Progress in Obstetrics & Gynecology

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CHAPTER 24

Application of Stem Cells in Endometrial Rejuvenation

Sunita Tandulwadkar, Rashmika Gandhi

INTRODUCTION

The endometrium is a dynamic, regenerative tissue that undergoes >400 cycles of proliferation, differentiation, shedding, and repair during a woman's reproductive life. This remarkable regenerative ability depends on a population of endometrial stem/progenitor cells capable of self-renewal and differentiation.

However, in certain pathological states such as Asherman's syndrome, chronic endometritis, genital tuberculosis, or repeated curettage, this regenerative potential is impaired, leading to thin endometrium, poor vascularity, and suboptimal implantation.

A thin endometrium (<7 mm) during embryo transfer is associated with lower implantation and live-birth rates, and current therapies—estrogen supplementation, vasodilators, sildenafil, granulocyte colony-stimulating factor (G-CSF), and platelet-rich plasma (PRP)—offer only modest or transient benefits.

In this context, stem-cell-based therapies have emerged as a promising strategy for endometrial rejuvenation, aiming to restore structure and function by inducing angiogenesis, paracrine repair, and cellular proliferation.

PHYSIOLOGY OF ENDOMETRIAL REGENERATION

The human endometrium is among the most regenerative tissues in the body, undergoing cyclical proliferation, differentiation, shedding, and repair roughly 400–450 times during reproductive life. This capacity for regeneration reflects a finely coordinated interplay among hormones, local growth factors, immune mediators, vascular components, and a resident pool of stem/progenitor cells that reside primarily in the basal layer.

Anatomical and Cellular Basis

The endometrium consists of two layers:

1. The functionalis, which undergoes cyclical changes and is shed during menstruation.
2. The basalis, which remains intact and provides the germinal layer for post-menstrual regeneration.

Within the basalis, several progenitor populations have been identified:

- *Endometrial mesenchymal stem/stromal cells (eMSCs):* Perivascular cells expressing *CD146, PDGFR-β, SUSD2,* and *CD140b*; they are clonogenic and multipotent.
- *Epithelial progenitor cells (EpCs):* Located near glandular bases, expressing *SOX9,* N-cadherin, *LGR5;* regenerate glandular epithelium.
- *Endothelial progenitor cells (EnPCs):* Contribute to neovascularization during the proliferative phase.

These populations together drive the re-epithelialization and stromal

restoration that occur within days after menstruation.

Hormonal Regulation

Estrogen promotes proliferation via ER-α/ER-β-mediated upregulation of VEGF, IGF-1, and EGF, facilitating angiogenesis and extracellular-matrix synthesis.

Progesterone, acting through PR-A and PR-B, triggers stromal decidualization and limits excessive proliferation.

After progesterone withdrawal, controlled inflammation initiates menstruation; within 48–72 hours, VEGF, FGF-2, HGF, and matrix metalloproteinases (MMP-2 and -9) coordinate tissue breakdown and repair.[1]

Growth Factors and Cytokines

Regeneration depends on the interplay of:

- *VEGF, HGF, TGF-β:* Endothelial proliferation and angiogenesis.
- EGF and IGF-1: Epithelial proliferation.
- *LIF* and *IL-6:* Differentiation and immune modulation.
- MMPs and TIMPs: Extracellular-matrix turnover.

Impaired signaling—due to infection, ischemia, or fibrosis—disrupts this balance and leads to defective repair.

Stem-cell Niche and Regenerative Dynamics

The stem-cell niche within the basalis provides a microenvironment rich in paracrine cues, extracellular-matrix scaffolding, and immune-cell crosstalk.

- *SDF-1/CXCR4* signaling recruits bone-marrow progenitors.
- Hypoxia-inducible factor (HIF-1α) upregulates angiogenic genes during menstruation's transient hypoxia.
- Macrophages and uterine NK cells clear debris and secrete trophic cytokines.

Stem cells proliferate, migrate toward the surface, and differentiate into stromal and epithelial cells, reconstituting the functionalis layer.

BONE-MARROW CONTRIBUTION

Evidence shows that a subset of endometrial stromal and epithelial cells originates from bone-marrow-derived stem cells (BMDSCs). Chemokines such as *CXCL12* facilitate BMDSC homing to the uterus, where they integrate and contribute to endometrial repair.[2] This underpins the biological rationale for autologous bone-marrow stem-cell therapy.

VASCULAR AND IMMUNE COMPONENTS

Endometrial regeneration requires robust angiogenesis. Stem/progenitor cells and pericytes differentiate into endothelial cells and secrete VEGF, PDGF, and angiopoietins. Immune cells (macrophages, dendritic cells, and uNK cells) provide reparative cytokines and regulate fibrosis; chronic inflammation, however, promotes scarring and adhesions.

