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Original Research Article

Early serum progesterone rise after initiation of luteal support and pregnancy outcomes in hormone replacement frozen embryo transfer cycles: a retrospective cohort study

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ABSTRACT

Background: In hormone replacement frozen embryo transfer (HRT-FET), progesterone is deliberately started before embryo transfer to initiate secretory endometrial transformation. The clinical relevance of the early serum progesterone rise after starting luteal support is unclear. This study assessed whether serum progesterone on D1 and the early change from D0 to D1 after initiation of luteal support were associated with pregnancy and live birth outcomes in HRT-FET cycles.
Methods: This retrospective cohort (September 2024 to September 2025) screened 145 HRT-FET cycles; 100 cycles with paired progesterone values and outcome follow-up were analysed. D0 preceded progesterone administration; D1 represented early post-initiation exposure before subsequent support modification and embryo transfer. The primary outcome was live birth. Mann-Whitney U, chi-square/Fisher exact tests, receiver operating characteristic analysis and multivariable logistic regression were used.
Results: Median progesterone at D0, D1 and the D0-D1 increase were 0.21 (0.08-0.56), 10.40 (6.63-14.20) and 10.35 (6.44-13.64) ng/ml, respectively. Biochemical pregnancy, miscarriage and live birth occurred in 54 (54.0%), 12 (12.0%) and 57 (57.0%) cycles. Live birth cycles had lower median D1 progesterone than non-live birth cycles (8.68 (6.51-12.30) versus 13.30 (8.29-24.05) ng/ml; p=0.004). Each 1-ng/ml increase was associated with lower adjusted odds of live birth (odds ratio 0.92; 95% confidence interval 0.87-0.97; p=0.002).
Conclusions: A lower-to-moderate early progesterone level and a less steep D0-D1 rise were associated with higher live birth probability. These findings concern early exposure within a protocol allowing subsequent progesterone supplementation and should not be interpreted as a final transfer-day progesterone threshold.

Keywords: Frozen embryo transfer, HRT-FET, Serum progesterone, Luteal phase support, Live birth, Endometrial synchrony

INTRODUCTION

Frozen embryo transfer (FET) is now a routine component of assisted reproductive technology (ART) practice. The increasing use of vitrification and freeze-all strategies has allowed embryo transfer to be separated from the supraphysiologic endocrine environment of controlled ovarian stimulation. However, successful FET still depends on careful synchrony between embryo developmental stage, endometrial receptivity and the

endocrine changes induced during luteal preparation. This is particularly important in hormone replacement therapy FET (HRT-FET), where the timing and pattern of exogenous progesterone exposure determine the opening of the implantation window. Progesterone is essential for secretory transformation of the estrogen-primed endometrium. After progesterone initiation, the endometrium undergoes glandular secretion, stromal decidualization, immune modulation and temporal changes in receptivity. In clinical practice, adequate progesterone exposure is necessary before embryo transfer; therefore, progesterone levels later in the luteal phase or close to transfer are expected to be higher than baseline. The clinically relevant question in the present study is not whether progesterone should be high before transfer, but whether the initial rate of rise after progesterone initiation carries prognostic information. Available studies have generally focused on a single progesterone value measured before or on the day of embryo transfer.

Several reports and meta-analyses have suggested that low serum progesterone, often below approximately 7.8-10 ng/ml, may be associated with reduced clinical pregnancy or live birth rates, especially in cycles using vaginal progesterone, although natural-cycle studies involve a different endocrine setting.[1-3] In contrast, a large HRT-FET cohort found no detrimental effect of higher pre-transfer progesterone concentrations once minimum adequacy had been achieved.[4] Progesterone measured after transfer has also been associated with live birth, but such measurements address a later phase of treatment.[5] Evidence from natural-cycle supplementation trials and comparisons of preparation regimens further highlights the importance of cycle type and treatment context.[6,7] These differences require attention to the route of administration, sampling time, embryo stage and whether progesterone is measured before or after treatment modification.

