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Concise Review – Invited

Stem cells and female reproduction: endometrial physiology, disease and therapy

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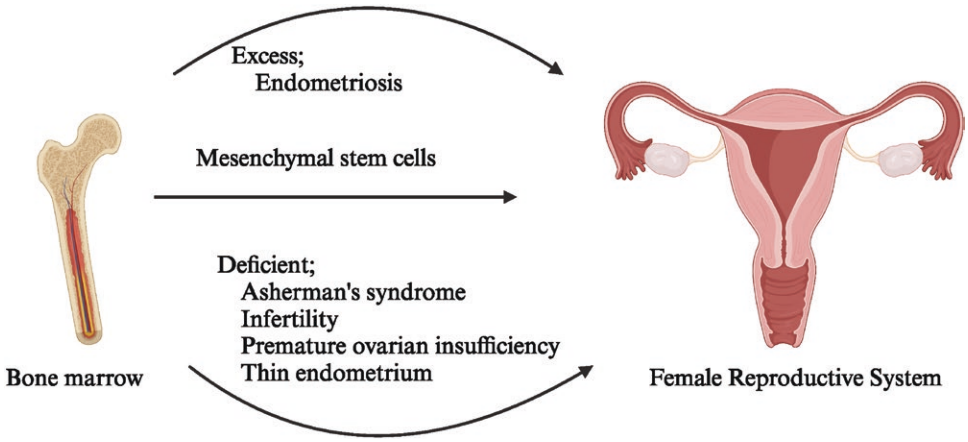
Abstract

The human endometrium, a dynamic tissue that undergoes cyclical shedding, repair, regeneration, and remodeling, relies on progenitor stem cells for replenishment. Bone marrow-derived mesenchymal stem cells (BM-MSCs) also may play a crucial role in the physiological process of endometrial regeneration, augmenting endometrial repair, supporting pregnancy, and thereby making a major contribution to reproduction. Notably, defective or inappropriate recruitment and engraftment of stem cells are implicated in various reproductive diseases, including endometriosis, highlighting the potential therapeutic avenues offered by stem cell-targeted interventions. Endometrial progenitor cells have shown promise in improving pregnancy outcomes and addressing infertility issues. Furthermore, BM-MSCs demonstrate the potential to reverse pathologies, including Asherman's syndrome and thin endometrium, offering novel approaches to treating infertility, implantation failure, and recurrent pregnancy loss. Mobilization of endogenous stem cells to areas of pathology through chemoattractants also presents a promising strategy for targeted therapy. Finally, endometrium-derived mesenchymal stem cells, characterized by their multipotent nature and ease of collection through minimally invasive techniques, hold promise in a wide range of reproductive and non-reproductive pathologies, including diabetes, kidney disease, Parkinson's disease, or cardiac disorders. As the best of our knowledge of stem cell biology continues to grow, the incorporation of stem cell-based therapies into clinical practice presents significant potential to transform reproductive medicine and enhance patient outcomes.

Key words: cell transplantation; endometrium; endometriosis; infertility; stem cells.

Graphical Abstract



Significance statement

This review explores how stem cells contribute to the regeneration and repair of the human endometrium; a tissue essential for reproduction. It highlights the potential for stem cell therapies to address infertility, pregnancy loss, and conditions like endometriosis and Asherman's syndrome. The ability to harness both bone marrow and endometrium-derived stem cells offers new hope for improving reproductive health. Additionally, these cells may provide novel treatments for diseases beyond reproduction, such as heart disease and diabetes. By advancing our understanding of stem cell biology, this work paves the way for future clinical applications in regenerative medicine.

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The endometrium, a carefully regulated mucosal tissue lining the uterine cavity, is pivotal in facilitating the intricate series of events leading to conception and pregnancy. The cyclic growth, differentiation, and regenerative capabilities of the endometrium are meticulously orchestrated to establish an optimal milieu for embryo implantation and the initiation of pregnancy. This recurrent self-renewal process relies, in part, on the presence of endometrial progenitor cells and a contribution from multipotent bone marrow derived mesenchymal stem cells (BM-MSCs).[1,2] Stem cells are integral contributors to endometrial physiology. These undifferentiated cells harbor the potential not only to sustain the structural and functional integrity of the endometrial lining but also to play a role in a spectrum of reproductive disorders.[1,2]

In this review, we describe the multifaceted role of stem cells within the context of the endometrium and female reproductive physiology. We delve into their significance in maintaining endometrial homeostasis, explore the potential ramifications of their aberrant behavior in the context of reproductive pathologies, and examine promising therapeutic applications harnessing their regenerative capabilities.

