ORIGINAL RESEARCH

Unraveling the Role of Progesterone and Endometrial Dynamics in Frozen-Thawed Embryo Transfer Success: A Comprehensive Study

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ABSTRACT

Background: Assisted reproductive technologies (ART) rely heavily on optimizing endometrial preparation for successful Frozen-Thawed Embryo Transfer (FET). Progesterone plays a crucial role in modulating endometrial receptivity, yet its specific influence in FET outcomes remains intricate and multifaceted.**Methods:**This study investigates the impact of progesterone and estrogen treatment on ongoing pregnancy rates in FET cycles. A standardized hormonal protocol involving exogenous estradiol (E2) and progesterone was employed. Endometrial thickness and compaction were meticulously assessed throughout the cycle.**Result:**The Clinical Pregnancy Rate (CPR) in the Compaction group stands at 57.6%, whereas the Increased ET group exhibits a lower CPR of 36.4%. Remarkably, the No compaction group shows the lowest CPR at 6% ($p = 0.039$). Further breakdowns depict distinct trends in pregnancy outcomes. Live birth rates are notably higher in the Compaction group (100%) compared to the Increased ET and No compaction groups (0%) ($p = 0.042$). Although no significant differences are observed in the Abortion rates across groups ($p = 0.155$), the Compaction group displays the highest rate at 57.1%. Ectopic pregnancies, prevalent in both Compaction and Increased ET groups (50% each), are absent in the No compaction group ($p = 0.245$).**Conclusion:**Progesterone's influence on endometrial dynamics is multifaceted, shaped by individualized responses. Individualized approaches, considering both quantitative and qualitative aspects of compaction, are essential for optimizing FET success.

Key words: Assisted Reproductive Technologies, Frozen-Thawed Embryo Transfer, Progesterone, Endometrial Dynamics, Pregnancy Outcomes, Hormonal Protocols.

INTRODUCTION

Assisted reproductive technologies (ART) have revolutionized fertility treatments, offering hope to couples facing challenges in conception. Among these techniques, Frozen-Thawed Embryo Transfer (FET) has emerged as a pivotal method, providing new avenues for achieving successful pregnancies[1]. Unlike traditional fresh embryo transfer, FET involves the cryopreservation of embryos, followed by their thawing and subsequent transfer into the uterus[2]. This approach has gained widespread acceptance due to its advantages, including increased cycle flexibility and improved outcomes[3]. As a result, FET has become a preferred choice for many couples undergoing fertility treatments, leading to its increasing prevalence in clinics worldwide[4].

In the context of ART, the success of FET hinges on various factors, with endometrial receptivity playing a central role. Endometrial receptivity refers to the receptive state of the uterine lining, which allows for the acceptance and implantation of embryos. The timely synchronization between embryo development and endometrial receptivity is crucial for achieving successful pregnancies[5]. Among the factors influencing endometrial receptivity, the thickness of the endometrium has emerged as a key parameter[6]. Studies have indicated that optimal endometrial thickness is essential for a successful pregnancy outcome[7-9].

However, despite advancements in understanding endometrial receptivity, there remains a notable gap in our understanding of specific dynamics, such as

endometrial compaction, during FET cycles. Endometrial compaction, characterized by decreased thickness, may have significant implications for the success of FET cycles[10]. The transition from the estrogen phase to the day of embryo transfer involves intricate changes in endometrial thickness, influenced by factors such as progesterone[11]. Understanding these nuanced changes is paramount for refining FET protocols and improving pregnancy outcomes[12].

The existing literature acknowledges the importance of endometrial receptivity in FET success but falls short in elucidating the specific impact of endometrial compaction on outcomes. Bridging this knowledge gap is crucial for advancing our comprehension of the complexities involved in FET cycles and optimizing treatment strategies[12-14]. By addressing this gap, the current study aims to contribute both theoretically and practically to the field of reproductive medicine.

Furthermore, the study's findings have implications beyond theoretical advancements, extending into the practical landscape of reproductive medicine. Fertility treatments, particularly FET, rely heavily on evidence-based practices. The insights generated by this research may serve as a catalyst for refining and personalizing fertility treatment protocols. Clinicians can leverage this knowledge to make informed decisions regarding the administration of progesterone and other aspects of FET, ultimately aiming to improve patient outcomes[14].