KEY FACTORS IN ENDOMETRIAL REGENERATION

The principal cellular and molecular components involved in endometrial regeneration and their clinical implications are summarized in **Table 1**.

CLINICAL IMPLICATIONS

When the basalis layer or its progenitor pool is destroyed—as in Asherman's syndrome, post-tubercular endometritis, or repeated curettage—regeneration fails.

Histologically, such endometria show fibrosis, glandular loss, and vascular

TABLE 1: Key cellular, molecular, and immunologic factors involved in endometrial regeneration and their clinical relevance.

Component	*Function in regeneration*	*Clinical correlation*
eMSCs (CD146+ and SUSD2+)	Stromal proliferation, angiogenesis	Targeted by autologous stem-cell therapy
Epithelial progenitors (SOX9+ and N-cadherin+)	Re-epithelialization of uterine surface	Essential for glandular reconstruction
VEGF, FGF, and HGF	Promote neovascularization	Enhanced by PRP and MSC therapy
HIF-1α and CXCL12	Recruit bone-marrow progenitors	Central to MSC homing
MMPs and TIMPs	ECM remodeling	Dysregulation leads to fibrosis
uNK cells and macrophages	Debridement and immune modulation	Chronic activation impairs healing

(ECM: extracellular matrix; FGF: fibroblast growth factor; HGF: hepatocyte growth factor; MMP: matrix metalloproteinase; MSC: mesenchymal stem cell; PRP: platelet-rich plasma; VEGF: vascular endothelial growth factor)

attenuation, resulting in estrogen resistance and persistent thin endometrium.

Restoring the regenerative niche through stem-cell therapy seeks to re-establish cellularity, vascularity, and normal cycling.

CAUSES OF REFRACTORY THIN ENDOMETRIUM

- Asherman's syndrome/intrauterine adhesions
- Post-tubercular endometritis
- Repetitive curettage or instrumentation
- Chronic endometritis or ischemia
- Prolonged hypoestrogenism or over-suppression by progesterone. These conditions yield persistently thin endometrium (<6 mm) unresponsive to estrogen and adjuvants.

TYPES OF STEM CELLS USED FOR ENDOMETRIAL REPAIR

1. *Bone-marrow-derived stem cells (BMDSCs):* Contain mesenchymal and hematopoietic components capable of homing to injured endometrium via *CXCL12/SDF-1* and differentiating into stromal, epithelial, and endothelial cells. Clinical use of autologous BM-MSC infusion increases endometrial thickness and perfusion.[3]
2. *Menstrual blood-derived stem cells (MenSCs):* Readily accessible, high proliferative capacity, expressing *CD29, CD44, CD73,* and *OCT-4*. They secrete angiogenic factors and demonstrate successful regeneration and resumption of menses in preliminary human trials.[4]
3. *Umbilical-cord-derived MSCs (UC-MSCs):* Wharton's-jelly-derived cells rich in VEGF, β-FGF, and IGF-1; used with collagen scaffolds or PRP for enhanced tissue restoration.
4. *Adipose-derived stem cells (ADSCs):* Easily harvested, potent paracrine secretors; their exosomes are being tested as cell-free therapy to reduce immunologic risk.

MECHANISMS OF ACTION

- Engraftment and differentiation into new stromal or endothelial cells
- Paracrine secretion of trophic factors (VEGF, IGF-1, and HGF)
- Immunomodulation by suppressing TNF-α/IL-6 and enhancing IL-10
- Recruitment of resident eMSCs via *SDF-1/CXCR4* signaling
- Exosomal communication transferring microRNAs for angiogenesis and remodeling[5]

METHODS OF ADMINISTRATION

Intrauterine Infusion

Autologous BM-MSCs or MenSCs suspended in PRP/saline instilled under ultrasound guidance—simple, localized, and minimally invasive.

Hysteroscopic Delivery

Direct injection into the basal endometrium or fibrotic areas ensures targeted engraftment. Dr Sunita Tandulwadkar et al.[6] pioneered hysteroscopic autologous BM-MSC injection in India, achieving mean endometrial thickness improvement from 4.1 ± 0.8 mm to 7.2 ± 1.1 mm, resumption of menses in 80%, and live births in previously refractory cases.

Scaffold-assisted Delivery

Collagen or hyaluronic-acid matrices enhance stem-cell survival and angiogenesis; animal models show superior vascular and glandular density.[7]

CLINICAL OUTCOMES

Restoration of Endometrial Thickness

- Across multiple small clinical studies (sample size = 10–60), average endometrial thickness increased by 2–3 mm following stem-cell therapy.
- Improved endometrial vascularity and receptivity markers (integrin β3 and LIF) were observed by immunohistochemistry.