A paired early measurement may be useful in HRT-FET because it reflects the trajectory of progesterone exposure rather than only a static value. A gradual rise after starting luteal support may indicate controlled transition from proliferative to secretory endometrium, whereas a sudden steep increase may theoretically advance endometrial maturation relative to embryo stage. Conversely, inadequate early rise may identify patients who require luteal support adjustment before transfer. In many clinical protocols, progesterone is subsequently supplemented or modified after early monitoring; therefore, D0-D1 progesterone dynamics should be interpreted as an early response pattern and not as the final progesterone level at embryo transfer. This study evaluated serum progesterone on D0, D1 and delta P4 [P4(D1)-P4(D0)] in HRT-FET cycles. D0 was considered the day progesterone support was initiated, and D1 was the early post-initiation measurement after initial progesterone exposure. The objective was to assess whether the early progesterone level and early rate of rise were associated with biochemical pregnancy, miscarriage and live birth.

METHODS

Study design and population

This retrospective cohort study was conducted at a tertiary ART center in Goa, India. The study period was September 2024 to September 2025. A total of 145 HRT-FET cycles were screened from institutional ART records. The final analysis included 100 cycles that fulfilled the study eligibility criteria and had paired progesterone measurements [P4(D0) and P4(D1)] together with pregnancy outcome follow-up. Cycles were eligible when they involved frozen-thawed embryo transfer with available demographic, hormonal, endometrial and outcome data. Cycles outside the defined study protocol or without essential exposure or outcome information were not considered for the final analytic cohort. The study received institutional ethics approval with waiver of individual informed consent for retrospective use of anonymized clinical data; the approval details are provided under Declarations.

Endometrial preparation, luteal support and embryo transfer

All included cycles were frozen hormone replacement transfer cycles. Endometrial preparation and cycle monitoring were performed according to the center's routine clinical protocol. Estradiol valerate was administered at a dose of 2 mg or 4 mg three times daily for at least 15 days before progesterone initiation. An endometrial thickness greater than 7 mm with satisfactory blood flow was preferred before starting luteal support. Natural micronised progesterone vaginal gel 8% (Crinone, 90 mg per application) was started twice daily from D0 (the day of Crinone initiation). The first dose was administered between 07:00 and 09:00. Oral dydrogesterone 10 mg twice daily was added from the evening of D0. All ongoing progesterone/progestogen supplementation, including Crinone, dydrogesterone and Gestone where prescribed, was continued until serum β-hCG testing and, if the test was positive, until at least 10 weeks of gestation.

Serum progesterone was measured on D1 after the initial progesterone exposure; in the routine protocol, sampling was performed after three doses of progesterone gel, 4-5 hours after the most recent vaginal application. Patients with a D1 serum progesterone concentration below 15 ng/ml received additional natural progesterone in oil, 50 mg (Gestone). Subsequent progesterone monitoring and luteal support modification were performed according to clinical protocol. Embryo transfer was performed later, on D3 or D5 according to the developmental stage at freezing. Therefore, the present analysis evaluates the early D0-D1 progesterone rise after luteal support initiation, not the final progesterone level on the day of embryo transfer. Endometrial thickness was assessed by transvaginal ultrasound before embryo transfer. Frozen embryos were thawed using standard laboratory operating procedures

and transferred under ultrasound guidance. The number and stage of embryos transferred were determined clinically based on embryo availability, patient characteristics and center policy. Transfers were usually performed between 08:00 and 10:00.

Progesterone assessment and exposure variables

Serum progesterone values were extracted from clinical records. P4(D0) represented the baseline progesterone value on the day of progesterone initiation, with blood collected before administration of the first progesterone gel dose. P4(D1) represented the early post-initiation serum progesterone value, with blood collected 4-5 hours after the most recent vaginal progesterone application on D1. Delta P4 was calculated as P4(D1)-P4(D0). Delta P4 represented the absolute concentration change between the paired samples, rather than a rate normalized to elapsed time or a direct measure of endometrial progesterone exposure. Progesterone was analysed as a continuous variable and in clinically interpretable P4(D1) categories: <10 ng/ml, 10-<20 ng/ml and ≥20 ng/ml. An exploratory data-derived cut-off was also estimated by receiver operating characteristic (ROC) analysis. This cut-off was treated as hypothesis-generating and was not interpreted as a target for transfer-day progesterone management. Serum progesterone was measured using a competitive electrochemiluminescence immunoassay. Concentrations were expressed in ng/mL and interpreted in relation to the day of progesterone administration and the interval from the preceding dose.

