doi: 10.30934/kusbed.1836274 **e-ISSN:** 2149-8571

Journal of Health Sciences of Kocaeli University

Review Article

http://dergipark.org.tr/kusbed

ENDOMETRIAL RECEPTIVITY: MOLECULAR MECHANISMS, THIN ENDOMETRIUM SUBTYPES, AND MECHANISM-BASED THERAPEUTIC APPROACHES

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Received: 05.12.2025 **Accepted:** 26.02.2026 **Published:** 31.05.2026

Abstract

Endometrial receptivity is a transient and highly coordinated biological state regulated by hormonal, molecular, vascular, metabolic, and immune pathways that collectively enable embryo implantation. This narrative review aims to synthesize contemporary evidence on the mechanisms governing endometrial receptivity and the heterogeneous etiologies of thin endometrium. A comprehensive literature search of PubMed, Scopus, and Web of Science published between 1998 and 2025 identified studies addressing morphological, molecular, metabolic, immunological, and microbiota-related determinants of receptivity. Current evidence demonstrates that receptivity is orchestrated through the interplay of the HOXA10–LIF–αvβ3 integrin axis, angiogenic signaling, extracellular matrix dynamics, mitochondrial bioenergetics, and AMPK–mTOR–mediated cellular energy regulation. Thin endometrium represents not a simple proliferative deficiency but a multifactorial phenotype shaped by vascular insufficiency, downregulation of key receptivity markers, metabolic stress, oxidative imbalance, fibrosis, immune disruption, and alterations in the uterine microbiota.
Mechanism–directed therapeutic strategies including sildenafil, granulocyte colony-stimulating factor, platelet-rich plasma, mesenchymal stem cell–based regeneration, antioxidants, folate supplementation, and ERA-guided personalized embryo transfer target these underlying biological phenotypes rather than endometrial thickness alone. Shifting from thickness–based evaluation to a phenotype- and mechanism-oriented clinical framework is essential for improving implantation and pregnancy outcomes in assisted reproductive technologies.

Keywords: *Endometrial receptivity, Thin endometrium, AMPK, mTOR, ERA, Implantation.*

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Introduction

Endometrial receptivity is a brief and tightly regulated biological phase during which the endometrium acquires the structural, biochemical, immunological, and molecular characteristics required for embryo attachment and early implantation.[1] Historically, receptivity was assessed through histological staging and macroscopic parameters such as endometrial thickness, glandular morphology, and circulating hormone levels.[2] However, extensive molecular evidence now demonstrates that implantation competence emerges from the coordinated activity of steroid hormone signaling, transcriptional regulators, adhesion molecules, angiogenic mediators, immune tolerance pathways, mitochondrial function, and cellular energy–sensing networks.[3]

A central regulatory pathway in this process is the HOXA10–LIF–αvβ3 integrin axis, which governs epithelial–embryo communication, stromal differentiation, and pinopode development.[4] Disruption of this axis is consistently associated with recurrent implantation failure (RIF) and impaired decidualization.[5] Transcriptomic advances have further revealed that the window of implantation (WOI) is not a fixed chronological interval but a dynamic, patient–specific molecular phase characterized by coordinated expression of receptivity–related genes across epithelial and stromal compartments.[6]

Thin endometrium, frequently characterized by an endometrial thickness of <7 mm, has traditionally been regarded as a result of proliferative insufficiency.[7] Yet contemporary data demonstrate that its pathophysiology extends far beyond reduced thickness. Rather than a single entity, thin endometrium represents a heterogeneous phenotype shaped by diverse biological defects, including impaired angiogenesis, suppression of HOXA10/LIF/integrin signaling, metabolic stress driven by AMPK–mTOR imbalance, mitochondrial dysfunction, extracellular matrix fibrosis, chronic inflammation, immune dysregulation, and alterations in the uterine microbiota.[8]

These insights challenge the adequacy of thickness-based assessments and support a mechanism–oriented interpretation of endometrial receptivity.[9] In parallel with this evolving biological understanding, clinical practice has progressively shifted away from morphology–centered evaluation toward mechanism-driven assessment of uterine function. The emerging paradigm of precision reproductive medicine emphasizes the identification of dominant pathophysiological pathways underlying impaired receptivity and the alignment of therapeutic strategies with these mechanisms.[10]

