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Individualized Luteal Phase Support Strategies and their Effectiveness on Clinical Pregnancy Rate for Women Undergoing Frozen Embryo Transfer (FET) Cycle

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ABSTRACT

Progesterone (P4) is a crucial hormone for implantation and pregnancy maintenance, particularly in frozen embryo transfer (FET) cycles. While previous research has identified a correlation between low progesterone levels and reduced pregnancy success, the optimal serum P4 threshold remains unclear. Additionally, the impact of additional progesterone in patients who had a previous failed FET cycle, is unclear. This study aims to assess the pregnancy outcomes of 2 different strategies for luteal phase support; adding additional subcutaneous progesterone (SP, Lubion, 25mg, qd) in patients below a P4 threshold of 30nmol/L on the day of embryo transfer (ET), and in patients with a previous failed FET cycle, regardless of progesterone level.

This observational study was conducted at the London Women's Clinic, Infertility Centre in Darlington, UK, between January 2023 and December 2023. A total of 288 patients underwent FET with artificial endometrial preparation, using progesterone pessaries alone or in combination with injectable progesterone. Serum progesterone levels were measured on the day of embryo transfer, and additional supplementation was provided if levels were below 30 nmol/L. Patients who had a previous failed FET received additional SP commencing from 5 days prior to embryo transfer (ET). Patient characteristics, hormone levels, and pregnancy outcomes were analysed using multivariate logistic regression.

The findings indicate no significant association between progesterone blood levels at embryo transfer and pregnancy outcomes. Additionally, patients receiving supplemental SP had similar pregnancy rates to patients with P4>30nmol/L and patients who received SP due to a previous failed FET cycle. Additionally, though non-significant, there was an association between higher pregnancy rates and the use of Utrogestan pessaries compared to Cyclogest. These results signal that additional SP could be beneficial for patients with a previous failed FET cycle, however, further large-scale studies are warranted to investigate this.

Overall, this study contributes to the ongoing debate regarding luteal phase support strategies in FET cycles, highlighting the need for individualized hormone monitoring and supplementation strategies.

ABBREVIATIONS

Abbreviation	Definition
ANOVA	Analysis of Variance
BMI	Body Mass Index

CI	Confidence Interval
HCP	Healthcare professional
OR	Odds Ratio
SAP	Statistical Analysis Plan
SD	Standard Deviation

INTRODUCTION

Progesterone (P4) plays a fundamental role in implantation and pregnancy maintenance (1). It is a steroid hormone produced by the corpus luteum and later by the placenta. Research by Csapo et al. demonstrated that luteectomy in early pregnancy induces abortion, emphasizing the hormone's essential role (1973). Progesterone is responsible for inducing a secretory phase transformation of the endometrium, preparing it for pregnancy (hCG) [1].

Given the significance of P4 in reproduction, there is growing interest in determining optimal systemic P4 levels during HRT-FET cycles to enhance the success of assisted reproductive techniques (ART) [2]. Recent studies suggest that serum P4 levels below 9.2 ng/ml (29.3nmol/L) or 10 ng/ml (31.8 nmol/L) on the day of embryo transfer negatively impact pregnancy rates [3]. In cases of insufficient progesterone, known as luteal phase defect, inadequate progesterone levels may prevent normal secretory endometrial development, thereby hindering embryo implantation and growth [1].

The number of FET procedures has been increasing worldwide over the last decade [4]. The adoption of "freeze-all" policies—implemented to mitigate the risk of ovarian hyperstimulation syndrome and the adverse effects of supraphysiologic estradiol (E2) levels and premature progesterone elevation—has contributed to the growing demand for FET cycles [5]. Despite this, there is limited evidence for the use of additional progesterone in patients with previous failed cycles. This study aims to assess the pregnancy outcomes of 2 different strategies for luteal phase support; adding additional subcutaneous progesterone (SP, Lubion, 25mg, qd) in patients below a P4 threshold of 30nmol/L on the day of embryo transfer (ET), and in patients with a previous failed FET cycle, regardless of progesterone level.

STUDY AIM AND OBJECTIVES

Research question

What is the association between progesterone blood levels and pregnancy outcome following embryo transfer?

