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CASE REPORT

OPTIMIZING LUTEAL PHASE SUPPORT IN A PATIENT WITH THIN ENDOMETRIUM UNDERGOING FROZEN EMBRYO TRANSFER: A CASE REPORT

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Abstract

Introduction. Thin endometrium and suboptimal luteal phase progesterone levels are recognized factors that may reduce implantation and live birth rates in frozen embryo transfer (FET) cycles. A major focus in the literature is the comparison of different endometrial preparation protocols and their impact on pregnancy outcome. No significant evidence has yet been reported to recommend one over the other endometrial preparation methods in terms of success rate and pregnancy rate.
Case presentation. We report the case of a 37-year-old woman with primary infertility and a history of thin endometrium during prior FET cycles. She underwent FET of two day-4 embryos after individualized endometrial preparation and tailored progesterone supplementation with term live birth of a healthy female.
Conclusions. Close monitoring of endometrial development and serum progesterone levels, along with individualized luteal support, may improve FET outcomes in patients with a history of thin endometrium.

Keywords: FET, progesterone, natural cycle, endometrium.

Résumé

Optimisation du soutien de la phase lutéale chez une patiente présentant un endomètre fin et bénéficiant d'un transfert d'embryons congelés: un cas clinique

Introduction. Un endomètre mince et des taux suboptimaux de progestérone en phase lutéale sont des facteurs connus pouvant réduire les taux d'implantation et de naissance vivante lors des cycles de transfert d'embryons congelés (FET). La comparaison des protocoles de préparation endométriale — programmée, naturelle ou stimulée — montre peu de différences en termes de succès de grossesse, bien que les cycles spontanés semblent offrir un effet protecteur contre les complications obstétricales à long terme, comme l'hypertension gravidique et les nouveau-nés grands pour l'âge gestationnel.
Rapport du cas. Nous rapportons le cas d'une femme de 37 ans avec infertilité primaire et antécédents d'endomètre mince lors de cycles FET précédents. Après une préparation endométriale individualisée et une supplémentation en progestérone adaptée, elle a bénéficié du transfert de deux embryons au jour 4,

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List of abbreviations:
FET – frozen embryo transfer
NC- FET – natural cycle FET
mNC-FET – modified natural cycle
hCG – human chorionic gonadotropin
HRT – hormone replacement therapy
LH – luteinizing hormone
GnRH – gonadotropin-releasing hormone
IVF – in-vitro fertilization
ICSI – intracytoplasmic sperm injection
FSH – follicle-stimulating hormone
AMH – anti-mullerian hormone
IM – intramuscular
SC – subcutaneous
ART – assisted reproductive technology
ET – endometrial thickness

conduisant à la naissance à terme d'une fille en bonne santé.
Conclusions. Une surveillance précise du développement endométrial et des taux sériques de progestérone, associée à un support lutéal personnalisé, pourrait améliorer les résultats des cycles FET chez les patientes présentant un endomètre mince.

Mots-clés: FET, progestérone, cycle naturel, endomètre.

Introduction

Frozen embryo transfer (FET) has become an integral part of assisted reproductive technology, offering the potential for embryo storage and transfer in hormonally optimized cycles. Endometrial preparation for FET can be achieved through several approaches, each with distinct physiological and clinical implications. In the natural cycle FET (NC-FET), follicular development and ovulation occur spontaneously, with embryo transfer timed according to the endogenous luteinizing hormone (LH) surge. This approach preserves the physiological hormonal milieu and the function of the corpus luteum[1,2]. A modified natural cycle (mNC-FET) achieves similar physiological conditions but employs pharmacological ovulation triggering, most commonly with human chorionic gonadotropin (hCG), to improve scheduling flexibility while maintaining corpus luteum support. In NC and mNC cycles, the corpus luteum secretes progesterone, relaxin, and other vasoactive mediators critical for maternal vascular adaptation[3]. By contrast, HRT cycles depend exclusively on exogenous hormones and lack corpus luteum–derived factors, potentially predisposing to placental dysfunction and hypertensive disorders[4]. Excessive estrogen exposure in HRT may further disrupt trophoblast invasion. An alternative strategy involves letrozole-stimulated cycles, in which the aromatase inhibitor letrozole promotes mild ovarian stimulation and ovulation. Evidence suggests that this approach may enhance endometrial receptivity and improve pregnancy outcomes in certain patient populations[1-4].