Accordingly, mechanism-specific interventions such as platelet–rich plasma–based regeneration, mesenchymal stem cell therapy, vascular–targeted treatments, immune–modulating strategies, metabolic support therapies, and ERA–guided personalized embryo transfer are increasingly employed to correct specific biological deficiencies rather than aiming solely to increase endometrial thickness.[11] The purpose of this narrative review is to synthesize current evidence on the molecular, metabolic, immunological, and structural determinants of endometrial receptivity; clarify the mechanistic diversity underlying thin endometrium; and propose a phenotype–based framework for individualized therapeutic strategies in assisted reproductive technologies.[12]

Methods

This narrative review was conducted to synthesize contemporary evidence on endometrial receptivity and the mechanistic heterogeneity underlying thin endometrium. A comprehensive literature search was performed in PubMed, Scopus, and Web of Science to identify studies published between 1998 and 2025. The search strategy used combinations of terms including endometrial receptivity, thin endometrium, implantation failure, HOXA10, LIF, integrin alpha–v beta–3, angiogenesis, AMPK, and mTOR. Inclusion criteria prioritized original human research, clinical guidelines, and systematic reviews available in English that addressed morphological, molecular, metabolic, and immunological determinants of receptivity. Animal studies were selectively included only when providing essential mechanistic insights.

Ethics Statement

This narrative review is based exclusively on previously published data and did not require approval from an institutional ethics committee.

Concept and Historical Background of Endometrial Receptivity

The concept of endometrial receptivity has evolved substantially over recent decades.[13] Early descriptions were predominantly morphology–based, relying on histological assessment of cyclic glandular and stromal changes and assuming that accurate histological dating reflected functional readiness for implantation.[14] However, clinical observations soon demonstrated that histological appearance alone could not reliably predict reproductive outcomes, as implantation failure frequently occurred in morphologically normal endometrium, while conception was possible in atypical cases.[15,16]

This discrepancy prompted deeper investigation into the biological mechanisms governing uterine readiness, leading to recognition of the central roles of estrogen and progesterone in coordinating endometrial transformation.[17,18] Subsequent research expanded this framework by identifying a broad range of molecular mediators–including transcription factors, cytokines, adhesion molecules, angiogenic regulators, and metabolic sensors–that collectively determine implantation competence.[19] Advances in high–throughput technologies further revealed that receptivity is defined by dynamic gene-expression signatures rather than by a single morphological or hormonal parameter.[20]

A major conceptual shift occurred with the recognition of the window of implantation (WOI) as a distinct molecular phase.[15,21] Beyond its chronological timing, experimental models have demonstrated that the molecular orchestrators of this phase, such as HOXA10, are essential for the structural manifestations of receptivity, including the formation of pinopodes.[22] This molecular paradigm, which prioritizes functional readiness over mere histological dating, enabled the development of transcriptomic tools such as the Endometrial Receptivity Array (ERA) and reinforced the view that implantation competence is fundamentally molecular rather than structural.[23]

Overall, these developments transformed endometrial receptivity from a morphology–centered concept into a multidimensional biological paradigm integrating endocrine, molecular, metabolic, vascular, and immunological processes. This perspective underpins contemporary diagnostic approaches and provides the foundation for mechanism-based therapeutic strategies aimed at optimizing implantation outcomes.[24,25]

Morphological and Physiological Processes Determining Receptivity

Endometrial receptivity is established through tightly coordinated morphological and physiological transformations that prepare the uterine environment for embryo attachment and implantation.[26] These changes are primarily driven by cyclic ovarian hormone fluctuations and involve synchronized remodeling of the epithelial, stromal, vascular, and immune compartments.[27]