Outcome measures

The primary outcome was live birth per FET cycle, defined as delivery of at least one live-born neonate after the transferred cycle.[8] Secondary outcomes were biochemical pregnancy, defined by positive β-hCG or positive clinical notation in the record, and miscarriage after documented pregnancy. For descriptive reporting, live birth counts (n) represent individual live-born infants. Outcomes were interpreted from the clinical follow-up data available in the dataset. Serum β-human chorionic gonadotropin (β-hCG) testing was performed on progesterone day 15 (D15), usually between 08:00 and 10:00. Pregnancy follow-up included repeat β-hCG measurement after 48 hours and the first ultrasonographic pregnancy assessment 7 days (1 week) after the positive D15 β-hCG result.

Statistical analysis

All statistical analyses and graphical representations were performed using GraphPad Prism software, consistent with the analytical approach used in our previous publications. Continuous variables were expressed as median and interquartile range (IQR) because distributions were non-normal. Categorical variables were reported as number and percentage. Between-group differences were analysed using the Mann-Whitney U test for continuous variables and chi-square or Fisher exact test for categorical variables, as appropriate. ROC analysis evaluated whether early P4(D1) discriminated live birth. Because live birth was associated with lower early P4(D1) in this dataset, inverse P4(D1) was used for ROC analysis. Multivariable logistic regression estimated adjusted odds ratios (aORs) for live birth after adjustment for P4(D1), age, BMI and endometrial thickness. Sensitivity models evaluated delta P4 and P4(D0). A two-sided $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 145 FET cycles were screened. After application of the eligibility criteria, 100 cycles were included in the final analysis. Baseline characteristics are shown in Table 1. Median maternal age was 35.0 (32.0-40.0) years, and median BMI was 26.0 (24.0-28.0) kg/m². Median endometrial thickness was 10.00 (9.28-11.00) mm. Median P4(D0), P4(D1) and delta P4 were 0.21 (0.08-0.56), 10.40 (6.63-14.20) and 10.35 (6.44-13.64) ng/ml, respectively. These progesterone values represent the early response from initiation of luteal support to D1, before later transfer-day progesterone exposure.

Early progesterone rise and live birth

Live birth cycles had significantly lower median early P4(D1) than non-live birth cycles (8.68 (6.51-12.30) vs 13.30 (8.29-24.05) ng/ml; p=0.004). Delta P4 followed the same pattern (8.56 (6.29-12.08) vs 13.25 (8.16-23.06) ng/ml; p=0.003), indicating that a less steep early rise from D0 to D1 was observed among cycles resulting in live birth. P4(D0) did not differ meaningfully according to live birth status (Table 2). The distribution of early P4(D1) by live birth outcome is shown in Figure 1.

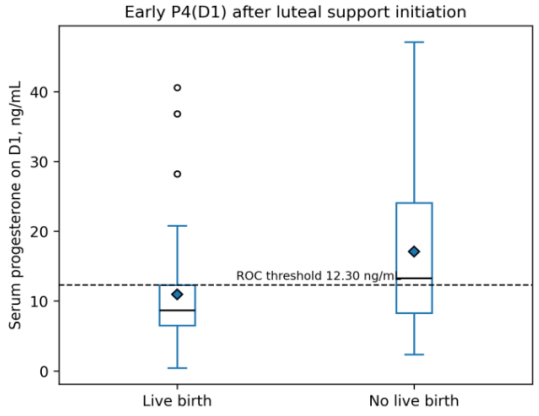


Figure 1: Box plot of early P4(D1) according to live birth outcome.

Outcomes according to early P4(D1) categories

When early P4(D1) was grouped into clinically interpretable ranges, live birth rates declined across

increasing early progesterone categories (p=0.010). Live birth occurred in 34 of 48 cycles (70.8%) with P4(D1) <10 ng/ml, 17 of 33 cycles (51.5%) with P4(D1) 10-<20 ng/ml and 6 of 19 cycles (31.6%) with P4(D1) ≥20 ng/ml (Table 3). This pattern describes the early progesterone response after luteal support initiation, before later support modification and embryo transfer.

ROC analysis and multivariable model

Because lower early P4(D1) values were associated with live birth in this dataset, ROC analysis was performed using inverse P4(D1). The area under the curve was 0.669. The exploratory threshold corresponding to the maximum Youden index was P4(D1) <12.30 ng/ml, with sensitivity 73.7% and specificity 58.1% for live birth (Figure 2). This threshold should be interpreted as hypothesis-generating and should not be used as a transfer-day progesterone target.

