed

up at 6–7 weeks period of gestation to assess the pregnancy outcome of that FET cycle. In case of a viable pregnancy, patients were followed up at 11–12 weeks period of gestation with an ultrasonography report to confirm foetal well-being (ongoing pregnancy) and to see how many underwent first-trimester miscarriage.

Primary outcome

1. Correlation between luteal phase serum P_4 levels and pregnancy outcome in FET cycles.
2. Cut-off level of luteal phase serum P_4 , which favours successful pregnancy outcome.

Secondary outcome

1. Implantation rate
2. Biochemical pregnancy rate
3. Clinical pregnancy rate
4. First-trimester miscarriage rate
5. Ongoing pregnancy rate

Statistical analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean \pm SD (standard deviation) and median. The normality of data was tested by the Shapiro-Wilk test. If the normality was rejected, then the non-parametric test was used. Statistical tests were applied as follows:

1. Quantitative variables were associated using an unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) with the outcome.
2. Qualitative variables were associated using the chi-square test/Fisher's exact test.
3. The receiver operating characteristic (ROC) curve was used to assess the cut-off point, sensitivity, specificity, positive predictive value and negative predictive value of the luteal phase serum P_4 for predicting successful pregnancy outcome.

A p-value of less than 0.05 was considered significant. The data was entered into an MS Excel spreadsheet, and the analysis was done using the Statistical Package for Social Sciences (SPSS) version 25.0.

RESULTS

A total of 100 patients undergoing HRT-FET were included in our study. The mean age of our patients was 33.58 years, and the mean BMI was 23.91 kg/m². Patients were divided into four groups on the basis of raw data of the luteal phase serum P_4 levels available after completion of the study: Group 1 (<15 ng/mL), Group 2 (15.1-25 ng/mL), Group 3 (25.1-35 ng/mL) and Group 4 (>35 ng/mL). The baseline characteristics of all four groups were similar [Table 1].

Out of the 56% of patients who became pregnant, 52% were clinical pregnancies, and 4% were biochemical pregnancies [Figure 1]. The overall implantation rate among our study population was 36.08%. A significant association was found between luteal phase serum P_4 levels and implantation rate, with the highest implantation rate (45.45%) seen in the 25.1–35 ng/mL group ($p = 0.004$). The clinical pregnancy rate (CPR) among our study population was 52%, with the highest CPR in the third group (25.1-35 ng/mL; 68.3%). A significant association was seen between CPR and luteal phase serum P_4 levels ($p = 0.018$). A significant association was also found between the biochemical pregnancy rate (4%) and luteal phase serum P_4 levels ($p = 0.013$), with all the biochemical pregnancies belonging to the second P_4 group (15.1-25 ng/mL). No significant association was seen between miscarriage rate (10%) and luteal phase serum P_4 levels ($p = 0.542$). A significant association was found between the ongoing pregnancy rate (42%) and luteal phase serum P_4 levels amongst our study population ($p = 0.010$), with the highest ongoing pregnancy rate in the third group (25.1-35 ng/mL) followed by the second group (15.1-25 ng/mL) [Figure 2]. The CPR and ongoing pregnancy rate peaked around the 25 ng/mL mark [Figure 3]. Both below and above this value, the pregnancy rates showed a decreasing trend.

Table 1: Baseline characteristics of study subjects (n = 100)

P_4 groups (ng/ml) (Mean \pm SD)	P_4 <15	P_4 15.1–25	P_4 25.1–35	P_4 >35	p-value
Age (years)	34 \pm 4	33.26 \pm 3.34	34.37 \pm 3.83	32.32 \pm 3.46	0.158
BMI (kg/m ²)	24.38 \pm 1.64	23.07 \pm 2.4	24.08 \pm 2.75	24.42 \pm 2.78	0.436
Duration of infertility (years)	8.4 \pm 7.38	6.07 \pm 3.55	7.56 \pm 3.14	5.36 \pm 3.55	0.386
AMH (ng/ml)	4.2 \pm 3.87	3.63 \pm 3.37	3.6 \pm 5.02	3.72 \pm 3.22	0.3
Antral follicle count	12.6 \pm 10.19	12.15 \pm 9.08	9.95 \pm 7.21	10.36 \pm 4.28	0.117
Endometrial thickness (mm)	9.84 \pm 0.58	9.65 \pm 0.84	9.29 \pm 0.89	9.22 \pm 0.94	0.102

SD = Standard deviation, P_4 = Progesterone, BMI = Body Mass Index, AMH = Anti Mullerian Hormone

