Review

Endometrial Preparation Useful to Embryo Implantation

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Endometrial Preparation Useful to Embryo Implantation

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Abstract: Endometrial preparation is crucial in in vitro fertilization (IVF) protocols to create optimal conditions for embryo implantation and pregnancy. Successful embryo nidation requires a receptive endometrium, which is influenced by factors such as endometrial thickness, hormonal environment, autocrine and paracrine growth factors, and the presence of resident and non-resident stem cells within the endometrium basalis. Synchronization between endometrial and embryonic development is also essential. Endometrial preparation, whether achieved through spontaneous cycles, natural cycles with minimal support, ovulation induction, or hormone replacement therapy (HRT), results from a combination of biochemical and biophysical conditions, each independent of the others. These conditions are difficult to pinpoint within a fixed period (Window of Implantation, WOI) using any specific examination due to the variability in estrogen and progesterone production rates, their metabolic clearance rates (MCR) when administered exogenously, and their metabolism when given systemically, topically, or orally. These variations also occur in different phenotypes and over different durations. Moreover, the synchronization of endometrial preparation with incomplete decidualization and the uncertain duration of the implantation window pose challenges. It is also unknown if there are compliance mechanisms similar to diapause seen in other species. This review aims to outline a clinical approach that, while not an absolute clinical recommendation due to the lack of definitive certainties, assists in understanding complementary phenomena and provides a useful orientation for clinical practice.

Keywords: endometrium; basalis and functionalis; estradiol; progesterone; production; metabolic clearance rate; transport ; growth factors; endometrial thickness; factors influencing endometrial thickness; markers of decidualization; histological dating; pinopodes; treatment for endometrial assessment useful to embryo implanytation

1. Introduction

Endometrial preparation is essential in IVF protocols to optimize conditions for embryo implantation and subsequent pregnancy. The primary determinant for successful embryo nidation within a prepared endometrium is the embryo quality (Gill P et al., 2024). A receptive endometrium, influenced by factors such as endometrial thickness, hormonal environment, and the synchronization of endometrial and embryonic development, is also crucial (Thomas Strowitzki A et al., 2006; Bulletti

 doi:10.20944/preprints202408.0733.v1

C et al., 2022). Despite many studies suggesting a link between endometrial thickness and successful implantation, conclusive evidence is still lacking (Mathyk B et al., 2023; Brodeur TY et al., 2024). Therefore, endometrial thickness cannot yet be established as an evidence-based criterion for determining endometrial receptivity before embryo transfer.

In natural cycles, specific endometrial characteristics are required for implantation (Tomic V et al., 2020). The preparation of the endometrium for embryo transfer aims to mimic these characteristics. Studies, including randomized controlled trials (RCTs), have shown that an endometrial thickness of ≥9 mm on the day of hCG administration is associated with significantly higher pregnancy rates, with the optimal range being 8-14 mm (Chen et al., 2010; Kovacs et al., 2003; Demirol and Gurgan, 2004). Women with an endometrial thickness of 10-12 mm have the highest pregnancy rates.

Despite over 500 peer-reviewed studies on endometrial thickness (ET) and ART outcomes, establishing a clear relationship between ET and successful embryo implantation remains challenging due to significant heterogeneity in study designs (Craciunas et al., 2019; Gao et al., 2020; Kasius et al., 2014; Momeni et al., 2011).

1.1. Criticisms of Endometrial Thickness Studies:

- **Study Variability**: Differences in stimulation protocols (Lv et al., 2020), the number of embryos transferred (Gallos et al., 2018; Kasius et al., 2014), and increments in ET measurements (Liu et al., 2018; Shakerian et al., 2021) contribute to inconsistent results.
- **Sample Size Issues**: Early studies had small sample sizes (Fleischer et al., 1986; Gonen et al., 1989), while recent larger studies face issues like missing data and confounding factors (Liu et al., 2018; Mahutte et al., 2022).
- **Ultrasound Variability**: Advances in ultrasound technology and high inter- and intraobserver variability impact the reliability of ET measurements (De Geyter et al., 2000).
- **Measurement Timing**: Variations in ET measurement timings in IVF and IUI cycles affect the comparability of results.

The clinical significance of small differences in ET, such as 0.5 mm, is debatable due to measurement variability. While extensively studied, ET's role in predicting implantation success remains controversial and requires cautious interpretation.

This study critically examines factors influencing endometrial adequacy for embryo implantation, aiming to balance the role of the endometrial interface at implantation. Although no single factor, procedure, or molecule significantly impacts embryo implantation alone, endometrial progesterone-mediated differentiation is essential for early pregnancy (Csapo et al., 1973).

1.2. Key Findings:

- **Endometrial and Myometrial Function**: Studies show higher implantation rates in gestational carriers compared to intentional mothers during the first embryo transfer, suggesting a functional syncytium between the endometrium and myometrium that is involved in successful embryo implantation (US Registry Data on Gestational Carriers, 2021).
- **Controversies in Endometrial Preparation**: The debate persists on the impact of endometrial preparation on embryo implantation. Tailored treatments should not solely rely on sequential euploid embryo transfer due to age and ovarian reserve constraints but also consider extra-embryonic causes of implantation failure.

Recommendations include Sequential Euploid Embryo Transfer (SEET) as a strategy when possible, ensuring all known extra-embryonic causes of implantation failure are excluded or corrected. Without excluding these potential causes, SEET can be considered an add-on rather than a primary strategy.

Collected studies suggest that optimal endometrial thickness is significant for embryo implantation and pregnancy success following embryo transfer. However, it is not the sole determinant. Other factors, including endometrial receptivity, embryo quality, and overall uterine health, also play crucial roles. This study emphasizes a comprehensive approach to assessing and

 doi:10.20944/preprints202408.0733.v1

optimizing endometrial conditions for successful embryo implantation, recognizing the complexity and multifactorial nature of implantation success.