The significance of the study's findings lies in their potential to reshape established paradigms in reproductive science. By unraveling the nuances of how progesterone-induced changes in endometrial thickness influence FET outcomes, the study seeks to make a substantial contribution to the field of reproductive medicine. Moreover, the practical applications of the findings are of paramount importance, as they have the potential to enhance the effectiveness of fertility treatments and improve patient outcomes[15].

This study aims to address existing gaps in knowledge surrounding endometrial compaction and its specific implications for FET outcomes. By advancing our understanding of the intricate dynamics governing endometrial receptivity during FET cycles, the research aims to provide actionable insights for refining treatment protocols and improving pregnancy outcomes.

MATERIALS AND METHODS

Study Setting: The study was conducted at CIMAR Fertility Centre in Edappal, Kerala, over a one-year period. A retrospective-prospective observational design was employed in adherence to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) criteria. This design facilitated the comprehensive examination of endometrial compaction dynamics during Frozen-Thawed Embryo Transfer (FET) cycles.

Study Participants: The participants comprised women undergoing FET at CIMAR Fertility Centre, Edappal, Kerala. Inclusion criteria encompassed women exclusively undergoing FET cycles, including both self and donor cycles. Additionally, participants' embryos were limited to grades 1 or 2 to ensure homogeneity in embryo quality and increase internal validity.

Exclusion criteria excluded patients undergoing fresh embryo transfer cycles, as well as those utilizing natural or modified natural cycles. This exclusion aimed to maintain a clear focus on the specific dynamics of FET cycles and their association with endometrial compaction. Moreover, participants with uterine pathologies such as adenomyosis, endometriosis, and fibroid uterus were excluded to minimize confounding effects on endometrial receptivity.

Sample Size: To determine the sample size, a conservative estimate of 50% for the estimated proportion of the population was assumed. This estimate maximized the sample size to ensure adequate statistical power. With a 95% confidence level and an 8% margin of error, the required sample size was calculated using the formula for estimating a proportion. After accounting for a 10% loss to follow-up and non-response rate, the total sample size was determined to be 165. A total of 170 participants were included in the study.

Sampling Technique: Participants were selected through consecutive sampling, ensuring that all eligible women undergoing FET during the study period were included. This sampling technique facilitated the recruitment of a representative sample, enhancing the generalizability of the study findings.

Study Methodology: The study employed a treatment protocol designed to provide a comprehensive and systematic approach to endometrial preparation for FET. This protocol included a standardized hormonal regimen comprising exogenous administration of estradiol (E2) and progesterone. Transvaginal ultrasound was utilized to monitor endometrial thickness at critical time points during the FET cycle. Progesterone supplementation was initiated based on specific criteria, ensuring optimal endometrial conditions for embryo implantation. Serial ultrasound assessments were conducted to evaluate endometrial response and adjust hormonal support as necessary.

Ethical Issues: The study protocol received approval from the ethics committee of CIMAR Fertility Centre, ensuring compliance with ethical guidelines and regulations. Informed consent was obtained from all participants, emphasizing their autonomy and right to withdraw from the study at any time. Confidentiality of participant information was strictly maintained throughout the study process.

Statistical Analysis: Data analysis was conducted using IBM SPSS software version 25. Descriptive statistics were used to summarize demographic and clinical characteristics of the study participants.

Inferential statistics were employed to analyze the impact of endometrial compaction on clinical pregnancy rate and secondary outcomes. The significance level was set at $p < 0.05$ to determine statistical significance.

RESULT

Out of 170 study participants, endometrial thickness remained same both before and after treatment in 15 (8.8%), while compaction was found in 100 (58.8%), and increase in endometrial thickness was observed in 55 (32.4%).