Comparative studies have investigated reproductive performance across these protocols. A retrospective analysis of 108 NC-FET and 224 HRT-FET cycles reported no significant differences in implantation, clinical pregnancy, or live birth rates between the groups[5]. Similarly, a Swiss registry-based cohort study including 4,636 singleton live births between 2014 and 2019 confirmed comparable pregnancy outcomes across NC and HRT cycles[2]. In a larger retrospective analysis involving 10,333 FET cycles, no significant differences in live birth rates were observed among NC, HRT, GnRH agonist–suppressed, and ovarian stimulation cycles[6]. However, in a cohort of 2,849 ovulatory women, letrozole-stimulated cycles yielded significantly higher live birth, clinical pregnancy, and ongoing pregnancy rates compared with both NC and HRT cycles[7]. Collectively, these findings suggest broadly comparable live birth rates across most protocols, though letrozole-stimulated cycles may confer superior efficacy in selected populations.

Taken together, current evidence indicates that while reproductive outcomes are broadly comparable across endometrial preparation strategies, programmed HRT-FET cycles may increase the risk of maternal and perinatal complications. In contrast, NC-FET and letrozole-stimulated protocols appear to provide safer alternatives, particularly in women at elevated risk of hypertensive disorders[8,9]. Clinical decision-making should therefore incorporate not only the convenience of cycle scheduling but also individual patient risk profiles, with a focus on optimizing both maternal health and perinatal outcomes.

Endometrial thickness and adequate luteal phase progesterone are critical determinants of implantation and live birth rates in FET cycles. Thin endometrium and suboptimal progesterone levels remain challenges that can compromise clinical outcomes, necessitating individualized monitoring and adjustment of hormone supplementation protocols.