2. Relevant Sections

2.1. Endometrial Thickness:

- Ideal thickness is between 7-14 mm for optimal implantation rates, measured via transvaginal ultrasound. Thickness below 7 mm is associated with lower implantation rates and higher chances of miscarriage (Liu KE et al., 2018; Weiss NS et al., 2017; Kasius A et al., 2014). Thickness greater than 14 mm may negatively impact implantation success (Mahutte N et al., 2022; Liao S et al., 2021; Yuan X et al., 2016; Chen XJ et al., 2012; Josse J et al., 2020; Kolibianakis EM et al., 2004; Noyes N et al., 1995; Sundstrom P et al., 1998; Check JH et al., 2011; El-Toukhy T et al., 2008; Vaegter KK et al., 2017; Zhao J et al., 2014; Kumbak B et al., 2009; Kovacs P et al., 2003; Al-Ghamdi A et al., 2008; Aydin T et al., 2013; Wu Y et al., 2014; Bu Z et al., 2015).
- The issue remains debated with differing evaluations among authors (Eva R et al., 2018; Mathyk B et al., 2023; ESHRE WORKING GROUP ON RIF D Cimadomo et al., 2023).

2.2. Triple-Line Pattern Diagnosed by Ultrasound:

A trilaminar or "triple-line" pattern on ultrasound around the time of embryo transfer indicates a receptive endometrium (Ju W et al., 2023). This pattern, showing a central echogenic line surrounded by hypoechoic regions, correlates with higher implantation and pregnancy rates (Check JH et al., 2003).The trilaminar endometrial pattern is a key indicator of endometrial receptivity, associated with higher implantation success rates in IVF treatments.

2.3. Hormonal Environment:

Adequate estrogen levels stimulate endometrial growth, while progesterone transforms the proliferative endometrium into a secretory lining, preparing it for embryo implantation (Mackens S et al., 2017; Yuan X et al., 2016; Simeonov M et al., 2022; Onogi S et al., 2020; Bulletti C et al., 2022).Proper synchronization between endometrial development and embryo stage is critical for successful implantation, often achieved by mimicking the natural menstrual cycle through hormonal supplementation (Greco E et al., 2016; Glujovsky D et al., 2020; Quaas AM et al., 2021; Patel JA et al., 2021). The "window of implantation," typically occurring 6-10 days after ovulation, is when the endometrium is most receptive (Wilcox AJ et al., 1999; Lessey BA, 2000). Identifying or predicting this window has proven difficult (Aplin J et al., 2022; Doyle N, 2022).

2.4. Future Perspectives in Endometrial Features Assessment:

EndoClassify: An AI model developed to improve endometrial assessment and embryo receptivity in ART, using a dataset of 402 endometrial ultrasound images expanded to 14,989 through augmentation (Asch Schuff RH et al., 2024). Achieved 95% accuracy, 10% loss, 93% sensitivity, and 93% specificity. Identified 'good endometrium' with 71% accuracy, corresponding to a 74% pregnancy rate. Despite the study's retrospective design, EndoClassify shows significant potential for clinical use, enhancing decision-making efficiency.

2.5. Endometrial Dating:

Histological dating of an endometrial biopsy assesses the tissue's readiness for embryo implantation, particularly during the luteal phase (Noyes R et al., 1950; Lessey BA et al., 2019; Díaz-Gimeno P et al., 2011). Key features assessed include tortuous glands with secretory activity, increased stromal fluid, transformation of stromal cells, and coiling of spiral arteries. Histological dating helps ensure embryo transfer aligns with the receptive phase, increasing implantation and pregnancy success. Newer methods like molecular markers of endometrial receptivity and

 doi:10.20944/preprints202408.0733.v1

transcriptomic assays (e.g., the Endometrial Receptivity Array) aim to provide more precise assessments but have yet to significantly advance clinical diagnostics.

2.6. Immunohistochemical Evaluation:

Immunohistochemical (IHC) evaluation assesses specific markers indicating the endometrium's readiness for implantation.

PR (Progesterone Receptor): Decreases in the secretory phase.
ER (Estrogen Receptor): Downregulated in the secretory phase.
LIF (Leukemia Inhibitory Factor): Peaks during the mid-secretory phase.
Glycodelin: Levels increase during the secretory phase.
Integrins: Upregulated in the mid-secretory phase, important for embryo attachment.
Ki-67: High in the proliferative phase, decreases in the secretory phase.
HOXA10: Increases in the secretory phase, indicating receptivity.
VEGF (Vascular Endothelial Growth Factor): Upregulated during the secretory phase for increased vascularization.
MUC1 (Mucin 1): High levels during the mid-secretory phase suggest receptivity.

These markers help in dating the endometrium and determining its adequacy for embryo nidation.

3. Strategies for Low Endometrial Thickness

When the endometrium does not grow adequately after normal ovarian steroid stimulation, it can impact embryo implantation and pregnancy success. Here are key consequences and potential reasons for inadequate endometrial growth (Santamaria X et al., 2012; Macklon NS et al., 2002; Xu B et al., 2013; Margalioth EJ et al., 2006):

3.1. Hormonal Supplementation

- **Estradiol**: Oral, transdermal, or injectable forms can increase endometrial thickness (Lutjen P et al., 1984; Navot D et al., 1986; Rosenwaks Z et al., 1987). Higher doses or extended administration may be required for patients with thin linings (Simon C et al., 1995; Paulson RJ et al., 1990; Zhang T et al., 2018; Alur-Gupta S et al., 2018; Yarali H et al., 2016; Groenewoud ER et al., 2016; Wright KP et al., 2006; Tourgeman DE et al., 2001; Liao X et al., 2014; Sekhon L et al., 2019). Adequate thickness is critical for improving pregnancy rates (Racca A et al., 2023).
- **Human Chorionic Gonadotropin (hCG)**: Low-dose hCG can stimulate endometrial growth and improve thickness (Eftekhar M et al., 2014).

An inadequately developed endometrium may not support embryo implantation, leading to lower implantation rates and increased risk of early miscarriage. Insufficient endometrial lining can result in poor placentation, intrauterine growth restriction (IUGR), and preterm birth.