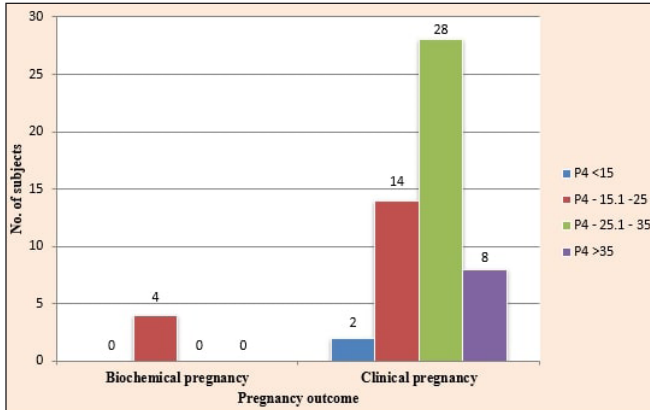


Figure 1: Distribution of study subjects according to pregnancy outcome at 6–7 weeks period of gestation.

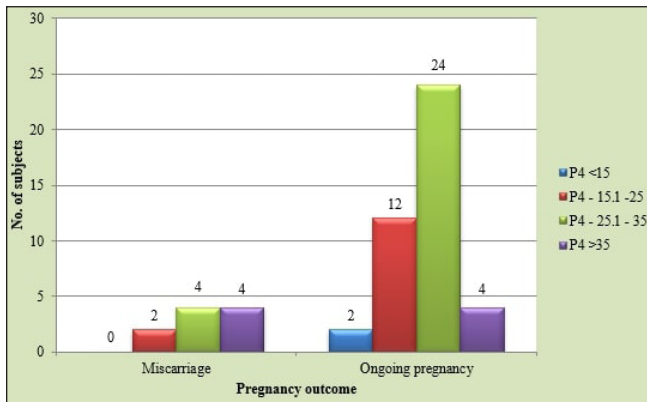


Figure 2: Distribution of study subjects according to pregnancy outcome at 12 weeks period of gestation.

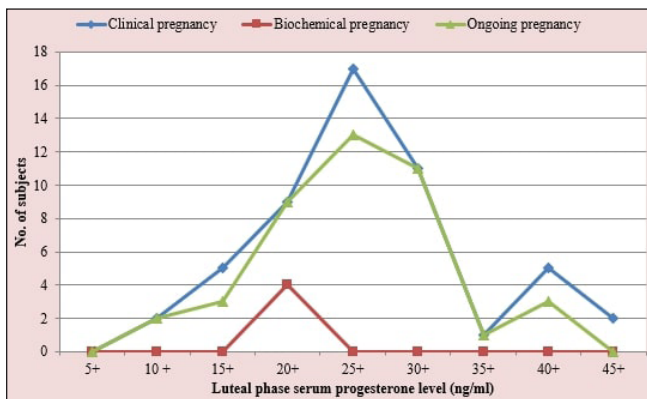


Figure 3: Pregnancy outcome in relation to the luteal phase serum progesterone levels (n = 100).

The ROC curve defined an optimal cut-off value for serum P₄ of 22.3 ng/mL, with a sensitivity of 86.5% and specificity of 33.3% for predicting clinical pregnancy [Figure 4] and a sensitivity of 88.1% and specificity of 31% for predicting ongoing pregnancy [Figure 5]. The ROC analysis indicated

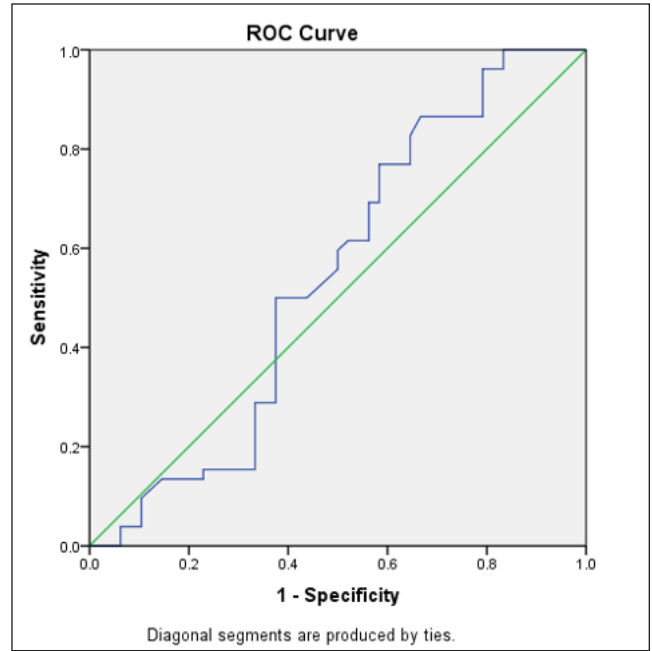


Figure 4: Receiver Operating Characteristic (ROC) curve for predicting clinical pregnancy (n = 100).