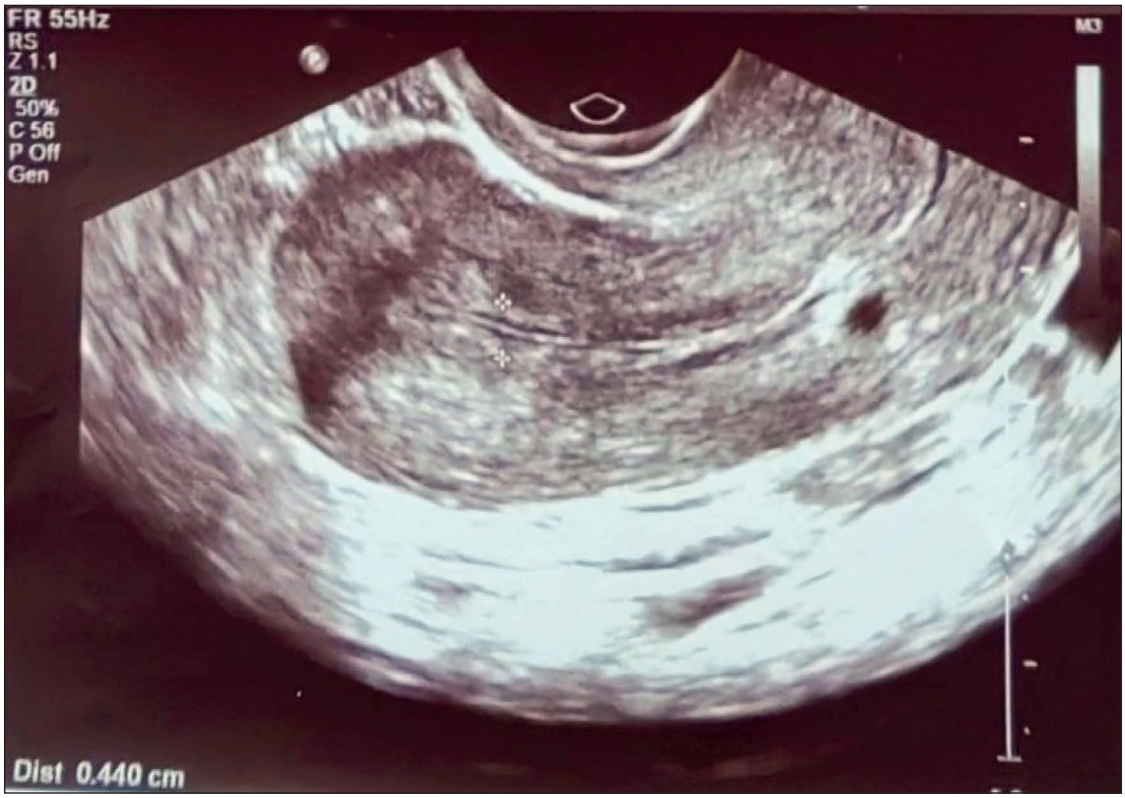


Fig. 1. Endometrial thickness on day 12 of HRT measured 4.4 mm, with a trilaminar (type M) appearance.

While it is well known that inadequate luteal support impairs IVF outcomes, consensus on how much, how long, and by which route P4 should be given—plus what serum level is good enough—remains unsettled. Variability arises from pharmacokinetics across routes, assay differences, and embryo stage/synchrony.

Case presentation

A 37-year-old female patient presented with primary infertility of unexplained etiology. Baseline hormonal evaluation revealed FSH 6.39 mIU/mL and anti-mullerian hormone (AMH) 0.80 ng/mL. She had previously undergone three IVF attempts in other clinic, including two embryo transfers performed as FET with hormone replacement therapy (HRT) cycles with estradiol regimen as follows: 2 tablets of 2 mg estradiol, 3 times per day from day 2 of menstrual cycle (12 mg estradiol per day). Each transfer involved two cleavage-stage embryos (day 3). Following the last IVF cycle, two day-4 embryos remained cryopreserved. The patient had no comorbidities or prior surgeries.

She was referred for FET of the remaining two day-4 embryos in a hormonal replacement cycle. Given a history of thin endometrium during prior FET preparations, with higher than usual estradiol preparation regimen, estradiol valerate was administered orally at 2 mg three times daily from day 2 of the menstrual cycle as usual in HRT.

On day 9 of the menstrual cycle, transvaginal ultrasound revealed no dominant follicle as expected. Endometrial thickness was 4.4 mm, with a trilaminar (type M) appearance. No adjustments were made to the estradiol regimen. A follow-up ultrasound on day 12 showed no change in endometrial thickness or morphology (Fig. 1).

FET preparation was continued without altering estradiol dosing. Luteal support with subcutaneous progesterone (25 mg once daily) was initiated, and the embryo transfer was scheduled for cycle day 18 (5 days of progesterone supplementation). Serum progesterone on the day of embryo transfer was 9.18 nmol/L. Due to suboptimal progesterone levels, additional vaginal progesterone gel (90 mg daily) was added. One day post-transfer, serum progesterone increased to 44.0 nmol/L, indicating adequate luteal support.

The patient achieved a positive pregnancy test. The pregnancy progressed as a normal singleton gestation, prophylactically managed with aspirin 150 mg daily from 12 weeks of gestation, without complications. The pregnancy ended successfully with the delivery of a healthy term female infant weighing 3100 g and measuring 51 cm.