3.2. Potential Reasons for Inadequate Endometrial Growth

Hormonal Imbalances: Low estrogen or inadequate progesterone response can result in thin endometrial lining. **Uterine Blood Flow Issues**: Insufficient blood flow due to uterine artery abnormalities or systemic vascular issues. **Chronic Endometritis**: Chronic inflammation can prevent proper growth and development. **Structural Damage**: Surgeries, infections, or conditions like Asherman's syndrome can damage the endometrial lining. **Molecular Abnormalities**: Abnormal expression of growth factors and cytokines necessary for proliferation and differentiation. **Lifestyle Factors**: Smoking, stress, poor nutrition, and environmental toxins can negatively impact growth.

3.3. Management Strategies for Inadequate Endometrial Growth

- **Hormonal Adjustments**: Increasing dose or changing the route of estrogen administration, ensuring adequate progesterone levels.
- **Improving Blood Flow**:

 doi:10.20944/preprints202408.0733.v1

  - **Aspirin or Low-Molecular-Weight Heparin (LMWH)**: Improve endometrial blood flow.
  - **Pentoxifylline and Vitamin E**: Enhance thickness by improving blood flow.
- **Addressing Chronic Endometritis**:
  - **Antibiotic Treatment: Treating infections to restore normal growth.**
- **Surgical Interventions**:
  - **Hysteroscopic Surgery: Remove adhesions or polyps interfering with development.**
- **Lifestyle Modifications**:
  - **Healthy Diet and Exercise: Improve overall health, though evidence for restorative functions is limited.**
  - **Stress Reduction: Techniques like relaxation, counseling, or yoga (Domar AD et al., 2000).**
  - **Smoking Cessation: Improve reproductive health and receptivity.**
- **Use of Growth Factors**:
  - **Granulocyte-Colony Stimulating Factor (G-CSF): Some studies suggest improvement in thickness, though debated for biases.**

3.4. Adjuvant Therapies

- **Low-Dose Aspirin**: May improve blood flow, enhancing thickness and receptivity (Rubinstein M et al., 1999).
- **Pentoxifylline and Vitamin E**: Believed to improve thickness by enhancing blood flow and reducing oxidative stress (Lédée-Bataille N et al., 2002).
- **Platelet-Rich Plasma (PRP) Therapy**: PRP enhances vascularization, increases VEGF expression, and stimulates proliferation, supporting thickness and receptivity (Huniadi A et al., 2023; Stewart J Russel et al., 2022; Shalma NM et al., 2023).
- **Granulocyte-Colony Stimulating Factor (G-CSF)**: Improves thickness and pregnancy outcomes when injected into the uterine cavity (Lebovitz O et al., 2014; Gleicher N et al., 2013; Tehraninejad E et al., 2015; Sarvi F et al., 2017; Kamath MS et al., 2020).
- **Sildenafil**: Enhances uterine blood flow by potentiating nitric oxide effects, leading to better endometrial proliferation and preparation (Li X et al., 2021).

  - **Dehghani-Firouzabadi et al. (2013)**: Increased thickness and improved implantation and pregnancy rates.
  - **Li et al. (2020)**: Meta-analysis showed increased thickness and improved pregnancy outcomes.
  - **El-Maghrabi et al. (2020)**: Improved thickness and pregnancy rates in frozen-thawed embryo transfer cycles.
  - **Firouzabadi et al. (2013)**: Enhanced endometrial preparation and improved implantation chances.
  - **Moini et al. (2020)**: Improved thickness and receptivity, contributing to higher success rates.

3.5. Endometrial Scratching

- **Procedure**: Causes minor injury to endometrium before transfer, inducing an inflammatory response that promotes tissue repair and growth (Lensen SF et al., 2021).
- **Pros**: Increased implantation rates in some studies (Barash et al., 2003; Aflatoonian et al., 2016; Iakovidou et al., 2023).

 doi:10.20944/preprints202408.0733.v1

- **Cons**: No significant difference in large-scale RCTs and reviews (Lansen et al., 2019; Cochrane Database of Systematic Reviews, 2021).

3.6. Uterine Factors

- **Myomas**: Negative impact when distorting the lumen cavity.
- **Salpinges**: Infections, occlusions, or stenoses impacting implantation, with salpingectomy often considered.
- **Intrauterine Adhesions (IUA)**: Surgical treatment effective if endometrial functionalis is still working.
- **Uterine Abnormalities**: Some abnormalities allow for normal implantation, while others may require gestational carriers.

Endometrial preparation for embryo transfer involves optimizing thickness, hormonal environment, and overall receptivity. For low thickness, various strategies, including hormonal supplementation, adjuvant therapies, and innovative treatments like PRP and G-CSF, show promise. Continuous research and tailored approaches based on individual profiles are essential for enhancing implantation and pregnancy success in IVF cycles.

4. Vascularization and Blood Flow

Adequate blood flow to the endometrium is crucial for delivering nutrients and hormones necessary for implantation and early embryonic development, which can be assessed using Doppler ultrasound. Endometrial vascularization is partly regulated by nitric oxide (NO) produced by endothelial nitric oxide synthase (eNOS). NO helps maintain adequate blood flow and vascular tone (Roberto da Costa RP et al., 2006). Studies have shown that higher endometrial and subendometrial blood flow, indicated by increased blood flow, is positively correlated with successful embryo implantation and pregnancy outcomes (Raine-Fenning NJ, 2003; Kupesic S et al., 2001). VEGF plays a crucial role in angiogenesis in the endometrium. A study found that VEGF levels, regulated by nitric oxide production, are critical for enhancing endometrial vascularity, which supports implantation (Sher G et al., 2000). Another study highlighted that increased endometrial and subendometrial blood flow, measured by three-dimensional power Doppler ultrasound, was associated with higher clinical pregnancy rates (Ng E et al., 2006).Adequate blood flow to the endometrium, assessed by Doppler ultrasound, is crucial for successful embryo implantation. VEGF and nitric oxide are key regulators of endometrial vascularity, promoting angiogenesis and improving blood supply. Higher endometrial and subendometrial vascularity are associated with improved implantation and pregnancy rates in assisted reproductive technologies.

5. Hormonal Environment

Estrogen is essential during the proliferative phase of the menstrual cycle. It stimulates the proliferation and thickening of the endometrial lining, increasing the expression of estrogen receptors and preparing the endometrium for subsequent progesterone action. Adequate levels of estradiol are associated with increased endometrial thickness and improved implantation rates (Marquardt RM et al., 2019; Roberto da Costa RP et al., 2006).

