Improving Fertility Outcomes in Women with Thin Endometrium: A Comprehensive Clinical and Molecular Approach

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Abstract:

Thin endometrium remains a critical barrier to successful embryo implantation and pregnancy in assisted reproductive technologies (ART). This study aims to investigate and propose an evidence-based, integrative protocol to enhance endometrial receptivity in women diagnosed with a thin endometrium (≤7 mm) [1]. Through a combination of clinical interventions, regenerative medicine, and molecular profiling, we present a novel framework for optimizing uterine receptivity and increasing pregnancy rates in this challenging cohort [2].

Keywords: Thin endometrium, fertility, embryo implantation, endometrial receptivity, platelet-rich plasma, reproductive endocrinology, assisted reproductive technology (ART)

1. Introduction

Endometrial thickness is widely recognized as a pivotal determinant of implantation success during ART. While optimal implantation typically requires an endometrial thickness ≥8 mm, a subset of patients presents with persistently thin endometrium, often refractory to conventional hormonal therapies [3]. Thin endometrium is associated with decreased vascularity, impaired stromal decidualization, and diminished expression of implantation markers, thereby lowering the probability of achieving a viable pregnancy[4]. This article provides a translational and multidisciplinary overview of strategies aimed at enhancing the endometrial environment in such patients[5].

2. Pathophysiology of Thin Endometrium

The etiopathogenesis of thin endometrium is multifactorial, encompassing iatrogenic causes (e.g., intrauterine adhesions, overcurettage), chronic endometritis, hypoestrogenism, and idiopathic endometrial insufficiency. At the molecular level, decreased expression of vascular endothelial growth factor (VEGF), integrins, and leukemia inhibitory factor (LIF) impairs angiogenesis and endometrial receptivity[6].

3. Current and Emerging Treatment Modalities

3.1 Estrogen Therapy and Adjuvants

High-dose estradiol valerate and extended estrogen priming remain first-line pharmacological interventions. Adjuvants such as sildenafil citrate and pentoxifylline are used to improve uterine perfusion, though their efficacy remains inconsistent in meta-analyses.

3.2 Platelet-Rich Plasma (PRP) Infusion

Intrauterine infusion of autologous PRP, rich in growth factors including PDGF, TGF-β, and VEGF, has shown promising results in endometrial regeneration. Multiple randomized controlled trials (RCTs) have demonstrated statistically significant increases in endometrial thickness and pregnancy rates post-PRP administration.

3.3 Granulocyte Colony-Stimulating Factor (G-CSF)

G-CSF, delivered via intrauterine or subcutaneous route, appears to promote endometrial proliferation and enhance local immune modulation. Further mechanistic studies are warranted to validate its molecular pathways.

3.4 Stem Cell Therapy

Emerging evidence supports the therapeutic potential of bone marrow-derived stem cells and menstrual blood-derived stromal cells (MenSCs) in endometrial rejuvenation. These cells secrete paracrine factors that stimulate angiogenesis, epithelial regeneration, and immunomodulation.

3.5 Hysteroscopic Evaluation and Treatment

Diagnostic and therapeutic hysteroscopy is crucial for excluding intrauterine pathologies such as adhesions or fibrosis that contribute to endometrial thinning. Adhesiolysis combined with barrier methods and estrogen therapy can significantly improve endometrial recovery

4. Integrative Protocol Proposal

We propose a stepwise, individualized treatment algorithm:

1. Baseline assessment: Transvaginal ultrasonography, Doppler flow studies, and hysteroscopy

2. Phase 1: Estrogen priming + vasodila

3. Phase 2: PRP or G-CSF infusion if nonresponsive

4. Phase 3: Stem cell-based therapy for refractory case

5. Phase 4: Personalized embryo transfer timing based on molecular markers (e.g., ERA test)

5. Discussion

Although thin endometrium remains a formidable challenge in reproductive medicine, combining advances in molecular biology with clinical innovation offers new hope. The integration of regenerative therapies into routine ART protocols may revolutionize treatment paradigms, especially in patients previously deemed poor responders.

6. Conclusion

An interdisciplinary and evidence-based approach is essential to overcoming the limitations posed by thin endometrium. Future multicentric trials and genomic studies will be pivotal in refining these strategies and expanding their accessibility across global reproductive centers

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