Primary objective

To investigate whether progesterone blood levels at the time of embryo transfer are associated with pregnancy outcome following embryo transfer

Secondary objectives

1. To investigate whether use of SP for patients with P4<30nmol/L on the day of ET will result in similar pregnancy outcomes to patients with P4>30nmol/L.
2. To investigate whether patients receiving SP due to P4 < 30nmol/L have a similar odds of positive pregnancy outcome compared to patients given Lubion due to previous failed FET cycle.
3. To investigate the impact of progesterone levels, BMI, age and the type of vaginal pessary (Utrogestan and Cyclogest) on pregnancy outcomes.

METHODS AND MATERIALS

This observational study was conducted at the London Women's Clinic, Infertility Centre in Darlington, United Kingdom, from January 2023 to December 2023. Informed consent for non-contact research was obtained from all participants before inclusion. All patients underwent artificial endometrial preparation prior to FET, utilizing progesterone pessaries (Cyclogest, 400mg, BD or Utrogestan, 200mg, TDS) with or without progesterone injections. Serum progesterone levels were assessed on the day of embryo transfer, and additional P4 supplementation (Lubion, 25mg, OD) was administered when levels were found to be suboptimal (<30 nmol/L). For patients with previous failed FET cycles, additional P4 supplementation commenced simultaneously with VP, prior to P4 testing. All participants underwent a single embryo transfer.

Inclusion and Exclusion Criteria

Participants included women younger than 45 years with a BMI <30 and no systemic diseases. An endometrial thickness of ≥7 mm at the time of transfer was required. Exclusion criteria encompassed recurrent miscarriage (three or more pregnancy losses), endometrial thickness <7 mm at the time of transfer, uterine abnormalities (e.g., fibroids, polyps, adenomyosis), congenital uterine anomalies, and the presence of hydrosalpinx.

Hormone Replacement Protocol

For artificial FET cycles, estradiol (8 mg daily) was initiated on day 2 of the menstrual cycle. An ultrasound examination was performed on day 10, and if the endometrial thickness was ≥7 mm, embryo transfer was scheduled for day 5 of progesterone administration (initiated on day 10 of the cycle). VP was either Cyclogest (400mg, BD) or Utrogestan (200mg, TDS). In patients with P4<30nmol/L on the day of embryo transfer, Lubion (25mg, OD) was added. In patients with a previous failed FET cycle or with a missing previous history, VP was administered alongside Lubion (25mg, once daily) from 5 days prior to embryo transfer. All patients received progesterone until the 12th week of gestation.

A blood sample was obtained on the day of embryo transfer to verify that progesterone levels met the target threshold (≥30 nmol/L). Embryos were generated through in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), and graded using the Gardner criteria. Embryo transfer was performed under ultrasound guidance. A home pregnancy test was conducted on day 10 post-transfer.

Statistical Analysis

Data were cleaned and analysed using R studio version 4.2.3. Descriptive statistics were computed and described before analyses for primary and secondary research objectives were conducted.

A multivariate logistic regression model was built with progesterone as the predictor variable and pregnancy outcome (positive or negative) as the outcome variable. Models included age, BMI, and a categorical concomitant treatment variable as covariates. Results are reported as odds ratio (OR) with 95% CI of positive pregnancy test (given a one-point increase in progesterone).

For analysis of secondary objective 1, patients recorded as having received SP prior to their progesterone level test were excluded. Differences in mean BMI, age, and progesterone results between patients received SP and patients not received SP was compared using T-tests. Differences in the proportion of positive pregnancy tests and other concomitant medications between those two groups was compared using Chi-squared tests. For analysis of secondary objective 2, All patients, including those received SP prior to testing, were included. Differences in mean BMI, age, and progesterone results between patients received SP prior to receipt of progesterone blood test results, patients received Lubion following receipt of progesterone blood test results, and patients not received Lubion were compared using one-way ANOVA. Differences in the proportion of positive pregnancy tests and other concomitant medications between these groups were compared using Chi-squared tests.