Progesterone is critical during the secretory phase, transforming the proliferative endometrium into a secretory state. This includes glandular development, stromal edema, and the expression of secretory proteins essential for embryo implantation. Progesterone support during the luteal phase enhances the chances of successful implantation and pregnancy. It also modulates the immune environment of the endometrium, facilitating tolerance to the embryo (Marquardt RM et al., 2019; Roberto da Costa RP et al., 2006; Bulletti C et al., 2022).

Estrogen and Progesterone Balance: The balance of estrogen and progesterone regulates uterine contractions, influencing implantation success (Bulletti C et al., 2002). The first uterine pass effect, where hormones delivered directly to the uterus have a significant impact on endometrial preparation, improves implantation outcomes (Bulletti C et al., 1998).

 doi:10.20944/preprints202408.0733.v1

Challenges in Estrogen and Progesterone Response: Variability in response to hormones due to genetic and physiological differences, hormonal imbalances, and external factors like lifestyle can impact endometrial preparation and implantation success.

6. Cellular Markers of Adequate Endometrial Differentiation for Embryo Nidation

Successful embryo nidation requires a well-differentiated endometrium exhibiting specific cellular and molecular markers indicative of receptivity. These markers ensure the endometrial environment is conducive to embryo implantation and early pregnancy.

- **Pinopodes**: Small, finger-like projections on the surface of the endometrial epithelium appear during the implantation window and are believed to facilitate embryo adhesion (Quinn KE et al., 2019; Zhang Y et al., 2021; Marquardt RM et al., 2019).
- **Stromal Decidualization**: Transformation of endometrial stromal cells into decidual cells is crucial for maintaining pregnancy and preventing early pregnancy loss (Zhang Y et al., 2021; Marquardt RM et al., 2019; Bulletti C et al., 2022).
- **Molecular Markers**: The expression of specific genes and proteins, such as integrins, leukemia inhibitory factor (LIF) (Stewart CL et al., 1992; Borini A et al., 1997), and homeobox genes (e.g., HOXA10) (Bi Y et al., 2022), is crucial for endometrial receptivity. These markers play roles in cell adhesion, immune modulation, and tissue remodeling (Roberto da Costa RP et al., 2006; Marquardt RM et al., 2019; Zhang Y et al., 2021).

Growth Factors

- **VEGF, TGF-β, IGF, HGF, EGF, PDGF**: These factors work synergistically through autocrine and paracrine signaling to create a receptive endometrial environment, enhancing the chances of successful implantation and pregnancy (Al-Jefout M et al., 2009; Salamonsen LA et al., 2009; Giudice LC, 2006; Lessey BA, 2002; Dimitriadis E et al., 2005; Zhu LJ et al., 2000).
- **Homeobox A10 (HOXA10)**: Regulates gene expression during endometrial differentiation, with impaired expression linked to lower implantation rates (Bagot CN et al., 2001; Roberto da Costa RP et al., 2006; Marquardt RM et al., 2019; Zhang Y et al., 2021).
- **Prostaglandins**: Regulate inflammation, vascular permeability, and uterine contractions, critical for implantation (Roberto da Costa RP et al., 2006; Marquardt RM et al., 2019; Zhang Y et al., 2021).

Successful embryo nidation requires a well-differentiated endometrium with specific cellular and molecular markers indicative of receptivity. Growth factors and prostaglandins play crucial roles in endometrial preparation, ensuring a conducive environment for embryo implantation and early pregnancy.

7. Endometrial Preparation for Embryo Transfer

The best routes of administration for achieving adequate endometrial thickness during hormone replacement therapy (HRT) for embryo transfer vary based on patient needs, preferences, and clinical protocols. Commonly used routes include:

Estrogens)Zhang Y et al., 2023).**:**

- **Oral Administration:** Convenient and easy to adjust dosage but subject to first-pass metabolism, leading to variable serum levels and potential side effects like nausea or liver enzyme alterations.
- **Transdermal Administration:** Provides steady hormone levels and bypasses first-pass metabolism, generally with fewer side effects, though it may cause skin irritation and requires frequent patch changes.
- **Estradiol Gels:** Similar benefits to patches but can be messy and risk transferring the gel to others via skin contact.
- **Vaginal Administration:** Delivers high local concentrations with reduced systemic side effects but may be uncomfortable for some patients.
- **Intramuscular (IM) or Subcutaneous (SC) Injections:** Provide consistent hormone levels with less frequent dosing but can be painful with potential injection site reactions.

 doi:10.20944/preprints202408.0733.v1

Progesterone (Zhang Y et al., 2023).**:**

- **Vaginal Administration:** Provides high local concentrations with effective endometrial transformation and lower systemic side effects but may be messy or uncomfortable.
- **Intramuscular Injections:** Ensure high serum levels and reliable endometrial transformation but can be painful with injection site reactions.
- **Oral Administration:** Convenient but has lower bioavailability and potential systemic side effects like drowsiness.

Combination Approaches: Examples include oral estradiol with vaginal progesterone or oral estradiol with IM progesterone.

Monitoring and Individualization: Regular monitoring of endometrial thickness via ultrasound and hormone levels in the blood is crucial to adjust dosages and routes of administration effectively. Patient response, tolerance, and preference play significant roles in determining the best regimen.

7.1. Alternative Methods for Needle Phobia or Oral Tablet Aversion

- **Estradiol:**
  - **Transdermal Patches:** Steady hormone release (e.g., Vivelle-Dot, Climara).
  - **Vaginal Gels:** Steady release of estradiol (e.g., Divigel, Estrogel).
  - **Vaginal Tablets or Rings:** Localized hormone delivery with systemic absorption (e.g., Vagifem, Estring).
- **Progesterone:**
  - **Intramuscular or Subcutaneous Administration:** Mimics endogenous production.
  - **Vaginal Suppositories or Capsules:** Direct delivery with minimal systemic side effects (e.g., Endometrin, Prometrium).
  - **Vaginal Gels:** Consistent levels with vaginal application (e.g., Crinone).
  - **Transdermal Creams:** Variable absorption and efficacy.