Discussion

Thin endometrium is a recognized challenge in FET cycles, often associated with reduced implantation and live birth rates[10-12]. In this case, endometrial growth remained suboptimal despite standard estradiol supplementation, highlighting individual variability in endometrial responsiveness. Research demonstrates a narrow optimal progesterone window (13.7–20 ng/mL) on embryo transfer day; values outside this range correlate with significantly lower clinical pregnancy rates[13]. Meanwhile, mid-luteal progesterone levels of 150–250 nmol/L (~47–79 ng/mL) have been linked with highest live birth rates, whereas lower or excessively higher levels were suboptimal[14].

Progesterone supplementation is a cornerstone of luteal phase support in assisted reproductive technology (ART), with multiple administration routes utilized to optimize endometrial receptivity and pregnancy outcomes[15]. Intramuscular (IM) injections represent a long-standing standard in ART, providing high and sustained systemic progesterone concentrations. A typical 50 mg IM dose achieves peak serum levels of approximately 50 ng/mL, which remain elevated for ≥48 hours. Despite its efficacy, IM administration is associated with local adverse effects, including injection site pain and sterile abscesses, and may compromise patient adherence[16].

Vaginal administration of progesterone provides the "first uterine pass effect," achieving high endometrial tissue concentrations despite relatively low systemic levels. This route is convenient and widely used in hormone replacement therapy (HRT) FET protocols. However, absorption variability remains a limitation, with 30–50% of women exhibiting suboptimal serum concentrations (<11 ng/mL) even under standard dosing regimens. While the uterine "first pass" effect makes vaginal P4 highly efficient locally, multiple studies associate low serum P4 near ET with reduced implantation/ongoing pregnancy and higher miscarriage in HRT FET cohorts. Subcutaneous (SC) progesterone has emerged as an alternative to IM injections, offering rapid absorption, high systemic bioavailability, and improved ease of administration. Sublingual micronized progesterone achieves moderate systemic concentrations but requires frequent dosing, while oral dydrogesterone has demonstrated live birth rates comparable to vaginal progesterone, though serum monitoring is unreliable due to the measurement of inactive metabolites[17,18].

Evidence consistently supports the existence of a minimum serum progesterone threshold necessary for successful implantation and maintenance of pregnancy in HRT-FET cycles. Serum concentrations below 10 ng/mL are associated with significantly reduced live birth rates and increased miscarriage risk[10,11,18]. Conversely, levels ≥10 ng/mL are correlated with improved ongoing pregnancy and live birth rates (relative risk ~1.47) and lower miscarriage risk (RR 0.62) as confirmed by meta-analysis[12]. An 11 ng/mL cutoff is frequently cited as a clinical benchmark, although up to 40% of women receiving vaginal progesterone may remain below this threshold at the time of embryo transfer[19]. Furthermore, day 16 post-transfer serum progesterone levels ≥15.7 ng/mL (50 nmol/L) are associated with higher live birth rates and reduced pregnancy loss[10].

Optimal serum progesterone ranges have been proposed based on both fresh and frozen embryo transfer cycles. In HRT-FET, a concentration of 10–15 ng/mL is generally considered optimal[11,19], whereas in fresh IVF/ICSI cycles, levels between 22–31 ng/mL (70–99 nmol/L) are associated with maximal implantation, with sub- and supra-physiological levels correlating with reduced success[20]. Several studies in euploid FET cycles have identified a "window of receptivity" between 10 and 20 ng/mL, with adverse outcomes reported below 10 or above 20 ng/mL[10,21].

Data regarding potential upper limits of progesterone exposure remain inconsistent. Some studies suggest that serum levels exceeding 20 ng/mL may reduce implantation rates and increase miscarriage risk, potentially due to premature endometrial advancement[21,22]. Other investigations, particularly in IM or SC regimens, report no detrimental effect of higher serum concentrations, indicating that systemic levels may not accurately reflect endometrial tissue exposure[23]. While excessively high progesterone may impair endometrial synchrony in fresh cycles, its clinical significance in FET remains uncertain.