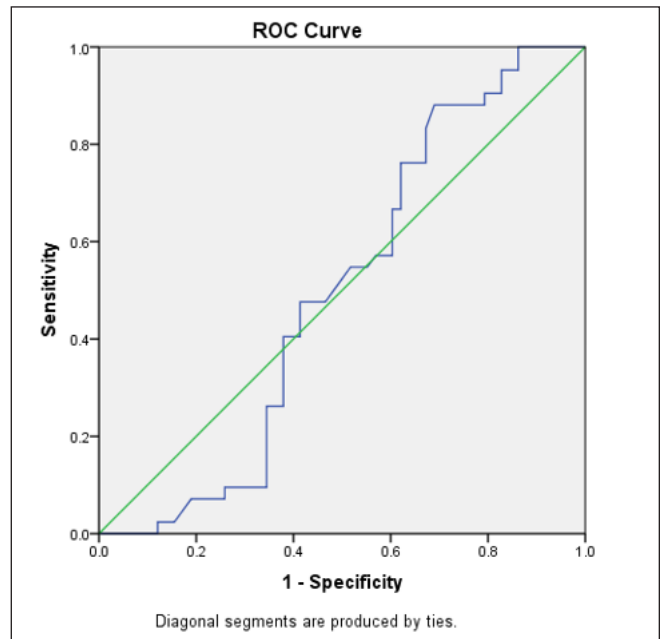


Figure 5: Receiver Operating Characteristic (ROC) curve for predicting ongoing pregnancy (n = 100).

that the luteal phase serum P₄ levels were neither predictive of clinical pregnancy, being the area under the curve (AUC) (95% CI [confidence interval]) = 0.543 (p-value = 0.456), nor predictive of ongoing pregnancy with AUC (95% CI) = 0.497 (p-value = 0.955).

DISCUSSION

Out of the 194 embryos transferred in 100 patients undergoing HRT-FET, 70 embryos were implanted, resulting in an overall implantation rate of 36.08%. A significant association was found between the luteal phase serum P₄ levels and implantation rate, with the highest implantation rate (45.45%) seen in the 25.1 to 35 ng/mL group. Yovich *et al.* identified that an ideal P₄ range of 70–99 nmol/L (28–39.6 ng/mL; $p < 0.005$) was linked to optimal outcomes in their study population. P₄ levels below 50 nmol/L (20 ng/mL) or above 99 nmol/L (39.6 ng/mL) were found to correlate with reduced implantation rates.^[17]

Among our study population, the CPR was significantly higher in the third group (25.1-35 ng/mL; 68.3%), followed by the second group (15.1-25 ng/mL; 51.9%; $p = 0.018$). In the study by Yovich *et al.*, the CPR among 529 HRT-FET cycles was found to be significantly high in the mid-luteal serum P₄ group 70–99 nmol/L (28–39.6 ng/mL).^[17] Similarly, in a study conducted by Varma *et al.* on HRT-FET cycles with intramuscular P₄ as LPS, the CPR was found to be most significant in the P₄ group 32.2–43.7 ng/mL ($p = 0.02$).^[18]

The biochemical pregnancy rate was also observed to have a significant association with the luteal phase serum P₄ levels ($p = 0.013$), with the highest biochemical pregnancy rate found in the second P₄ group (15.1–25 ng/mL; 14.8%). Kaur *et al.* found a significantly higher biochemical pregnancy rate in the FET group with P₄ levels <15 ng/mL ($p = 0.024$). This implies that an adequate level of serum P₄ is essential to ensure successful implantation of the embryo and pregnancy maintenance. An embryonic factor may play a role, though all patients in our study were under 40 years old, suggesting a comparable rate of aneuploidy among them.^[15]

Overall, 10% of patients in our study population suffered a first-trimester miscarriage. The highest miscarriage rate was seen in the fourth P₄ group (>35 ng/mL; 18.2%), but it was not statistically significant. Lek *et al.* found a cut-off level of 35 nmol/L (14 ng/mL) as a predictor of miscarriage, which was not comparable with our study. Thus, we can infer that an optimum level of serum P₄ is required for pregnancy sustenance; both below and above this level, the risk of miscarriage increases.^[19]