The dynamic nature of the uterine endometrium

Parts of the luminal epithelium and the superficial functionalis layer of the endometrium make up a remarkably dynamic tissue; the endometrium undergoes cyclical shedding, repair, regeneration, and remodeling more than 400 times throughout a woman's reproductive lifespan.[3] The endometrial lining is prepared for potential implantation of an embryo under the regulation of ovarian estrogen and progesterone during the menstrual cycle,[3] creating an optimal environment for embryo development.[3,4] However, this environment is lost in a piecemeal fashion during menstruation.[4,5]

Role of stem cells in the endometrial physiology

In addition to the proliferation and regeneration of fully differentiated endometrial cells, supplemented by progenitor cells, the endometrium harbors a population of stem cells with high clonogenic activity and multilineage differentiation potential, which contribute to the regeneration of the endometrium after menstruation.[1] Endometrium-derived mesenchymal stem cells (eMSCs) were identified and characterized in adult human endometrial tissue.[1] They are multipotent progenitor cells, resembling classic MSCs in their abilities of self-renewal, clonogenicity, plastic adherence, and multilineage differentiation into other endometrial cell types, such as stromal, epithelial, and endothelial cells. These cells are characterized by MSC surface marker expression, including Stro-1, CD90, CD133, CD146, and SUSD2.[1,6] A distinct population of epithelial progenitor cells has also been identified in the mouse endometrium.[7] Endometrial stem cells are present near the luminal and glandular epithelia in both the functional and basal layers of the mouse endometrium. While mice do not menstruate, humans lose the superficial luminal epithelium and functionalis layer upon menstruation. This implies that specific progenitor cell subgroups may be differentially located in humans and menstruating species compared to other mammals; the human endometrium has a distinct basal layer, not shed at menstruation, allowing progenitor and multipotent stem cells to endure.[8]

In addition, perivascular cells, including pericytes around capillaries and micro vessels, as well as adventitial cells in the outermost layer of large vessels, exhibit similar characteristics to MSCs.[9-11] Their stem cell like features include adherence, morphology, the ability to be differentiated into fibroblast-like cells in vitro, and the expression of classic MSC markers such as CD29, CD44, CD73, CD90, and CD105.[9,10] CD146 + pericytes primarily reside in the capillaries and micro vessels of both the functionalis and basalis layers of the endometrium.[12] Their perivascular niche was identified when specific surface markers were identified that could be used to enrich clonogenic endometrial stromal cells. These cells, co-expressing CD146=+ and PDGF-Rβ+, are closely associated with stromal fibroblasts in the endometrium and have the ability to differentiate into various mesodermal lineages, including adipogenic, osteogenic, neural-like cells, and stromal fibroblasts.[9,10]

While it is widely believed that the majority of endometrial stem cells originate within the endometrial tissue itself, a subset is sourced externally from circulating stem cells derived from the BM. BM donor-derived endometrial cells can contribute up to approximately 50% of endometrial cells. These cells were first identified by evaluation of HLA-mismatched human BM transplant recipients.[2] In murine models, following transplantation, labeled BM-MSCs in the recipient murine uterus expressed markers associated with stromal, epithelial, endothelial, and muscle cell populations, demonstrating a contribution to the various differentiated cell types of the uterus.[13] These studies suggested that BM-MSCs play a role in the maintenance of normal uterine tissue homeostasis. There was also a population with sustained expression of stem cell markers, an indication that certain BM-MSCs were not only functioning as progenitor cells for endometrial regeneration but some also remained as MSCs.[13] Contrary to these findings, one study suggested that the differentiation of BM cells into endometrial stroma, epithelium, and endothelium is improbable since there was no evidence of green fluorescent protein (GFP) expressing BM-derived stroma, epithelium or endothelium in the endometrium of recipient mice after transplant of BM from a GFP transgenic mouse strain.[14] However, this work has significant limitations, as GFP was not expressed in all cells of the transgenic donor, which means that key populations of BM-MSCs might not have been successfully tagged.[15] In fact, multiple groups have demonstrated the incorporation of BM-MSCs in endometrium and it remains widely accepted that a subset of endometrial stem cells originates externally from circulating stem cells derived from the BM.[16-19]