During the proliferative phase, estrogen promotes epithelial and stromal proliferation, increases endometrial thickness, and enhances progesterone receptor expression, thereby priming the tissue for secretory transformation.[28] Following ovulation, progesterone initiates decidualization, a stromal differentiation process characterized by cytoskeletal reorganization, glycogen accumulation, and the secretion of implantation–related molecules such as prolactin and IGFBP-1.[29] Concurrent epithelial remodeling–including changes in polarity, membrane composition, glycosylation patterns, and secretory activity–facilitates embryo apposition and adhesion at the luminal surface.[30]

A hallmark morphological feature of the receptive endometrium is the transient formation of pinopodes, apical epithelial protrusions that emerge during the window of implantation. Although their diagnostic value remains debated, pinopodes reflect cytoskeletal and membrane remodeling associated with epithelial readiness for embryo interaction.[31]

Vascular adaptation is another essential component of receptivity. Progesterone and locally produced angiogenic mediators, including vascular endothelial growth factor (VEGF), angiopoietins, and nitric oxide, regulate spiral artery remodeling and enhance subendometrial blood flow, ensuring adequate oxygen and nutrient delivery to the implantation site.[32] Impairment of these processes is particularly evident in thin endometrium and is associated with adverse implantation outcomes.[33]

Physiological receptivity also requires a finely balanced immune environment. Uterine natural killer (uNK) cells, macrophages, dendritic cells, and regulatory T (Treg) cells collaborate to promote maternal–fetal tolerance, support trophoblast invasion, and maintain antimicrobial defense within the endometrial microenvironment.[34] Dysregulated inflammatory signaling or inadequate immune tolerance can disrupt implantation even in morphologically normal endometrium, contributing to recurrent implantation failure and pregnancy loss.[35]

Collectively, epithelial remodeling, stromal decidualization, vascular adaptation, and immune modulation constitute the structural and physiological framework upon which molecular mechanisms orchestrate successful embryo implantation.[36] While pinopode formation has historically been used to delineate the window of implantation, contemporary evidence indicates that transcriptomic signatures, such as the Endometrial Receptivity Array (ERA), provide a more robust and patient–specific assessment of uterine readiness.[10,11]

Molecular Basis of Endometrial Receptivity

Endometrial receptivity is governed by an integrated network of molecular pathways that coordinate epithelial differentiation, stromal decidualization, immune tolerance, and vascular adaptation during the window of implantation, thereby determining the capacity of the endometrium to support embryo attachment and invasion.[37,38]

HOXA10–LIF–Integrin Axis

A central regulatory module in this process is the HOXA10–LIF–αvβ3 integrin axis, which mediates epithelial–embryo communication and stromal functional transformation.[4] Progesterone-induced HOXA10 upregulates leukemia inhibitory factor (LIF) and enhances αvβ3 integrin expression on the luminal epithelium, facilitating embryo adhesion and decidual responses.[4] Suppression of any component of this axis has been consistently associated with recurrent implantation failure (RIF) and thin endometrium, highlighting the link between molecular receptivity defects and adverse clinical outcomes.[35]

Steroid Hormone Signalingand Adhesion Molecules

Steroid hormone signaling further shapes receptivity through progesterone receptor–mediated transcriptional programs regulating decidualization, extracellular matrix (ECM) remodeling, angiogenesis, and immune modulation.[18] Disruption of progesterone receptor isoform balance or aberrant estrogen–progesterone interactions may impair receptivity even in the presence of normal endometrial thickness, contributing to progesterone resistance in conditions such as endometriosis and adenomyosis.[32]

Cell–cell adhesion molecules, including selectins, cadherins, and integrins, modulate epithelial polarity and ECM composition at the implantation interface, thereby facilitating embryo apposition and attachment.[26] Glycodelin, MUC1, osteopontin, and hyaluronan–binding complexes further contribute to a permissive epithelial surface conducive to controlled blastocyst interaction and invasion.[39]

Angiogenesis and Immune Modulation

Angiogenic and vasodilatory mediators, including vascular endothelial growth factor (VEGF), angiopoietins, nitric oxide, and prostaglandins, support vascular remodeling and subendometrial perfusion required for early implantation and placentation.[28] Their regulation integrates oxygen sensing, metabolic cues, and progesterone-dependent signaling pathways within the endometrial microenvironment.[40]