Combined Methods: Combining patches and vaginal applications or using both estradiol and progesterone in vaginal forms can be effective for specific administration challenges.

Example Protocol:

- **Estradiol Patches:** Apply one patch (0.1 mg/day), replace every 3-4 days.
- **Progesterone Vaginal Gel:** Administer 90 mg daily.

Monitoring and Adjustments:

- **Monitoring:** Regular checks of hormone levels and endometrial thickness.
- **Adjustments:** Based on individual response and side effects.

7.2. Schematic Schedule for HRT in Embryo Nidation Preparation:

Estradiol Administration:

- **Days 1-14:** Start low, increase gradually.
  - **Day 1-4:** 2 mg daily (oral or patch).
  - **Day 5-8:** 4 mg daily.
  - **Day 9-12:** 6 mg daily.
  - **Day 13-14:** 8 mg daily.

Progesterone Administration:

- **Start on Day 15:**
  - **Days 15-28:** 200 mg twice daily (vaginal or oral).
  - **Day 15-28:** Continue estradiol 8 mg daily.

Embryo Transfer: Typically around Day 19-21, depending on the protocol. **Post-Embryo Transfer:** Continue hormones until the pregnancy test (Day 28):

 doi:10.20944/preprints202408.0733.v1

- **Estradiol:** 8 mg daily.
- **Progesterone:** 200 mg twice daily.
    - **If pregnant:** Continue as per physician's advice.
    - **If not pregnant:** Stop hormone therapy.

7.3. Strategies for Inadequate Endometrial Thickness

Hormonal Approaches:

- **Estradiol:** Administered orally, transdermally, or subcutaneously.
- **Progesterone:** Multiple routes including IM, vaginal, and subcutaneous.
- **Dydrogesterone:** Oral progesterone analogue combined with vaginal progesterone.

Innovative Approaches:

- **Platelet-Rich Plasma (PRP):** Intrauterine administration to improve thickness and receptivity(Tang Y et al., 2023).
- **Stem Cell Therapy:** Using stem cell-derived exosomes to regenerate endometrial tissue.

RCT Evidence:

- **Endometrial Thickness:** Critical for embryo nidation (LU J et al., 2024).
- **ERA Test:** Does not significantly improve ongoing pregnancy rates compared to standard protocols (Doyle JO et al., 2022).

8. The Possible Role of Endometritis

Diagnosing Endometritis involves a combination of clinical assessment, laboratory tests, and sometimes imaging studies:

Clinical Presentation: Patients may present with pelvic pain, abnormal vaginal bleeding or discharge, fever, and tenderness in the lower abdomen. A pelvic exam can reveal tenderness, especially in the uterus, and sometimes discharge from the cervical os.

Histological Examination: A small sample of the endometrial tissue is taken and examined histologically for signs of inflammation, such as the presence of plasma cells.

Microbial Cultures: Culturing endometrial samples or cervical swabs can identify infectious agents like bacteria, mycoplasmas, or sexually transmitted infections. PCR tests can detect specific bacterial DNA, useful for identifying chronic infections that may not show up in cultures.

Imaging Studies: Ultrasound can help detect abnormalities in the uterine lining, though it is more often used to rule out other conditions.

Hysteroscopy: A more direct method where a small camera is inserted into the uterus to visualize the endometrial lining and possibly take targeted biopsies.

Blood Tests: Complete blood count (CBC) may show elevated white blood cells, indicating infection. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can indicate inflammation.

Laparoscopy: In some cases, particularly when the diagnosis is unclear, laparoscopy may be performed to directly visualize the pelvic organs and obtain samples.

Several studies have shown the detrimental impact of endometritis on embryo implantation (Vitagliano A et al., 2018; Kitaya K et al., 2017; Pantos K et al., 2021; Sfakianoudis K et al., 2018) and reported the efficacy of antibiotic treatment in reversing chronic endometritis and improving reproductive outcomes in women with recurrent implantation failure (Sfakianoudis K et al., 2018; Song D et al., 2021; Pantos K et al., 2021; Vitagliano A et al., 2018; Kitaya K et al., 2017; Zhang Y et al., 2019).

9. Initial Assessment and Preparation

Clinical History and Examination: Detailed reproductive history, including previous IVF attempts and any history of endometritis or other uterine abnormalities.

 doi:10.20944/preprints202408.0733.v1

Ultrasound Examination: Baseline transvaginal ultrasound to assess endometrial thickness and morphology.

Hysteroscopy: Consider diagnostic hysteroscopy to evaluate the uterine cavity for polyps, fibroids, or adhesions.

Endometrial Dating: Hormone Replacement Therapy (HRT) and Endometrial Preparation.

Embryo Transfer: Transfer the euploid embryo on the optimal day based on the endometrial receptivity and the type of cycle (fresh or frozen). For most, this is around 5 days after progesterone administration begins (P+5).

In Case of Inadequate Endometrial Thickness:

Extended Estrogen Therapy: Increase the dose or duration of estradiol to achieve the desired endometrial thickness.

Adjunct Therapies: Consider the use of adjunctive treatments like low-dose aspirin, sildenafil (Viagra), or pentoxifylline to improve endometrial blood flow and growth.

Natural Cycle Transfer: If HRT fails to achieve adequate thickness, a natural cycle with close monitoring of natural endometrial development and ovulation may be considered.

Gonadotropin Stimulation: Mild ovarian stimulation can sometimes improve endometrial thickness and quality.

10. Addressing Chronic Endometritis

Diagnosis: Perform an endometrial biopsy and microbial cultures to diagnose chronic endometritis. Histopathological examination for plasma cells confirms the diagnosis.

Antibiotic Therapy: Administer antibiotics based on culture results, such as oral doxycycline or intrauterine antibiotic infusions.These treatments can resolve chronic endometritis and improve IVF outcomes (Eftekhar M et al., 2014.).

Re-Evaluation: Re-evaluate the endometrium post-antibiotic treatment to confirm the resolution of endometritis. Ensure adequate endometrial preparation before proceeding with embryo transfer.

Timing and Protocol: Conduct embryo transfer in the subsequent cycle after confirming an optimal endometrial environment.