The regulation of BM-MSC translocation to the endometrial tissue involves both steroid hormones and various chemokines/growth factors. Notably, heightened estradiol secretion is recognized as stimulating the homing and translocation of circulating endothelial progenitor cells into endometrial blood vessels during the early stages of the menstrual cycle.[20] Menstruation is also associated with elevated levels of inflammatory cytokines and a rapid rise in the number of immune cells. The menstruating endometrium is a physiologically injured tissue that requires monthly repair.[21] Several types of stimuli, including inflammation or ischemia/reperfusion injury, can also trigger this translocation and BM-MSC engraftment.[16,22] Likewise, in vitro studies have demonstrated

that estrogen-induced secretion of CXCL12 from endometrial stromal cells can enhance the migratory capability of bone marrow-derived cells; the CXCL12/CXCR4 signaling cascade plays a pivotal role in orchestrating the chemotactic migration of BM-MSCs towards the endometrium in the late proliferative phase of the menstrual cycle where they enhance fertility.[23]

In tissue renewal and repair, cell plasticity also plays a pivotal role. It is increasingly recognized that the ability of cells to adaptively change their differentiation state or identity is crucial for maintaining tissue integrity. In addition to the recruitment of circulating stem cells, the dedifferentiation of committed cells into stem-like progenitor cells in response to acute inflammatory events has been identified as a key driver of tissue regeneration.[24] When injury or ablation occurs, tissues utilize de-differentiation to restore the stem cell pool as a backup mechanism for potential stem cell depletion.[25] In fact, many tissues do not have dedicated stem cells and instead depend on cellular plasticity to replace lost cells, since mature cells can activate an evolutionarily conserved process known as paligenosis to reenter the cell cycle and regenerate damaged tissue.[26] Stem cells can actively or passively manipulate the de-differentiation process, maintaining continuous communication with their progeny. This identity change happens through the activation of specific signaling pathways, either in experimental settings or in response to injury or inflammation in physiological conditions. These processes are tightly regulated to prevent tissue destabilization or cancer. Epigenetic changes necessary for de-differentiation and trans-differentiation help control cellular identity and maintain tissue homeostasis when disrupted by injury.[25] Through de-differentiation, a pool of progenitor cells can be created, compensating for cell loss, and preventing organ failure.[27] The role of these processes in the endometrium is an active area of investigation.[28]

During the menstrual cycle, progesterone production after ovulation causes endometrial stromal cells to differentiate into epithelioid decidual cells.[29] This differentiated transient tissue, called "decidua," exists in animals with hemochorial placentas, including mice and humans.[30] Decidua allows blastocyst attachment to the uterine wall and initiation of implantation.[31] Both implantation and pregnancy are associated with a large increased mobilization of BM-MSCs into circulation and the recruitment to the uterus.[30] Bone marrow-derived cells recruited from circulation to the endometrium during implantation and early gestation differentiate into non-hematopoietic stromal decidual cells that express progesterone receptors and prolactin-classic decidual cell functional markers. This non-hematopoietic contribution of BM-MSCs to the pregnant uterus is far more pronounced than in the non-pregnant uterus. This is evidenced by an increase in BM-MSC population in the pregnant decidua, as well as differentiation into non-hematopoietic decidual cells (CD29 + CD45−) which express surface markers consistent with resident decidual cells. Throughout pregnancy, BM-MSCs proliferate to meet the demands of rapid growth and turnover.

To ascertain the functional role of BM-MSC flux to the uterus we examined the ability of BM transplant to rescue the infertility phenotype of Hoxa11 deficient mice. Hoxa11 -/- mice produce normal eggs and embryos, however even wild-type embryos fail to implant in the uterus; heterozygotes show a large number of pregnancy resorptions and reduced litter size. The Hoxa11 −/− uterus is abnormal in appearance and there is a complete absence of uterine glands, reduced stroma, and incomplete decidualization. Wild-type BM transplant resulted in the appearance of endometrial glands, stromal expansion, marked decidualization in homozygotes and rescue of heterozygotes from pregnancy loss by normalizing litter size.[30] BM-MSCs altered the uterine implantation transcriptome in heterozygote mice to promote normal decidualization, playing a critical role in overcoming implantation defects, sustaining pregnancy, and endometrial regeneration. The influx of BM-MSCs resulted in significant downstream consequences, including increased uterine LIF expression, a transcriptional target of Hoxa11 that is associated with decidualization, prolactin signaling, and Wnt gene expression, all essential for embryo implantation.[30]

While the BM is traditionally recognized as a vital component of the hematopoietic system, emerging evidence suggests it may play additional roles beyond hematopoiesis, possibly contributing to reproductive biology. This evolving perspective encourages further exploration of the interaction between the BM and reproductive processes. Such an adaptive role may support the high turnover and growth demands of the pregnant uterus, aligning with its dynamic nature.