Table 1: Endometrial thickness before and after treatment in different groups

Groups		Endometrial thickness before treatment	Endometrial thickness after treatment
Compaction group	Mean ± SD	9.41 ± 1.76	8.48 ± 1.70
	Median (IQR)	9.25 (8.08-10.63)	8.10 (7.20-9.60)
	(minimum, maximum)	(5.8, 15)	(5.3, 14)
Increased endometrial thickness	Mean ± SD	8.38 ± 1.06	9.62 ± 1.63
	Median (IQR)	8.35 (7.53-9.10)	9.40 (8.40-10.08)
	(minimum, maximum)	(6.5, 11.4)	(7.1, 13.9)

Clinical Pregnancy Rate (CPR) in Relation to Endometrial Compaction:

The study examined the clinical pregnancy rates (CPR) in association with different percentages of endometrial compaction within each group. Notably, the CPR varied across compaction categories, suggesting a potential impact of compaction levels on pregnancy outcomes. In the compaction category of ≤5%, a CPR of 64.3% was observed, indicating a positive clinical pregnancy outcome, while the no pregnancy rate stood at 35.7%. Similarly, in the 6-9% compaction category, the CPR reached 68.8%, with a corresponding 31.2% no pregnancy rate. However, the ≥20% compaction category exhibited a lower CPR of 33.3%, accompanied by a higher no pregnancy rate of 66.7% (Figure 1).

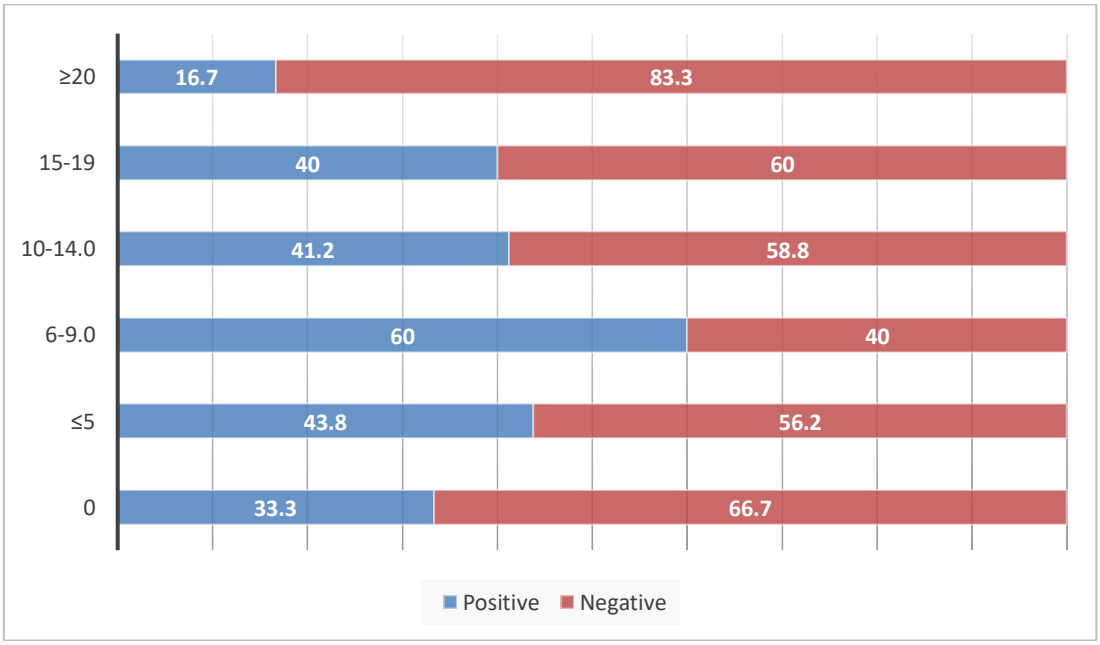

Figure 1: Association between endometrial compaction and pregnancy results

Association Between Clinical Pregnancy Rate and Increased Endometrial Thickness (ET):

The study also explored the association between different percentages of increased endometrial thickness (ET) and their corresponding CPR within each group. The results indicated varied CPRs across categories of increased ET, suggesting a nuanced relationship between ET and pregnancy outcomes. Notably, while the ≤5% increased ET category demonstrated a 50% CPR, the 6-9% category exhibited a 0% CPR, with a 100% no pregnancy rate (Figure 2).