Post-Transfer Care: Continue progesterone support and monitor serum hCG levels to confirm pregnancy.Follow up with ultrasounds to monitor implantation and early pregnancy development.

By following these steps, healthcare providers can maximize the chances of successful embryo implantation and pregnancy in women undergoing IVF with euploid embryos, regardless of initial endometrial thickness.

11. Metabolism of Estradiol and Progesterone in the Endometrium

Estradiol (E2) Metabolism (Roberto da Costa RP et al., 2006) **and Action:** Estradiol binds to estrogen receptors (ERα and ERβ) in endometrial cell nuclei, triggering gene transcription for cell proliferation and vascularization. Estradiol induces endometrial lining proliferation during the first half of the menstrual cycle, increasing thickness. Estradiol upregulates nitric oxide synthases (NOS), particularly endothelial NOS (eNOS), increasing nitric oxide (NO) production. NO is crucial for maintaining endometrial vascular tone and facilitating increased blood flow during the proliferative phase.

The Coordinated Metabolism of Estradiol and Progesterone: Estradiol promotes initial proliferation and vascularization, while progesterone facilitates the transition to a secretory phenotype necessary for implantation. Understanding these processes can aid in managing conditions like endometriosis and improving fertility treatments.

Molecular Sizes: **Free Steroid Hormones** have molecular sizes in the range of a few angstroms (e.g., estradiol ~8 Å, testosterone ~7 Å). Complexes of steroid hormones and their carrier proteins (e.g., albumin, SHBG) are significantly larger, usually above 50,000 Å.

Basement Membrane Pore Size: A pore size of 70,000 Å (7,000 nm) is large on a molecular scale, but the effective pore size in a physiological context acts as a selective barrier due to various factors like charge and matrix structure.

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Selective Permeability Mechanism: Despite the large nominal pore size, the effective pore size is smaller due to the complex structure of the basement membrane, including collagen, laminins, and proteoglycans. Protein-bound hormones have a lower diffusion rate across membranes compared to free hormones due to size and binding constraints.

Charge and Chemical Environment: Basement membranes are typically negatively charged. Free steroid hormones are neutral and can pass through more readily than the larger, often negatively charged hormone-protein complexes.

Hydrophilicity vs. Hydrophobicity: The hydrophobic nature of free steroid hormones allows them to diffuse through the lipid-rich environment of cell membranes more efficiently than hydrophilic protein-bound complexes.

Physiological Factors:

Enzymatic Action: Enzymes present in the endometrial environment might free hormones from their binding proteins, enhancing their local availability.

Local Concentration Gradients: Higher local concentrations of free hormones due to selective binding and release mechanisms at the target site.

12. Schematic Design of Steroid Hormone Action (Bulletti C et al 1988a,b)

Endometrial Gland and Vessel Structure: **Basement Membrane** are composed of a dense matrix of proteins and glycoproteins with effective pore sizes influenced by physiological conditions. Lining the blood vessels, allowing selective passage of molecules.

Free Hormone Diffusion: Small, lipophilic molecules (e.g., estradiol, progesterone) diffuse through the endothelial cell membranes and basement membranes into the target tissues. Larger complexes remain in the bloodstream due to size exclusion and lower diffusion rates.

Illustration: **Bloodstream** c ontains both free and protein-bound hormones. **Capillary Endothelium and Basement Membrane** acts as a selective barrier. Free hormones diffuse with intercellular fluid and bind to intracellular receptors.

By following these protocols and understanding the molecular mechanisms involved, healthcare providers can optimize the chances of successful embryo implantation and pregnancy in women undergoing IVF treatments. This comprehensive approach ensures that all potential factors affecting endometrial receptivity and embryo implantation are addressed, improving overall reproductive outcomes.

13. Detailed Pathway of Steroid Hormone Action in Endometrial Tissue

Steroid hormones are synthesized and secreted by endocrine glands such as the ovaries (e.g., estradiol, progesterone) and adrenal cortex (e.g., cortisol, aldosterone). In the bloodstream, steroid hormones often bind to specific carrier proteins (e.g., sex hormone-binding globulin, corticosteroid-binding globulin) to increase their solubility and stability. A small fraction of steroid hormones remain unbound and free, which are biologically active and able to diffuse across cell membranes.

Crossing the Vascular Wall:

Diffusion Through the Endothelial Cells: Steroid hormones can diffuse through the endothelial cells lining the blood vessels due to their lipophilic nature. This process can occur through transcellular (through the cells) or paracellular (between the cells) pathways.

Interstitial Fluid: After crossing the vascular wall, the hormones diffuse through the interstitial fluid surrounding tissue cells.

Target Cell Interaction: Steroid hormones diffuse across the plasma membrane of target cells due to their lipophilic properties. Inside the target cells, steroid hormones bind to specific intracellular receptors located in the cytoplasm or nucleus.

Intracellular Receptors and Gene Regulation: The receptor-hormone complex translocates to the nucleus if it initially binds in the cytoplasm. The receptor-hormone complex binds to specific DNA regulatory sequences, modulating gene transcription. This process results in the synthesis of new proteins, which bring about the physiological effects associated with the hormone.

 doi:10.20944/preprints202408.0733.v1

Physiological Effects: Estradiol promotes cell proliferation and vascularization in the endometrium. Progesterone facilitates the transition to a secretory phenotype in the endometrial glands, essential for embryo implantation. Progesterone modulates the immune environment and promotes the secretion of nutrients and growth factors necessary for embryo support.

14. Detailed Molecular Mechanisms of Hormonal Actions

Estradiol binds to estrogen receptors (ERα and ERβ) in endometrial cells, which then dimerize and translocate to the nucleus. The estradiol-receptor complex binds to estrogen response elements (EREs) on DNA, initiating the transcription of genes involved in cell proliferation, such as cyclins and growth factors. Estradiol induces the expression of vascular endothelial growth factor (VEGF), enhancing blood flow to the endometrium. It also increases nitric oxide (NO) production through upregulation of endothelial nitric oxide synthase (eNOS).