Immune–modulatory factors also play essential roles in receptivity. LIF, interleukin–10 (IL–10), and transforming growth factor–β (TGF–β) regulate the recruitment and differentiation of uterine natural killer (uNK) cells, macrophages, and regulatory T (Treg) cells, thereby promoting maternal–fetal tolerance.[41]

Transcriptomic Insights

High–throughput transcriptomic analyses have identified numerous differentially expressed genes defining the receptive endometrium.[42] These signatures involve pathways related to epithelial differentiation and cell-cycle regulation, extracellular matrix (ECM) dynamics and Wnt/Notch signaling, as well as mitochondrial metabolism and cytokine networks.[43,44] This complexity reinforces the concept that receptivity represents a systems-level phenomenon rather than the output of a single dominant pathway, and disruption of these networks may impair implantation even in morphologically normal endometrium.[35,42,44]

Taken together, steroid hormone signaling, adhesion molecules, angiogenic pathways, immune regulation, and metabolic control should be interpreted as interdependent components of a unified biological network, and disturbances in any of these interacting systems may shift the endometrium toward a non–receptive phenotype.

Energy Metabolism, Autophagy, and the AMPK/mTOR AXIS

Endometrial receptivity depends on tightly regulated cellular energy homeostasis, as implantation is a metabolically demanding process involving epithelial remodeling, stromal

decidualization, angiogenesis, and immune adaptation.[8,35,45] Two key metabolic regulators–AMPK and mTOR–form an antagonistic signaling network that integrates nutrient availability, oxidative stress, hormonal cues, and mitochondrial function to maintain endometrial competence.[8,45]

AMPK is activated under conditions of cellular energy deficit or oxidative stress, promoting catabolic pathways while inhibiting energy–intensive processes such as proliferation and protein synthesis.[8,45] Excessive or prolonged AMPK activation within the endometrium has been associated with impaired stromal differentiation, reduced epithelial receptivity, increased autophagic activity, and a shift toward a non–receptive phenotype, particularly under chronic metabolic stress or mitochondrial dysfunction.[8,35]

In contrast, mTOR drives anabolic processes essential for establishing receptivity, including protein synthesis, cell growth, angiogenesis, and progesterone–dependent decidualization.[24,27,45] Appropriate mTOR activation is required for the expression of key receptivity markers such as HOXA10, IGFBP-1, and LIF, whereas suppression of this pathway disrupts decidualization and compromises epithelial–embryo interaction even in the presence of normal endometrial thickness.[3,8,24,27]

The balance between AMPK and mTOR is therefore central to endometrial physiology.[8,45] Autophagy, a downstream process regulated by this axis, supports cellular renewal and stress adaptation; however, excessive autophagic activity may impair epithelial integrity, stromal differentiation, and implantation potential, a pattern frequently observed in thin endometrium and conditions associated with metabolic stress or advancing reproductive age.[8,35,46]

Mitochondrial function further modulates AMPK–mTOR signaling, as adequate ATP production and mitochondrial integrity are essential for decidualization, angiogenesis, and immune regulation.[46] Mitochondrial dysfunction amplifies AMPK activation, suppresses mTOR signaling, and reduces the expression of critical receptivity molecules, contributing to implantation failure even when gross morphological features appear normal.[47]

Overall, disturbances in energy metabolism, excessive AMPK activation, impaired mTOR signaling, and dysregulated autophagy define a distinct metabolic phenotype characteristic of thin or functionally non–receptive endometrium, providing a mechanistic basis for targeted therapeutic strategies aimed at restoring endometrial competence.[8,35,45,47]

These metabolic pathways do not act in isolation but interact closely with hormonal, vascular, and immune mechanisms described in preceding sections, further supporting the concept that endometrial receptivity reflects an integrated, systems–level biological process.