For patients exhibiting low serum progesterone, rescue strategies have been explored. SC supplementation with 25 mg progesterone in women with concentrations <10 ng/mL restored adequate levels in 83% of cases and normalized pregnancy outcomes relative to women with sufficient baseline levels[18]. Combined regimens, integrating vaginal and SC or IM administration, can optimize both local uterine exposure and systemic adequacy. Oral dydrogesterone has also been used as a rescue strategy, although serum monitoring is not feasible.

Clinically, routine serum progesterone assessment on the day of embryo transfer or shortly beforehand can identify patients at risk of poor outcomes. Target thresholds of ≥10 ng/mL are recommended, with an optimal window of 10–15 ng/mL in HRT-FET cycles. Serum progesterone should be measured 12–24 hours prior to embryo transfer, or on the morning of transfer, after several doses have been administered, considering the time elapsed since

the last administration. Rescue interventions should be considered for individuals with suboptimal concentrations. Current evidence does not definitively establish a harmful upper limit; however, caution is warranted for levels exceeding 20 ng/mL. Evidence from prospective and retrospective studies indicates that same-cycle rescue is preferable to cycle cancellation. When timely rescue is administered, reproductive outcomes approximate those observed in patients with adequate baseline progesterone levels, supporting the clinical utility of monitoring and intervention rather than postponing embryo transfer[10,18,20,23].

Among the various parameters used to assess endometrial receptivity, endometrial thickness (ET) measured by transvaginal ultrasound is widely employed as a non-invasive marker. Although ET is commonly used in clinical practice, the optimal range for successful implantation remains a topic of ongoing investigation[24]. Recent evidence has clarified aspects of the relationship between ET and reproductive outcomes. Threshold analyses suggest that an ET between 8.7 mm and 14.5 mm is associated with the highest live birth rates, whereas endometrial measurements below 7 mm or above 14.5 mm may reduce the likelihood of successful implantation[5,25,26]. Additionally, large cohort studies indicate that clinical pregnancy and live birth rates increase progressively with each millimeter increment in ET up to approximately 12 mm, after which the rates plateau, highlighting a non-linear relationship between endometrial development and implantation potential[27,28,29]. Changes in endometrial morphology, including compaction during the secretory phase, have also been linked to lower clinical pregnancy rates, emphasizing the importance of monitoring dynamic ET changes throughout the luteal phase to optimize timing for embryo transfer[27].

The development of the endometrium is closely regulated by hormonal therapies administered during FET cycles. Estradiol is essential for promoting endometrial proliferation; however, supraphysiological levels can result in endometrial hyperplasia, which may negatively affect implantation[30]. Progesterone plays a pivotal role in endometrial maturation and the acquisition of receptivity, with adequate levels necessary to support embryo implantation and early pregnancy. Both the timing and dosing of hormonal supplementation influence endometrial morphology and function, underscoring the need for individualized protocols in assisted reproduction.

Accurate and timely assessment of ET is fundamental to optimizing FET outcomes. Transvaginal ultrasonography remains the standard method for evaluating endometrial development, and serial measurements during the luteal phase provide additional prognostic value. The timing of these assessments is critical, as measurements performed too early or too late may not accurately reflect the endometrium's receptive status, potentially leading to suboptimal transfer timing.

Collectively, these findings highlight the complex interplay between endometrial thickness, hormonal environment, and implantation success. Understanding the optimal ET range and the influence of estradiol and progesterone supplementation allows clinicians to individualize treatment strategies and improve reproductive outcomes in FET cycles. Continued research is warranted to refine these parameters further and to integrate them with emerging biomarkers of endometrial receptivity.

Conclusions

This case demonstrates that careful monitoring of endometrial thickness and serum progesterone, along with individualized adjustments to luteal support, can facilitate successful FET outcomes even in patients with a history of thin endometrium. Further studies are needed to define optimal protocols for endometrial preparation and progesterone supplementation.

Author Contributions:

S.A. and E.K. were responsible for the diagnostic procedures, clinical diagnosis, and treatment decisions. S.A. wrote the manuscript. Both authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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