Humaidan *et al.* found an inverse correlation between the mid-luteal serum P₄ concentrations and the rate of biochemical pregnancies. He also observed a significant reduction in the EPL rate, from approximately 80% to 10%, as mid-luteal-phase P₄ levels rose from around 40 nmol/L (12.57 ng/mL) to approximately 80–100 nmol/L (25.15–31.44 ng/mL).^[20]

Alsbjerg *et al.* investigated the reproductive outcomes in patients undergoing frozen-thawed ET before and after

increasing the dosage of vaginal P₄ gel from 90 mg to 180 mg. They reported a notable decrease in the EPL rate (67% versus 44%; $p = 0.014$) and a significant increase in the delivery rate (9% versus 21%; $p = 0.002$) with higher P₄ supplementation.^[21]

A significant association was found between the ongoing pregnancy rate (42%) and luteal phase serum P₄ levels in our study ($p = 0.010$), with the highest ongoing pregnancy rate in the P₄ range 25.1-35 ng/mL (58.6%). Labarta *et al.* found an overall ongoing pregnancy rate of 47.2% in their study, which is similar to the result of our study (42%).^[22] Most previous studies on mid-luteal serum P₄ levels in FET cycles followed the patients till delivery and hence calculated the live birth rate.^[18] Due to a paucity of time owing to a relatively short study period, we could not follow the patients till childbirth.

The ROC curve defined an optimal cut-off value of 22.3 ng/mL luteal phase serum P₄ level among our study subjects for a favourable pregnancy outcome. Labarta *et al.* found a cut-off of 9.95 ng/mL in the mid-luteal phase, which is not at all comparable to our cut-off value. This can be explained by the fact that Labarta *et al.* used vaginal P₄ 400 mg twice daily as the LPS, whereas we used intramuscular P₄ 100 mg/day, which increases the serum P₄ levels much more profoundly as compared to vaginal P₄ which has a more significant first uterine pass effect.^[22]

Ellenbogen *et al.* concluded in their study that a mid-luteal P₄ level of >15 ng/mL increased the odds of getting pregnant by 3.2 times.^[23] Kaur *et al.* also observed that in Indian women, mid-luteal serum P₄ levels <15 ng/mL negatively impact pregnancy outcomes in both fresh and frozen-thawed ET cycles.^[15] Mitwally *et al.* also found a similar cut-off level of 15 ng/mL.^[24]

On the contrary, Aslih *et al.* conducted a prospective randomised controlled trial, revealing that biochemical pregnancy, clinical pregnancy and live birth rates showed no significant differences between groups, regardless of P₄ levels on day 7 of the luteal phase (P₄ <15 or >15 ng/mL). They found that even increasing P₄ dosage in the low P₄ group did not alter these outcomes, suggesting that enhancing P₄ levels late in the luteal phase may not sufficiently improve the endometrial environment.^[25]

Strengths

- There are only a few studies worldwide that have demonstrated the association between the luteal phase serum P₄ levels and pregnancy outcomes when intramuscular P₄ is used as LPS in HRT-FET cycles. Most of the studies have used vaginal P₄ as LPS and include only fresh ET cycles.

Limitations

- Single-centre study with a small sample size.
- Shorter duration of study.
- Patients could not be followed till childbirth due to paucity of time owing to a shorter study period.

CONCLUSION

Larger studies are needed to establish a threshold level of serum P₄ in the late luteal phase that can differentiate between successful and unsuccessful implantation. However, it is still uncertain whether the issue of unsuccessful implantation can be resolved once it is detected on days 21–23 of the HRT-FET cycle. It is also unclear whether the variation in serum P₄ levels among patients, despite receiving identical P₄ doses for LPS, is a contributing factor or merely a reflection of pregnancy outcomes. We recommend all institutes to identify their personalised ideal range of luteal phase serum P₄ levels according to the HRT-FET protocol followed in their centre, the method of testing used and the timing of the test. Individualisation of the LPS based on that range can then be done to improve pregnancy outcomes.

Ethical approval

The research/study was approved by the Institutional Review Board at the Independent Ethical Committee - Indian Fertility Society, approval number F.1/IEC/IFS/2023/No.14, dated 20-12-2023.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Sachdeva M, Nayar KD, Singh S, Sethi A, Kant G, Arora S, *et al.* Correlation Between Luteal Phase Serum Progesterone Levels and Pregnancy Outcome in Frozen Embryo Transfer Cycles: A Prospective Cohort Study. *Fertil Sci Res.* 2024;11:11. doi: 10.25259/FSR_27_2024