After adjustment for age, BMI and endometrial thickness, early P4(D1) remained significantly associated with live birth. The primary multivariable logistic regression model is presented in Table 4. Additional sensitivity models evaluating progesterone dynamics, including delta P4 and P4(D0), are summarized in Table 5.

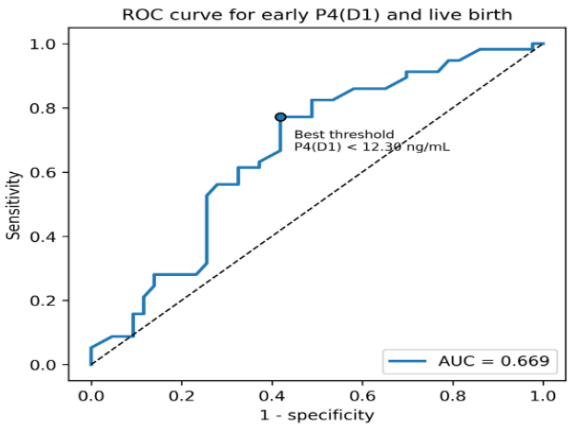


Figure 2: ROC curve for early P4(D1) predicting live birth.

Endometrial thickness and outcome

Median endometrial thickness was higher in live birth cycles than in non-live birth cycles (10.00 (9.60-11.00) vs 9.60 (9.00-10.00) mm; p=0.008). Using a 10-mm threshold, live birth was observed in 38 of 56 cycles (67.9%) with endometrium ≥10 mm compared with 19 of 44 cycles (43.2%) with endometrium <10 mm (p=0.023).

Table 1: Baseline clinical, hormonal and outcome characteristics of the analysed FET cohort (n=100).

Characteristics	Values
Maternal age (years)	35.0 (32.0-40.0)
BMI (kg/m²)	26.0 (24.0-28.0)
AFC	10.0 (9.0-13.0); available n=96
AMH (ng/ml)	2.71 (1.93-4.31)
E2 at D0 (pg/ml)	306.4 (178.2-1090.5); available n=99
P4(D0) (ng/ml)	0.21 (0.08-0.56)
P4(D1) (ng/ml)	10.40 (6.63-14.20)
Delta P4 (ng/ml)	10.35 (6.44-13.64)
Endometrial thickness (mm)	10.00 (9.28-11.00)
Biochemical pregnancy	54 (54.0)
Miscarriage	12 (12.0)
Live birth	57

Continuous data are median (interquartile range); outcomes are n (%).
AFC: antral follicle count; AMH: anti-Mullerian hormone; BMI: body mass index; E2: estradiol; P4: progesterone; D0: day of progesterone initiation; D1: early post-initiation progesterone measurement; delta P4: P4(D1)-P4(D0).

Table 2: Comparison of selected variables according to live birth status.

Variables	Live birth	No live birth	P value
Age (years)	35.00 (31.00-39.00)	38.00 (32.50-42.50)	0.060
BMI (kg/m²)	26.00 (24.90-28.30)	26.00 (23.30-28.00)	0.442
P4(D0) (ng/ml)	0.21 (0.07-0.60)	0.21 (0.10-0.54)	0.458
P4(D1) (ng/ml)	8.68 (6.51-12.30)	13.30 (8.29-24.05)	0.004
Delta P4 (ng/ml)	8.56 (6.29-12.08)	13.25 (8.16-23.06)	0.003
Endometrium (mm)	10.00 (9.60-11.00)	9.60 (9.00-10.00)	0.008
AMH (ng/ml)	2.60 (2.00-3.81)	2.76 (1.41-4.66)	0.519
AFC	10.00 (9.00-14.00)	10.00 (9.00-12.00)	0.246

Values are median (interquartile range). Between-group comparisons used the Mann-Whitney U test.
AFC: antral follicle count; AMH: anti-Mullerian hormone; BMI: body mass index; P4: progesterone; delta P4: P4(D1)-P4(D0).

Table 3: Pregnancy outcomes according to P4(D1) categories.

P4(D1) category (ng/ml)	Cycles (N)	Biochemical pregnancy	Miscarriage	Live birth
<10	48	32 (66.7)	4 (8.3)	34 (70.8)
10-<20	33	14 (42.4)	4 (12.1)	17 (51.5)
≥20	19	8 (42.1)	4 (21.1)	6 (31.6)

Outcomes are n (% of cycles within each P4(D1) category). P4: progesterone.
Chi-square p value for live birth across P4(D1) categories: 0.010.