Endometrial Immunology and Receptivity

Successful implantation requires a finely regulated immunological environment that permits tolerance toward the embryo while supporting angiogenesis and stromal remodeling.[15,26,28,32] During the window of implantation, the endometrium undergoes dynamic reorganization involving uNK cells, macrophages, and Treg cells.[16,40] Uterine natural killer (uNK) cells, the predominant mid–secretory leukocytes, display a pro-angiogenic phenotype and facilitate spiral artery remodeling and maternal–fetal tolerance.[20,21,24,25,28,30] Regulatory T (Treg) cells further support this tolerance by suppressing excessive inflammation via IL-10 and TGF–β signaling.[29,41]

Endometrial macrophages undergo a critical transition from a pro–inflammatory M1 phenotype toward a regulatory M2 phenotype.[29] M2 macrophages stabilize decidual transformation and support extracellular matrix remodeling.[5,29,38,41,42] In thin endometrium, this balance is frequently disrupted, leading to increased pro-inflammatory cytokines (IL–1β, IL–6, TNF–α) and reduced expression of HOXA10 and VEGF.[8,29,44] Furthermore, chronic endometritis and non–Lactobacillus-dominant microbiota profiles are significantly associated with recurrent implantation failure and impaired receptivity markers.[11,24,26,32,44]

Overall, coordinated interactions between immune cells and cytokine networks are essential, as dysregulation can result in a functionally non-receptive environment despite adequate endometrial thickness.[12,19,29,44]

Mechanism-Specific Therapeutic Strategies

Aligning interventions with the dominant underlying biological defect–whether vascular, molecular, metabolic, immune, or fibrotic–provides a rational framework for clinical management.

Hormonal and Vascular-Targeted Treatments

Estrogen and progesterone regimens remain first-line therapies, although their efficacy may be limited in cases of severe fibrosis or progesterone resistance.[23,37–40,44] For vascular–dominant phenotypes, sildenafil and acupuncture have been reported to improve subendometrial perfusion and reduce uterine artery resistance indices, particularly in small clinical studies and observational cohorts.[39,40,44]

Regenerative and Molecular–Restorative Therapies:

Platelet–rich plasma (PRP) therapy facilitates stromal proliferation and extracellular matrix remodeling, with reported upregulation of key markers such as HOXA10 and LIF.[4,5,11,14,19] Clinical evidence to date is derived primarily from small prospective studies and observational cohorts, and further randomized trials are needed to confirm longterm efficacy.

For severe basal layer damage or Asherman-like pathology, mesenchymal stem cell (MSC) therapies are increasingly explored to restore glandular architecture and reduce fibrosis.[43,44,47,48] Current data remain largely investigational and are based mainly on early-phase clinical studies and preclinical models.

Immune–Modulating and Microbiota-Directed Strategies

Management of chronic endometritis via antibiotics and probiotics aims to restore immune tolerance.[11,12,24,26,34,48] Granulocyte–colony stimulating factor (G-CSF) and intrauterine hCG may modulate the uNK cell phenotype and enhance stromal decidualization, although available evidence is heterogeneous and based on relatively limited clinical trials.[20,30,35,38] While corticosteroids may suppress excessive immune activation, their routine empirical use remains discouraged.[17]

Metabolic Support and Timing-Based Interventions

Metabolic support via coenzyme Q10, melatonin, and folate may alleviate mitochondrial stress and restore AMPK–mTOR balance, particularly in advanced reproductive age; however, supporting evidence is largely derived from small clinical studies and mechanistic investigations.[3,8,29,35,46]

Finally, ERA–guided personalized embryo transfer (pET) may correct temporal displacement of the window of implantation and restore embryo–endometrium synchrony in selected patients with recurrent implantation failure, although the magnitude of benefit appears to vary across patient populations and study designs.[6,10,17,18,32,37,39]

Rationale for Mechanism-Based Individualization

Because impairment of endometrial receptivity is multidimensional, no single therapeutic approach is universally effective.[1,12,39] Mechanism-directed treatment selection aligns each intervention with the dominant underlying biological defect, enabling a more rational and individualized clinical strategy.