Another multivariate logistic regression model was built with Lubion prescription (pre- test, post-test, not received) as a predictor, and pregnancy outcome as outcome. BMI, age and concomitant prescriptions (other than Lubion) were included as covariates. Progesterone level test results were not included as a covariate as they are likely to be correlated with Lubion provision prior to testing. Results are reported as OR with 95% CI of a positive pregnancy test for each Lubion prescription condition

RESULTS

Patient Characteristics

From a total sample of 290 patients, 288 were included in the analysis sample. Two patients were excluded due to: missing information on pregnancy outcome (n=1) and missing information on concomitant medications (n=1). Patient characteristics of the analysis sample are described in Table 1.

Table 1: Patient characteristics of the analysis sample

		Overall (N=288)
Age	Mean (SD)	38.4 (2.61)
	Median [Min, Max]	39.0 [29.0, 44.0]
BMI	Mean (SD)	31.1 (2.46)
	Median [Min, Max]	32.0 [26.0, 35.0]
SP received prior to P4 test	No	166 (57.6%)
	Yes	122 (42.4%)
Concomitant progesterone	Cyclogest (400mg, BD)	194 (67.4%)
	Utrogestan (200mg, TDS)	83 (28.8%)
	None	11 (3.8%)
History of previous IVF treatment or miscarriages	Previous IVF treatment	110 (38.2%)
	Previous miscarriage	2 (0.7%)
	Neither	176 (61.1%)
Progesterone (nmol/L)	Mean (SD)	44.1 (28.2)

	Median [Min, Max]	36.0 [7.80, 270]
	≤ 30 nmol/L on day of transfer	97 (33.6%)
SP received post-test	No	248 (86.1%)
	Yes	40 (13.9%)
Pregnancy outcome	Negative	139 (48.3%)
	Positive	149 (51.7%)

Primary Objective

Results of the logistic regression analyses are presented in Table 2. Univariate logistic regression analyses suggested that progesterone blood levels at embryo transfer were not significantly associated with pregnancy outcome following embryo transfer. Controlling for age, BMI and concomitant vaginal progesterone (VP) medication did not significantly influence the results.

Table 2: Logistic regression analysis results

Model	Variable	OR of positive pregnancy test	95% CI	p-value
Univariate	Progesterone	1.00	0.99–1.01	0.647
Multivariate	Progesterone	1.00	0.99–1.01	0.857
	Age	0.96	0.88–1.05	0.393
	BMI	1.04	0.94–1.14	0.483
	Concomitant medication: Cyclogest	2.32	0.67–9.13	0.193
	Concomitant medication: Utrogestan	1.30	0.36–5.31	0.693

Secondary Objectives

Patients with Low Serum P Levels and iLPS vs. Patients with Normal Serum P Levels

A total of 122 patients were excluded from this analysis due to prescription of Lubion prior to test, which may have impacted progesterone blood levels at transfer. A total of 166 participants were included.

Patient characteristics for this analysis are presented in Table 3. Progesterone blood levels at transfer were significantly lower in patients who were received subcutaneous progesterone following test results. There were no other significant differences between groups. All patients with a history of IVF or miscarriage had received Lubion prior to test, and were therefore not included in this analysis.

Table 3: Subgroup comparison: patients with P4 ≥ 30nmol/L not receiving SP and P4<30nmol/L receiving SP

Continuous variables		**P4 ≥ 30nmol/L not receiving SP (n=127)**			**P4<30nmol/L receiving SP (n=39)**			**Statistic[a]**	**p**
		n	Mean	SD	n	Mean	SD		
Progesterone (nmol/L)		127	47.29	28.11	39	26.22	21.04	4295.5	<.001
Age (years)		127	37.88	3.00	39	39.03	2.12	1983	.058
BMI (kg/m^2)		127	31.24	2.41	39	30.87	2.27	2777.5	.247
Categorical variables		**P4 ≥ 30nmol/L not receiving SP**			**P4<30nmol/L receiving SP**			**Statistic[b]**	**p**
		N	%		N	%			
Positive pregnancy test	No	66	52		17	43.6		0.54	.464
	Yes	61	48		22	56.4			
Concomitant medication	None	1	0.8%		0	0		2.38	.378
	Cyclogest	85	66.9		31	79.5			
	Utrogestan	41	32.3		8	20.5			
Previous history of failed IVF	Yes	0	0		0	0		-	-
Previous history of miscarriage	Yes	0	0		0	0		-	-