Progesterone binds to progesterone receptors (PRs) in stromal and epithelial cells, leading to receptor dimerization and nuclear translocation. The progesterone-receptor complex binds to progesterone response elements (PREs) on DNA, promoting the transcription of genes involved in secretory transformation, such as glycodelins and integrins. Progesterone drives the decidualization of stromal cells, which involves morphological changes and the production of cytokines and growth factors necessary for embryo support. Progesterone modulates the immune environment by promoting anti-inflammatory cytokines and reducing the activity of natural killer (NK) cells Bulletti C et al 2022).

Combined Estradiol and Progesterone Actions:

The combined actions of estradiol and progesterone ensure the endometrium is both proliferative and receptive, creating an optimal environment for embryo implantation. Progesterone reduces myometrial contractions (Bulletti C et al 2002, 1997) , stabilizing the endometrium and facilitating embryo attachment.

15. Advanced Diagnostic and Therapeutic Approaches

Genetic testing attempting to determine the best timing for embryo transfer based on endometrial gene expression profiles. Unfortunately not usefull for the clinical beneficial use (Doyle et al, 2022) High-resolution ultrasound and MRI to assess endometrial structure and vascularization in detail.

Therapeutic Innovations:

Platelet-Rich Plasma (PRP) Therapy: Intrauterine administration of PRP to enhance endometrial thickness and receptivity, particularly in cases of thin endometrium.

Stem Cell Therapy: Use of stem cell-derived exosomes and bioengineering techniques to regenerate endometrial tissue and improve functionality.

Personalized Medicine: Tailoring hormone therapy protocols based on individual genetic, biochemical, and clinical profiles to optimize endometrial preparation.

16. Conclusions

The comprehensive understanding of endometrial preparation for embryo transfer highlights the intricate balance of hormonal, cellular, and molecular interactions required for successful implantation. The coordinated metabolism and action of estradiol and progesterone are fundamental to creating a receptive endometrium, while advanced diagnostic tools and therapeutic innovations offer promising avenues for improving IVF outcomes. By leveraging these insights, healthcare providers can enhance reproductive success and support patients in their journey toward parenthood.

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Table 1. Key Features for Embryo Nidation.

Features	Facts
Endometrial Thickness:	**Optimal Thickness:** The endometrial lining should ideally be between 7-14 mm for optimal implantation rates. Thickness below 7 mm is often associated with lower implantation rates and higher chances of miscarriage . **Triple-Line Pattern:** A trilaminar or "triple-line" pattern observed on ultrasound around the time of embryo transfer is often indicative of a receptive endometrium .
Hormonal Environment:	**Estrogen and Progesterone:** Adequate levels of estrogen are necessary to stimulate endometrial growth, while progesterone transforms the proliferative endometrium into a secretory lining, preparing it for embryo implantation through the cascade of biochemical and physical modifications called pre-decidualization.Water inclusion in decidualized stromal cells contribute to enlarge the endometrial thickness produced from epithelial cells proliferation induced from estrogens **Synchronization:** Proper synchronization between the endometrial development and the embryo stage is critical for successful implantation. This is often achieved by mimicking the natural menstrual cycle through hormonal supplementation . The Era test or similar conceptual tests were not effective in the embryo synchronization transfer.
Endometrial Receptivity	**Receptive Window:** The period during which the endometrium is most receptive to embryo implantation is known as the "window of implantation," typically occurring 6-10 days after ovulation . Window of implantation is what we have when the implantation occur. It is not possible to call that when does not occur **Molecular Markers:** Several molecular markers such as integrins, leukemia inhibitory factor (LIF), and homeobox (HOX) genes are involved in creating a receptive endometrial environment .
Methods	**Interventions**
Abnormal Transport of Steroid Hormones to Endometrial Cells ion	**Hormone Transport Proteins:** Steroid hormones in the blood are largely bound (98%) to transport proteins such as sex hormone-binding globulin (SHBG) and albumin. Only the free, unbound fraction is biologically active and capable of entering cells. An abnormal balance between protein-bound and free hormones can affect the availability of hormones to the endometrial cells. High levels of SHBG can reduce the free hormone fraction, limiting the amount available for endometrial stimulation . **Receptor Functionality:** The effectiveness of hormone therapy also depends on the functionality and density of hormone receptors in the endometrium. Variations in the expression of estrogen and progesterone receptors can influence the response to HRT . Genetic mutations or polymorphisms in hormone receptors may alter their binding affinity and response to hormone therapy .

 doi:10.20944/preprints202408.0733.v1

	Blood Flow and Vascularization: Adequate blood flow to the endometrium is crucial for delivering hormones. Conditions that impair uterine blood flow, such as uterine fibroids, adenomyosis, or previous surgeries, can hinder hormone delivery and endometrial growth .
Variations in Endometrial Extraction of Steroids from Circulation. The extraction of steroid hormones from the bloodstream by endometrial cells can vary due to several reasons	**Metabolic Clearance Rate (MCR):**The MCR of circulating hormones refers to the rate at which hormones are removed from the bloodstream. A high MCR can reduce the overall availability of hormones for endometrial uptake . Factors influencing MCR include liver function, enzymatic activity, and overall metabolic health as well as body temperature and exercise. **Local Metabolism:**Endometrial cells can locally metabolize steroid hormones. Enzymes such as aromatase, 17β-hydroxysteroid dehydrogenase, and sulfatase play roles in converting hormones to their active or inactive forms within the endometrium . Dysregulation of these enzymes can affect the local concentration of active hormones, influencing endometrial response. The metabolism of steroids to the gluco-conjugates ans sulfo-conjugates are the depending from the source . If exogenous also from the route of administration being the fisrt liver pass promoting high sulfo-conjugation. **Hormone Resistance:** Some women may exhibit endometrial resistance to estrogen or progesterone, where despite adequate levels of circulating hormones, the endometrial response is suboptimal. This can be due to receptor desensitization or post-receptor signaling defects
Factors Contributing to Inadequate Endometrial Response	**Age and Ovarian Reserve:** Advanced age and diminished ovarian reserve are associated with poorer endometrial responses to hormone therapy. This is often due to reduced receptor sensitivity and altered endometrial receptivity . **Body Mass Index (BMI):** Both low and high BMI can negatively impact endometrial thickness. Obesity can alter hormone metabolism and increase the levels of SHBG, reducing free hormone availability. Underweight individuals may have insufficient hormone production and transport . **Chronic Inflammation:** Conditions like endometriosis, pelvic inflammatory disease (PID), or chronic endometritis can cause a pro-inflammatory environment that negatively impacts endometrial growth and receptivity . **Previous Uterine Surgery:** Surgeries such as curettage or myomectomy can cause scarring (Asherman's syndrome) and impair endometrial regeneration and response to hormonal stimulation .