Phenotype–therapy associations include vascular insufficiency (sildenafil, acupuncture, physiotherapy)[39]; fibrotic or extracellular matrix–dominant phenotypes (platelet-rich plasma and regenerative approaches)[11,43,44]; immune-dominant dysfunction (antibiotics/probiotics, granulocyte–colony stimulating factor, intrauterine hCG)[30,42]; metabolic impairment (coenzyme Q10, melatonin, omega–3 fatty acids, folate)[3,35,46]; displacement of the window of implantation (ERA–guided embryo transfer)[6,10,37]; and hormonal resistance requiring prolonged estrogen priming with optimized progesterone support.[18,37]

Overall, this phenotype-based framework provides a structured and individualized approach to optimizing implantation potential in assisted reproductive technologies.[1,8,35,39] Thin endometrium subtypes, their underlying pathophysiological mechanisms, and corresponding treatment strategies are summarized in Table 1.

Table 1. Biological phenotypes of thin or functionally non–receptive endometrium: pathophysiological mechanisms and targeted treatment options

Biological Phenotype	Typical Clinical Clues / Findings	Key Pathophysiological Mechanisms	Mechanism-Based Treatment Options (Ref)
Vascular/ Angiogenesis Insufficiency	High PI/RI; poor subendometrial perfusion; vascular risk factors (e.g., smoking, hypertension)	↓ VEGF; impaired spiral artery remodeling; subendometrial hypoxia; defective NO signaling	Low-dose aspirin[34]; sildenafil, intra uterine physiotherapy, or G-CSF may be considered in selected cases[40, 44]
Fibrotic / ECM-Dominant	History of curettage; Asherman features; adhesions; refractory thin endometrium	Basal layerinjury; collagen accumulation; ECM stiffness; glandularloss; ↓ HOXA10/VEGF	PRP[11]; MSC therapyor adhesiolysis[47,48]; intra uterine physiotherapy; long-term estrogen[43,44]
Metabolic / Mitochondrial Stress	Advanced maternalage; metabolic syndrome; oxidative stress; RIF with normal/mildly thin lining	Mitochondrial dysfunction; ↑ROS; ↑AMPK/ ↓mTOR signaling; ↓ HOXA10/LIF/IGFBP-1	CoQ10, melatonin, omega-3, orfolate/methylfolate may be considered to mitigate metabolic stress[3, 8,46]
Immune / Microbiota-Related	Chronicendometritis (CD138+); non-Lactobacillus flora; unexplained RIF; micropolyps	Tregdeficiency; uNK dysfunction; M2→M1 macrophageshift; ↑ IL-6/TNF-α; ↓ HOXA10/LIF/integrin	Antibiotics and probiotics[24, 26]; G-CSF or intra uterine hCG[30, 38]; PRP[11, 41]
WOI Timing-Dominant	Repeated implantation failure (RIF) with high-quality embryos; history of displaced WOI	Pre- or post-receptive transcriptomic profile; displaced window of implantation (WOI)	ERA-guided personalized embryo transfer (pET); individualized luteal support[6, 10,37]
Progesterone-Resistant	Endometriosis / adenomyosis; functional failure despite adequate thickness	Progesterone receptor (PR-A/PR-B) imbalance; HOXA10 suppression; NF-κB activation	Longestrogen + optimized progesterone; anti-inflammatory therapy; PRP and/or ERA-based strategies[4,5,18,37]
Mixed (Combined) Phenotype	Multiple overlapping risk factors; complex clinical history	Synergistic vascular, immune, metabolic, and fibrotic abnormalities	Individualized combination therapy prioritized by the dominant clinical mechanism[8,27,39,44]

Abbreviations: PI/RI: Pulsatility Index / Resistance Index; WOI: Window of Implantation; ERA: Endometrial Receptivity Array; RIF: Recurrent Implantation Failure; uNK: Uterine Natural Killer cells; Treg: Regulatory T cells; ECM: Extracellular Matrix; NO: Nitric Oxide; PRP: Platelet-Rich Plasma; MSC: Mesenchymal Stem Cell; AMPK: AMP-activated protein kinase; mTOR: Mechanistic target of rapamycin; ROS: Reactive Oxygen Species. **Note:** Some interventions remain investigational; clinical evidence levels vary by indication and specific patient phenotype.