[a]Mann-Whitney-Wilcoxon test; [b]Chi-Squared test

Logistic regression analyses results are presented in in Table 4. Univariate logistic regression analyses suggested that progesterone blood levels at transfer were not significantly associated with pregnancy outcome following embryo transfer in those not previously received Lubion. Lubion prescription did not significantly influence the non-significant association between progesterone and pregnancy outcome. Controlling for age and BMI also did not significantly influence the results.

Table 4: Logistic regression analyses of the association between progesterone levels and SP prescription following test results and pregnancy test outcome

Model	Variable	OR of positive pregnancy test	95% CI	p-value
Univariate	Progesterone	1.00	0.99–1.01	0.773
Multivariate	Progesterone	1.00	0.99–1.02	0.579
	SP received post-test	1.69	0.78–3.75	0.186
	Age	0.92	0.82–1.03	0.149
	BMI	1.06	0.93–1.21	0.401

OR: odds ratio; CI: confidence interval

Pregnancy outcomes in patients received SP for P4<30nmol/L or for previous failed cycle or miscarriage

One individual was excluded from analyses of secondary objective 2 due to prescription of SP both before and after progesterone blood level results. A total of 287 participants were included.

Patient characteristics for this analysis are shown in Table 5. There were significant differences in progesterone blood levels between the three groups (p<.001). Other concomitant medications received and history of IVF treatment or miscarriage also differed between groups (p=.015 and p<.001, respectively). There were no other significant differences between groups.

Table 5: Subgroup comparison: patients received SP prior to P4 test, P4<30nmol/L received SP and P4 ≥ 30nmol/L not received **SP**

		Received SP prior to P4 test	P4<30nmol/L received SP	P4 ≥ 30nmol/L not received SP	Statistic[a]	p

Variable		n	Mean	SD	n	Mean	SD	n	Mean	SD		
Progesterone (nmol/L)		121	46.67	28.43	39	26.22	21.04	127	47.29	28.11	46.68	<.001
Age (years)		121	38.76	2.19	39	39.03	2.12	127	37.88	3.00	5.55 (df=2)	.062
BMI (kg/m^2)		121	31.06	2.59	39	30.87	2.27	127	31.24	2.41	1.14 (df=2)	.567
Variable		**Received SP prior to P4 test**			**P4<30nmol/L received SP**			**P4 ≥ 30nmol/L not received SP**			**Statistic[b]**	**p**
		N	%		N	%		N	%			
Positive pregnancy test	Yes	65	53.7		22	56.4		61	48.0		1.23	.542
	No	56	46.3		17	43.6		66	52.0			
Concomitant medications	None	10	8.3		0	0		1	0.8		13.35	.015
	Cyclogest	77	63.6		31	79.5		85	66.9			
	Utrogestan	34	28.1		8	20.5		41	32.3			
Previous history of failed IVF or miscarriage	Failed IVF	109	90.1		0	0		0	0		248.32 (df=4)	<.001
	Miscarriage	2	1.7		0	0		0	0			
	No history	10	8.3		39	100		127	100			

[a]Kruskal-Wallis test; [b]Chi-Squared test

Note: df=degrees of freedom. p<.05 represents a significant difference.

Logistic regression analyses are presented in Table 6. Univariate logistic regression analyses suggested that SP prescription, either prior to, or after, progesterone blood level test results was not significantly associated with pregnancy test outcome. Controlling for age, BMI and other concomitant medications did not significantly influence the results.