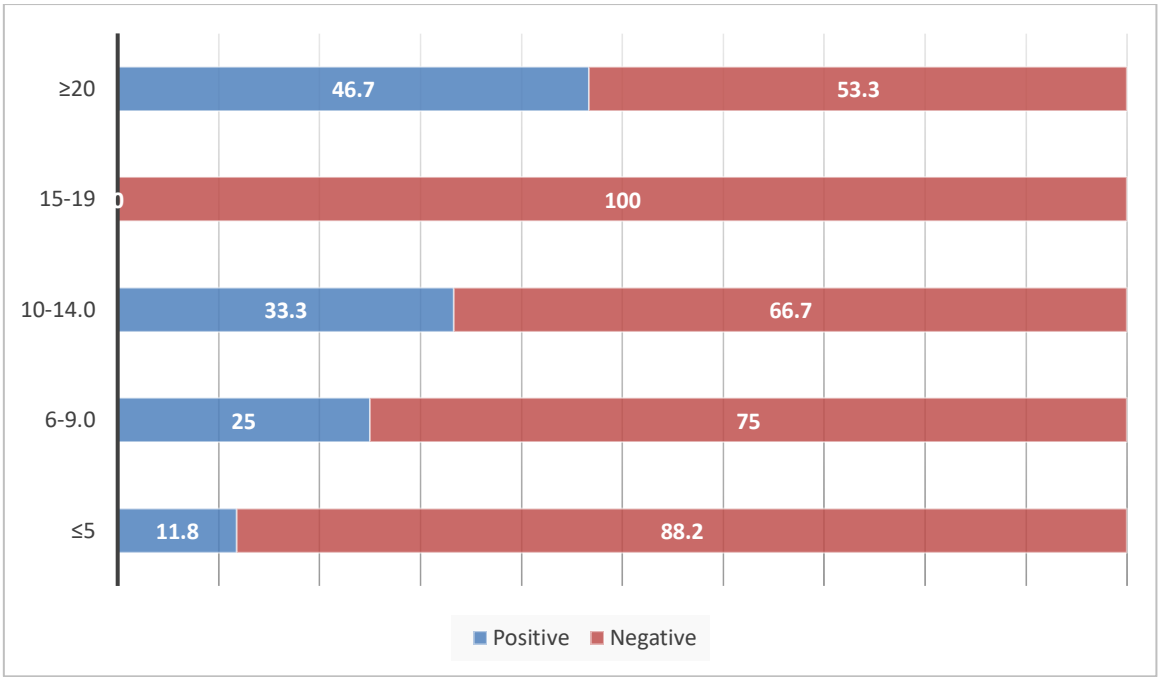

Figure 2: Association between increase in endometrial thickness and pregnancy results

Effect of Endometrial Compaction on Pregnancy Outcomes:
Further analyses revealed significant associations between endometrial compaction and diverse pregnancy outcomes (Table 2). Cases characterized by the absence of endometrial compaction demonstrated a higher likelihood of abortion, emphasizing the potential influence of endometrial dynamics on specific pregnancy outcomes within the study cohort. Additionally, the study highlighted varied pregnancy outcomes across compaction categories, suggesting a nuanced relationship between compaction levels and pregnancy success rates.

Table 2: Association between endometrial compaction and pregnancy outcomes

Percentage of endometrial compaction	Abortion	Ongoing pregnancy	Ectopic	Biochemical	Live birth
≤5	5 (45.5)	5 (45.5)	0 (0)	1 (9)	0 (0)
6-9	3 (18.8)	9 (56.3)	1 (6.2)	1 (6.2)	2 (12.5)
10-14	1 (16.7)	4 (66.6)	0 (0)	1 (16.7)	0 (0)
15-19	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)
≥20	2 (66.7)	0 (0)	0 (0)	1 (33.3)	0 (0)

Comparison of Pregnancy Outcomes Among Study Groups:
A comprehensive comparison of pregnancy outcomes among three distinct groups of study participants— the Compaction group, Increased ET group, and No compaction group— underscored significant differences in CPR and live birth rates among the groups (Table 3). These findings highlighted the pivotal role of endometrial dynamics in influencing pregnancy outcomes and underscored the need for further investigation into the underlying mechanisms.