Discussion

Endometrial receptivity is a multidimensional biological state arising from the coordinated interaction of hormonal signaling, vascular adaptation, immune regulation, and cellular energy homeostasis.[1,7,12] Current evidence demonstrates that implantation competence depends primarily on molecular and immunological pathways rather than morphological parameters alone.[3,9,10,17,30] Within this paradigm, thin endometrium is increasingly recognized as a heterogeneous phenotype driven by distinct pathophysiological mechanisms, including vascular insufficiency, suppression of key receptivity markers such as HOXA10 and LIF, metabolic stress, and fibrotic remodeling.[4,19,20,24–26] These mechanistic differences provide a biological explanation for the variability in reproductive outcomes observed among patients with comparable endometrial thickness.[3,9]

Contemporary therapeutic strategies increasingly align with this mechanistic framework, reflecting a shift toward phenotype-driven clinical decision-making. Regenerative approaches, including platelet-rich plasma and mesenchymal stem cell–based therapies, exert multi–level effects by restoring stromal architecture and enhancing the expression of receptivity–associated molecular markers.[4,18,26] Vascular-targeted interventions primarily benefit perfusion–dominant phenotypes, whereas immune–modulating strategies address dysregulated immune profiles, including reduced regulatory T–cell activity and dysfunctional uterine natural killer cell populations.[19,20,27,28,31,32,35,37,48] In parallel, metabolic support strategies such as coenzyme Q10 and melatonin may mitigate mitochondrial stress and restore cellular energy balance, thereby supporting decidualization and implantation competence.[29] Finally, ERA–guided personalized embryo transfer represents a mechanism–based approach to correcting patient-specific temporal displacement of the window of implantation and restoring embryo–endometrium synchrony.[30–32]

Endometrial receptivity is a transient biological state that requires precise integration of hormonal signaling and molecular regulatory pathways. This review underscores that thin endometrium represents a heterogeneous phenotype involving vascular, molecular, metabolic, and fibrotic defects rather than a single pathological entity. Adoption of a mechanism-oriented, phenotype-based clinical framework–aligned with the dominant underlying biological defect–appears essential for advancing precision reproductive medicine and improving implantation outcomes, particularly in patients with recurrent implantation failure.

Limitations

This narrative review synthesizes evidence from previously published studies that exhibit substantial heterogeneity in study design, sample size, diagnostic criteria, and therapeutic protocols. As a result, variability across the available literature represents an inherent limitation. Moreover, evidence supporting the proposed mechanistic subtypes of thin endometrium remains limited, with many molecular, metabolic, and immunological insights derived from small clinical cohorts or preclinical models.

Accordingly, although the phenotype- and mechanism-based framework presented herein provides a robust conceptual foundation for clinical translation, its practical applicability requires validation through large-scale, prospective, and ideally multicenter studies before incorporation into routine clinical decision-making.

Future Perspectives

Advancing the field of endometrial receptivity requires a shift from morphology-based assessment toward molecularly defined, phenotype-oriented diagnostic frameworks. Future research should focus on identifying and validating standardized, clinically applicable molecular signatures capable of distinguishing functional from non-functional endometrium, independent of endometrial thickness.

High-resolution approaches such as single-cell transcriptomics, spatial proteomics, and metabolomic profiling are expected to refine mechanistic subtyping and reveal actionable therapeutic targets. In parallel, well-designed prospective and multicenter clinical trials are needed to evaluate pathway-specific interventions, including regenerative, immune-targeted, and metabolic strategies, within clearly defined biological phenotypes.

Integration of endometrial microbiome profiling, mitochondrial function assessment, and window-of-implantation–specific molecular analyses into assisted reproductive technology workflows may further enhance patient stratification and treatment personalization. Establishing robust mechanism-based clinical pathways will be essential for optimizing reproductive outcomes and advancing precision medicine in reproductive care.

Conflict of Interest

The authors declare no conflict of interest.

Financial Support

The authors received no financial support for the research, authorship, or publication of this article.

Author Contributions

Both authors contributed to the conception and design of the review, literature search and analysis, drafting and critical revision of the manuscript, and approved the final version for submission.

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