Return of Menstruation

Amenorrheic women often resumed cyclic bleeding within 4–6 weeks post-therapy, suggesting functional regeneration of the endometrium.

Pregnancy Outcomes

- Reported clinical pregnancy rates range between 40 and 60%, with live-birth rates around 30–40% in refractory endometrium—figures superior to conventional therapy.[8]
- In Dr Tandulwadkar's series (2019), 10 out of 16 women conceived post-therapy, of whom 7 delivered healthy infants.[6]

SAFETY PROFILE

No major adverse events, malignancies, or ectopic tissue formation have been reported. Mild discomfort during aspiration or hysteroscopy remains the only significant complaint. Nevertheless, long-term oncologic safety requires continued surveillance.

ADJUNCTIVE AND COMBINATION APPROACHES

Stem Cells with Platelet-rich Plasma

Platelet-rich plasma provides a rich milieu of growth factors (PDGF, VEGF, and TGF-β) that enhance stem-cell survival and angiogenesis. Combining BM-MSCs with PRP intrauterinely has yielded faster endometrial response and improved implantation potential.

Stem-cell-derived Exosomes

Exosomes mimic paracrine signaling without requiring cell engraftment. They have been shown to upregulate VEGF, Ki-67, and CD31 expression in endometrial tissue, accelerating regeneration. This represents a promising cell-free therapy currently under investigation.

Hormonal and Adjuvant Optimization

Administration of estradiol valerate (6–8 mg/day) for 2–3 weeks post-therapy enhances proliferation, while low-molecular-weight heparin and sildenafil improve vascular perfusion. Adjunct antioxidants and pentoxifylline may further augment results.

CHALLENGES AND LIMITATIONS

- *Lack of standardized protocols:* Variability exists in stem-cell source, dose ($1–5 \times 10^6$ cells), timing, and route of delivery.
- *Limited sample sizes:* Most human studies are small, uncontrolled, and short-term.
- *Regulatory and ethical barriers:* Stem-cell manipulation requires good manufacturing practice (GMP) facilities and ethical oversight, restricting widespread use.
- *Cost and accessibility:* Current therapies cost INR 60,000–100,000 per cycle, limiting affordability in low-resource settings.
- *Need for long-term safety data:* Concerns about potential neoplastic transformation, ectopic growth, or abnormal decidualization necessitate ongoing follow-up.

FUTURE DIRECTIONS

- *Randomized controlled trials (RCTs):* Larger multicenter studies are essential to validate safety and efficacy.
- *Integration with genomic and transcriptomic profiling:* Personalized selection of patients likely to respond to stem-cell therapy.
- *Regenerative medicine guidelines:* Standardization of protocols through organizations such as ICMR and ISAR for ethical implementation in fertility practice.

CONCLUSION

Stem-cell-based endometrial rejuvenation exemplifies translational regenerative medicine. By replenishing the cellular and vascular deficit of the basal layer, it addresses the root pathology of refractory thin endometrium rather than offering transient hormonal augmentation.

Nonetheless, consolidation through robust trials and regulatory clarity is essential. As evidence matures, stem-cell and exosome therapy may become integral to managing endometrial insufficiency, fulfilling the promise of true regenerative fertility care.

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Sunita Tandulwadkar MD (Obs & Gyne) FICS (Gyne-Endoscopy) FICOG is the 63rd President of the Federation of Obstetric and Gynaecological Societies of India (FOGSI, 2025)—the largest organization of obstetricians and gynecologists in India with over 46,000 members. She is also the President–Elect of the Indian Society of Assisted Reproduction (ISAR, 2024–2026) and serves as Head, Department of Obstetrics and Gynecology, IVF and Endoscopy at Ruby Hall Clinic, Pune, Maharashtra, India. She is the Founder President of the Society of Ovarian Rejuvenation, Past President of the Indian Association of Gynaecological Endoscopists (IAGE), Past President of the Pune Obstetric and Gynecological Society (POGS), and Elected Board Member (2013–2017) of the International Society of Gynecologic Endoscopy (ISGE). In 2025, she was conferred the Honorary Fellowship of the Royal College of Obstetricians and Gynaecologists (RCOG, London) and the Lifetime Achievement Award by the 14th President of India for her outstanding contribution to women's health and medical education. A true pioneer in regenerative medicine, she achieved the world's first stem-cell baby at the age of 45 (2018)—a landmark in global reproductive science. With more than 400 lectures worldwide, 18 authored books, 85+ scientific papers, and training of over 300 gynecologists, she continues to shape reproductive medicine and endoscopic surgery both in India and internationally.

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