Table 4: Primary multivariable logistic regression model for live birth.

Variables	Adjusted OR	95% CI	P value
P4(D1), per ng/ml	0.92	0.87-0.97	0.002
Age, per year	0.88	0.79-0.96	0.007
BMI, per kg/m²	1.07	0.95-1.20	0.253
Endometrial thickness, per mm	1.22	0.89-1.67	0.219

The model included early P4(D1), age, BMI and endometrial thickness. OR less than 1 indicates lower odds of live birth per unit increase.
OR: odds ratio; CI: confidence interval; BMI: body mass index; P4: progesterone.

Table 5: Sensitivity models evaluating progesterone dynamics.

Models	Progesterone exposure	Adjusted OR	95% CI	P value
Primary model	P4(D1)	0.92	0.87-0.97	0.002
Delta P4 model	Delta P4	0.92	0.87-0.97	0.002
D0-D1 model	P4(D1)	0.92	0.87-0.97	0.002
D0-D1 model	P4(D0)	0.77	0.36-1.64	0.499

OR: odds ratio; CI: confidence interval; P4: progesterone; delta P4: P4(D1)-P4(D0).

DISCUSSION

This retrospective cohort study evaluated early serum progesterone dynamics in 100 HRT-FET cycles selected from 145 screened cycles. Cycles resulting in live birth had lower median P4(D1) than cycles without live birth (8.68 versus 13.30 ng/ml; p=0.004), and live birth rates decreased across the <10, 10-<20 and ≥20 ng/ml categories (70.8%, 51.5% and 31.6%, respectively). The adjusted odds ratio of 0.92 per 1-ng/ml increase indicates approximately 8% lower odds of live birth for each unit increase within the fitted model. This describes an association under the centre's treatment protocol; it does not establish that reducing progesterone would improve outcome.

The direction of this early association differs from much of the literature on progesterone measured near embryo transfer. Melo et al associated low peri-transfer luteal progesterone with poorer ongoing pregnancy or live birth outcomes in their systematic review.[1] In a prospective cohort of 1,150 artificial-cycle transfers using vaginal progesterone, Labarta et al reported lower live birth rates when transfer-day progesterone was <8.8 ng/ml (35.5% versus 52.0%).[9] The multicentre ProFET study also associated low transfer-day progesterone with reduced live birth, with relationships varying by administration route.[2] Our D1 samples were obtained after initial treatment exposure and before subsequent supplementation; therefore, these later measurements and their thresholds are not directly interchangeable with P4(D1). Subsequent progesterone supplementation is central to interpreting the present findings. A D1 concentration <15 ng/ml triggered additional progesterone, so the initial value also determined subsequent management. Álvarez et al found similar live birth rates in cycles with initially adequate progesterone and cycles receiving subcutaneous supplementation for low progesterone on the day before euploid FET (49.1% versus 52.3%), after adequate levels were restored before transfer.[10] Labarta et al likewise reported similar live birth rates after supplementation for low transfer-day progesterone and in women with adequate levels (44.9% versus 45.0%).[11]

These observational comparisons show why management after measurement matters. Our analysis cannot separate an association with lower D1 progesterone from the effects of subsequent supplementation, and adjustment for age, BMI and endometrial thickness does not resolve this treatment-related confounding. Reports concerning higher progesterone also require protocol-specific interpretation. Kofinas et al observed lower ongoing pregnancy/live birth rates with transfer-day progesterone >20 ng/ml in programmed single euploid transfers using intramuscular progesterone.[12] This resembles the direction of our association but differs in sampling day, route and treatment adjustment. Conversely, González-Foruria et al analysing 3,183 HRT-FET cycles with adequate pre-transfer progesterone, found comparable live birth rates in the highest progesterone centile group and the remaining cycles (43.9% versus 41.3%).[4] The conflicting findings do not support a universal upper progesterone limit, and our

D1 results should not be interpreted as evidence that high progesterone at transfer is harmful.