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Table 2. Intervention strategies to recover a low to normal thickness endometrium.

Methods	Interventions
Hormonal Supplementation	**Estradiol:** Oral, transdermal, or injectable estradiol can be used to increase endometrial thickness. Higher doses or extended duration of administration may be required for patients with thin linings **Progesterone:** Vaginal, Intramuscolar, Subcutaneous with oral as second line. Higher doses with moderate extended duration may be required **Human Chorionic Gonadotropin (hCG):** Low-dose hCG administration can also stimulate endometrial growth and improve thickness .
Adjuvant Therapies	**Low-Dose Aspirin:** May improve endometrial blood flow, enhancing thickness and receptivity . **Pentoxifylline and Vitamin E:** These agents are believed to improve endometrial thickness by enhancing blood flow and reducing oxidative stress .
Platelet-Rich Plasma (PRP) Therapy	**Intrauterine Infusion:** PRP therapy involves the infusion of autologous platelet-rich plasma into the uterine cavity to stimulate endometrial growth and improve implantation rates in patients with refractory thin endometrium
Granulocyte-Colony Stimulating Factor (G-CSF)	**Uterine Injection:** G-CSF has been shown to improve endometrial thickness and pregnancy outcomes when injected directly into the uterine cavity in patients with thin endometrium
Endometrial Scratching	**Procedure:** This involves causing a minor injury to the endometrium prior to the embryo transfer cycle, which is believed to enhance endometrial receptivity by inducing an inflammatory response that promotes tissue repair and growth . This issue is still debated
Lifestyle and Dietary Changes	**Healthy Diet and Exercise:** Ensuring adequate nutrition and maintaining a healthy weight can positively impact endometrial health **Stress Reduction** Managing stress through relaxation techniques, counseling, or yoga can also improve overall reproductive health .

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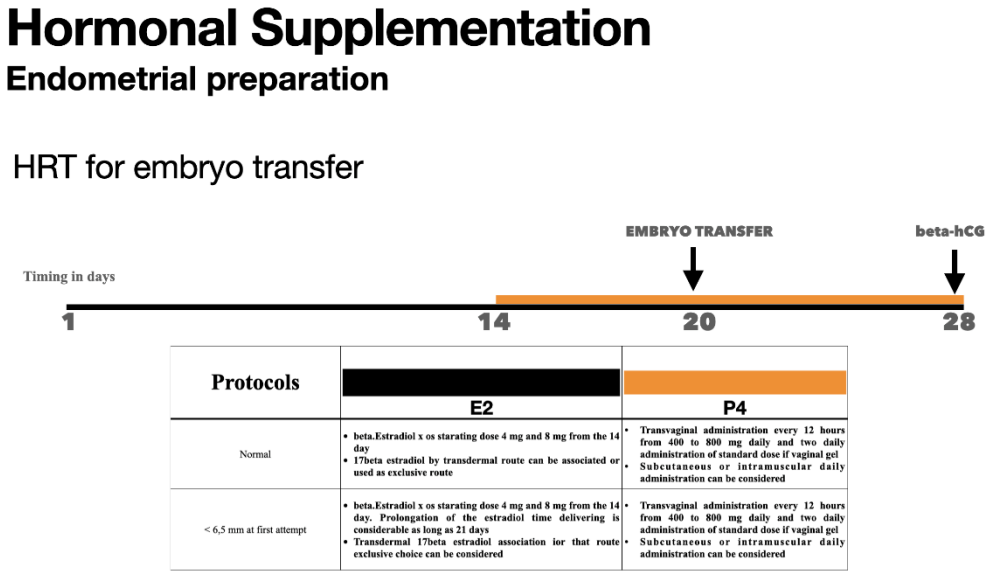

Figure 1. Shematic view of endometrial preparation for embryo transfer by HRT.

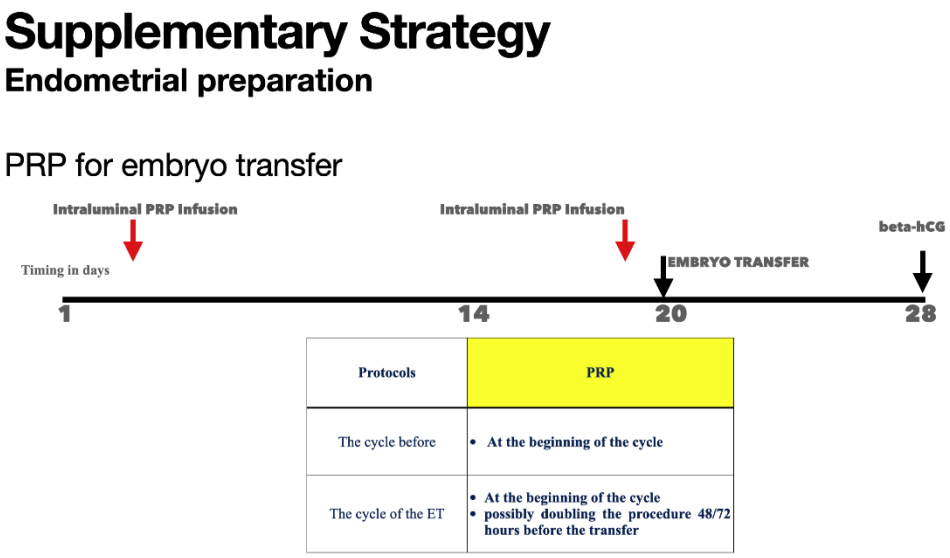

Figure 2. Schematic view of second line endometrial preparation strategy after failure od endometrial growth and receptivity after several euploid embryo transfer.

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Ethical Considerations are not applicable.

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