Table 6: Logistic regression of the association between SP prescription time and pregnancy test outcome

Model	Variable	OR of positive pregnancy test	95% CI	p-value
Univariate	Lubion prescription time (reference = never)			
	Received post test	1.40	0.68-2.91	.361
	Received pre-test	1.26	0.76-2.07	.371
Multivariate	Lubion prescription time (reference = never)			
	Received post test	1.41	0.68 – 2.99	0.361
	Received pre-test	1.40	0.83 – 2.37	0.208
	Age	0.95	0.86-1.04	.253
	BMI	1.04	0.94-1.14	.466
	Concomitant medication [Cyclogest]	2.60	0.73-10.50	.148
	Concomitant medication [Utrogestan]	1.48	0.40-6.20	.562

OR: odds ratio; CI: confidence interval

DISCUSSION

This observational study provides insights into the role of progesterone levels and supplementation strategies in frozen embryo transfer (FET) cycles. The results demonstrated no significant difference in pregnancy rates between patient groups, and no association to progesterone level on the day of ET. This indicates that in patients with adequate P4 (≥30nmol/L), higher progesterone levels won't result in an increased pregnancy rate. This result has been demonstrated in previous studies such as Ramos et al. in which patients who received SP alongside VP had no significant differences in clinical pregnancy rate varying across the quartiles of progesterone levels on the day of ET (2020). However, it should be noted that the patients in the top 50% of progesterone levels had significantly lower miscarriage rates. There could be a potential role of higher serum progesterone levels for miscarriage rate which was not examined in our study.

There were several other findings that offer valuable implications for clinical practice in assisted reproductive technologies (ART). First, the subgroup of patients with progesterone levels <30 nmol/L who were given subcutaneous Lubion showed pregnancy rates comparable to those with higher baseline P4 levels. This suggests a potentially beneficial effect of timely intervention through progesterone supplementation, particularly in patients identified as biochemically suboptimal on the day of transfer. This finding aligns with earlier literature suggesting that low P4 is associated with reduced implantation and pregnancy rates if not corrected in a timely manner [6,7].

Secondly, the comparison of pregnancy outcomes between patients receiving SP before versus after P4 measurement highlighted an important clinical consideration. Although not statistically significant, there was a trend towards higher success in patients treated pre-emptively due to prior failed FET cycles. This finding suggests that clinical history might serve as a surrogate marker for identifying patients at risk of inadequate luteal phase support and may guide empirical supplementation strategies [8]. Further research is warranted in this area to elucidate these findings.

Moreover, the association between the use of Cyclogest and higher pregnancy rates compared to the use of Utrogestan suggests that formulation and route of administration may play a role in treatment outcomes. Differences in pharmacokinetics between Cyclogest and Utrogestan could underlie this observation, though further research is warranted to confirm any differential effects [7].

Implications for Clinical Practice

These findings underscore the necessity for individualized luteal support strategies in FET cycles. Rather than adopting a one-size-fits-all threshold, a combination of serum hormone measurements and patient history may better identify those likely to benefit from additional progesterone support. Furthermore, rigid serum P4 thresholds (e.g., 30 nmol/L) may not be the best indicator for supplementation decisions, and further research to try and identify optimal and individualized thresholds would be beneficial.

Healthcare professionals might consider earlier or empirical intervention in select high-risk populations, such as those with previous implantation failure or miscarriage, even in the absence of real-time progesterone serum level data. Additionally, further exploration of the optimal route and formulation of progesterone could enhance treatment personalization.

Future Research Directions

Future studies should focus on prospective, randomized controlled trials stratifying patients based on both serum P4 levels and clinical history. Such trials would ideally include arms comparing different progesterone formulations, routes of administration, and initiation timing to better understand their influence on implantation and pregnancy outcomes. Further research to understand the optimal luteal support strategy for patients with previous failed FET cycles are needed.

In addition, mechanistic studies are warranted to elucidate why certain patients respond differently to similar progesterone levels and to explore biomarkers beyond serum progesterone that could guide therapy. Longitudinal studies could also assess the impact of individualized luteal support strategies on live birth rates and perinatal outcomes.

CONCLUSION

The study identified that pregnancy outcomes remained comparable between groups, suggesting that timely supplementation may offer a window of opportunity to optimize hormonal support and potentially salvage cycles with initially low progesterone levels or in patients with previously failed cycles.

Given the increasing use of FET cycles in assisted reproductive technology (ART), tailored progesterone supplementation strategies remain crucial. Future large-scale, randomized controlled trials are necessary to establish definitive progesterone thresholds and optimize clinical protocols for improving pregnancy success rates in FET cycles.

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