Table 3: Pregnancy outcomes among three groups of study participants

Pregnancy outcomes	Compaction group	Increased ET group	No compaction group	P value
CPR	19 (57.6)	12 (36.4)	2 (6)	0.039
Live birth	2 (100)	0 (0)	0 (0)	0.042
Abortion	12 (57.1)	6 (28.6)	3 (14.3)	0.155
Ectopic	1 (50)	1 (50)	0 (0)	0.245

DISCUSSION

Progesterone plays a pivotal role in optimizing endometrial preparation for Frozen-Thawed Embryo Transfer (FET), making it essential to understand its significance in achieving successful outcomes. Our study delved into the intricate interplay between

progesterone and estrogen treatments and ongoing pregnancy rates, highlighting the importance of the temporal sequence of hormonal interventions in shaping FET success[16].

The present study similar to Le et al.'s, focused on vaginal micronised progesterone supplemented with intramuscular progesterone, providing a critical reference point in our exploration of progesterone's modulation of endometrial dynamics[16]. By standardizing the hormonal protocol with exogenous estradiol (E2) and progesterone, our study aimed to elucidate how progesterone influences endometrial thickening, a key determinant in FET outcomes. This standardized approach allowed for a comprehensive evaluation of progesterone's role in achieving optimal endometrial thickness, a factor highlighted by Ye et al.'s extensive observational study encompassing 4465 first FET cycles[17].

Contrary to conventional assumptions, our study revealed variable changes in endometrial thickness on the day of FET, challenging the notion of a direct correlation between endometrial thickness and clinical pregnancy rates. This finding underscores the need for a more nuanced evaluation beyond traditional endometrial thickness metrics alone, reflecting a deeper understanding of endometrial dynamics in the context of FET[17].

Endometrial compaction emerged as a significant factor influencing FET outcomes in our study. Drawing insights from Poojari et al.'s exploration, our study underscored the clinical significance of evaluating endometrial compaction and vascularity for optimizing FET outcomes[18]. The meticulous assessment of endometrial thickness changes throughout the FET cycle allowed for a nuanced evaluation of the association between endometrial compaction and pregnancy outcomes.

Our findings revealed a nuanced relationship between the degree of endometrial compaction and pregnancy outcomes, suggesting a potential dose-response relationship. Notably, higher percentages of compaction were associated with higher positive pregnancy rates, highlighting the predictive value of endometrial compaction in FET success. These observations corroborated Haas et al.'s findings, which showcased a positive association between endometrial compaction and clinical pregnancy rates, further emphasizing the clinical relevance of evaluating endometrial compaction in optimizing FET outcomes[19].

The meticulous synchronization of hormonal interventions in our study reflects the emphasis on precise hormonal control in optimizing FET outcomes. Integrating insights from Le et al.'s randomized study, which focused on the role of progesterone administration methods, underscores the importance of fine-tuning hormonal interventions for optimal outcomes[20]. Additionally, Ye et al.'s expansive observational study accentuates the intricate interplay between hormonal protocols and endometrial responses, emphasizing the need for individualized approaches in FET[17].

While our study provides valuable insights into the role of progesterone and endometrial dynamics in Frozen-Thawed Embryo Transfer (FET), several limitations should be acknowledged. Firstly, the retrospective nature of the study design introduces inherent biases and limits the establishment of causal relationships. Secondly, the sample size may not capture the full spectrum of FET outcomes, potentially affecting the generalizability of our findings. Additionally, the study's reliance on a single center may limit the extrapolation of results to broader populations. Lastly, the absence of long-term follow-up data hinders a comprehensive assessment of neonatal outcomes and the durability of FET success.

Prospective investigations could delve deeper into personalized hormonal protocols tailored to individual endometrial responses. Exploring the interplay between endometrial compaction and specific embryo characteristics may unveil additional layers to the FET success narrative. Integrating advanced imaging techniques and molecular analyses could provide a more granular understanding of endometrial dynamics. Long-term follow-ups and assessments of neonatal outcomes may further enrich our comprehension, paving the way for enhanced clinical strategies in the realm of FET.

CONCLUSION

The present study sheds light on the intricate interplay between progesterone, endometrial dynamics, and Frozen-Thawed Embryo Transfer (FET) outcomes. The study results reveal association between endometrial compaction, thickness changes, and pregnancy outcomes, highlighting the multifaceted nature of endometrial dynamics in shaping FET success. Moving forward, prospective investigations should focus on refining hormonal protocols, integrating advanced imaging techniques, and conducting long-term follow-ups to enhance our understanding and clinical strategies in FET.

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