Differences between circulating progesterone and endometrial exposure provide a further reason for caution. Miles et al demonstrated higher endometrial progesterone concentrations after vaginal administration than after intramuscular administration despite differing systemic concentrations.[13] Serum progesterone therefore does not directly measure endometrial exposure. Our protocol also included oral dydrogesterone. Eggersmann et al found no relevant analytical interference of dydrogesterone or its active metabolite in commonly used progesterone assays, indicating that serum progesterone does not quantify the entire progestogen regimen.[14] Although altered embryo-endometrial synchrony is a possible explanation for associations with progesterone exposure, endometrial dating, tissue concentrations and receptivity were not measured here. The similar findings for P4(D1) and delta P4 need to be interpreted in light of the low baseline concentration. Median P4(D0) was 0.21 ng/ml, with a relatively narrow interquartile range; subtracting this small baseline value makes delta P4 numerically close to P4(D1).

Accordingly, the association with delta P4 does not demonstrate additional predictive information beyond D1 progesterone. Moreover, two measurements describe an early concentration change rather than the full pharmacokinetic trajectory, and delta P4 was not normalized to the exact elapsed time. Repeated sampling and a direct comparison of model performance would be needed to establish whether progesterone change improves prediction. The timing and endocrine setting of previous studies also explain limits to direct comparison. Beck-Fruchter et al. associated higher progesterone with live birth when hormones were measured 14 days after FET, a substantially later biological stage than our D1 assessment.[5] Gaggiotti-Marre et al studied progesterone before natural-cycle FET, while Wånggren et al evaluated progesterone supplementation in natural cycles with an endogenous corpus luteum.[3,6] Atkinson et al compared different endometrial preparation regimens.[7] These studies reinforce the need to distinguish natural and programmed cycles and the timing of hormone assessment; none validates an early D1 threshold for the combined vaginal progesterone and dydrogesterone protocol used here.

Endometrial thickness was associated with live birth in unadjusted comparisons, but its adjusted association was not statistically significant (aOR 1.22 per mm; 95% CI 0.89-1.67; p=0.219). Thus, the higher live birth rate with an endometrium ≥10 mm does not establish an independent or universal threshold. Liu et al reported declining live birth rates with decreasing thickness below 7 mm in frozen-thaw transfers, supporting the relevance of endometrial development without validating our 10-mm division.[15] Wang et al identified thickness, age and embryo-related factors as predictors of clinical pregnancy in a larger FET cohort, whereas our previous study concerned fresh IVF/ICSI cycles.[16,17] Jin et al evaluated thickness changes after progesterone in euploid transfers and found no association with pregnancy outcomes, illustrating that absolute thickness and endometrial change are distinct exposures.[18]

Embryo characteristics and the wider hormonal environment remain potential sources of residual confounding. Cai et al identified embryo quality and progesterone measured on the day of hCG administration as important predictors in fresh transfer cycles; those findings support attention to embryo quality but cannot be directly extrapolated to exogenous progesterone during HRT-FET.[19] Fritz et al reported an association between estradiol exposure and outcomes in artificial FET cycles.[20] The present regression did not include embryo stage, number, quality or estradiol exposure, so differences in these factors could contribute to the observed association. The clinical implications are exploratory. An AUC of 0.669, sensitivity of 73.7% and specificity of 58.1% indicate modest discrimination. The <12.30-ng/ml cut-off was selected in the same dataset in which performance was assessed and may therefore be optimistic. It lies below the protocol's 15-ng/ml supplementation trigger and cannot distinguish intrinsic prognosis from the consequences of treatment adjustment. It should not be used as a progesterone dosing target, a cancellation criterion or a reason to alter embryo-transfer timing. Prospective validation should standardize sampling relative to dosing and document subsequent progesterone exposure and supplementation.

The strengths of this study include a live birth endpoint, paired early progesterone measurements and adjustment for selected clinical covariates. Limitations include its retrospective design, modest sample size and selection of 100 of 145 screened cycles based on eligibility and available records. Embryo-related factors, detailed later hormone measurements and subsequent supplementation were not fully accounted for in the reported models. Restriction to cycles with recorded outcomes may also introduce selection bias. These limitations, together with the absence of external validation, prevent causal interpretation or recommendation of a clinical threshold.

CONCLUSION

In conclusion, lower early P4(D1) and a smaller D0-D1 concentration increase were associated with higher live birth probability in this retrospective HRT-FET cohort managed with subsequent progesterone supplementation when indicated. The findings describe an early marker within a specific treatment pathway and do not demonstrate that lower progesterone exposure is beneficial. Prospective studies with standardized sampling, complete follow-up and explicit evaluation of subsequent supplementation are needed before applying D1 progesterone or delta P4 to clinical decision-making.

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