Uterine implantation, decidualization, pregnancy maintenance, and healthy fetal growth all require active angiogenesis.[32] It is important to note that insufficient new blood vessel formation is associated with multiple pregnancy complications, such as spontaneous miscarriage and preeclampsia.[33,34] BM-derived endothelial progenitor cells contribute to the decidual vasculature of the pregnant mouse uterus,[35] playing a role in vascularization to establish and maintain pregnancy.

Immediately after parturition, the uterus undergoes dramatic regeneration as it returns to its pre-pregnancy state. Parturition and the postpartum period are characterized by endometrial tissue injury followed by rapid cellular turnover, regeneration, and postpartum uterine remodeling.[36] In mice, decidual expression of CXCL1 and CCL2 are elevated during labor and early postpartum period.[37] These chemokines as well as sex-steroid hormones take part in the recruitment of nonhematopoietic BM-MSCs. After BM transplantation from GFP donors into postpartum mice, there was an initial increase in GFP + cells. Donor-derived epithelial cells immediately repaired the parturition-related defects, demonstrating a direct contribution of BM-MSCs to postpartum re-epithelialization. This was followed by a rapid decrease in pre-pregnancy levels due to a gradual acquisition of cell senescence.[36] A transient role for a large BM-MSC flux is operative in postpartum uterine repair and healing.

Stem cells and endometriosis

Endometriosis is a disease characterized by the development of endometrial tissue outside the uterus. Endometriosis is a common disease, affecting 10%-15% of reproductive-age women and causing pelvic pain and infertility.[38] Stem cells have been implicated in this disease. Multiple hypotheses postulate an explanation for the pathogenesis of endometriosis. The most widely accepted explanation is the Sampson's theory of retrograde menstruation, which proposes the flow of menstrual debris, including endometrial cells, through the fallopian tubes into the peritoneal cavity.[39]

Progenitor stem cells with associated niche cells are sloughed off abnormally during menstruation and reach the peritoneal

cavity by retrograde menstruation, where they adhere and develop as endometriotic implants.[28,40,41] Endometrial stem cells are thought to differentiate into endometrial-like cells outside the uterus, contributing to the development and progression of endometriotic implants. This is supported by the observation that ectopic endometrial MSCs from endometriosis patients exhibit greater proliferation, migration, and vasculogenic capabilities compared to eutopic endometrial MSCs from the same individuals.[42] The presence of endometriosis in women with Mayer-Rokitansky-Küster-Hauser syndrome (Mullerian agenesis)[43] and adolescents[44] might be explained by Sampson's theory due to the presence of small amounts of uterine tissue and menstruation, however, the etiology of rare occurrences of endometriosis in males cannot be fully accounted for by this theory alone[45]; this suggests an alternative source of cells in some cases of endometriosis, and the possibility of a role for stem cells play in the etiology of endometriosis. The differentiation of circulating BM-MSCs into endometrial cells, possibly guided by neighboring epithelial and endometrial cells, could potentially explain these cases, and provide more evidence of the role of stem cells in endometriosis.

To ascertain whether BM-MSCs originating outside the uterus could migrate to and populate endometriotic implants, endometriosis was induced through the ectopic implantation of wild-type endometrial tissue into the peritoneal cavity of hysterectomized mice. Stem cells originating outside the uterus were integrated into the endometriotic implants, demonstrating the ability to differentiate into endometriosis and play a causative role in this disease.[46] In fact, following an introduction of syngeneic endometrial tissue into the peritoneal cavity of immunocompetent mice, endometriosis-derived stem cells were identified in the circulation and these cells were found to be present in multiple organs, including the lung, spleen, liver, and brain as shown by flow cytometry and immunofluorescence analyses.[47] We, therefore, speculate that endometriosis is a disease of aberrant stem cell trafficking and differentiation.

Endometriosis produces chemokines, including CXCL12, which are potent BM-MSC attractants. Endometriosis recruits more BM-MSC than the uterus or other reproductive organs. In endometriosis, CXCL12 is regulated in part by estradiol. The treatment of endometriosis with bazedoxifene, a selective ER modulator functioning as an ER antagonist in endometrial tissue, counteracts estrogen's ability to attract stem cells to areas of disease, potentially contributing to its regression.[48] Similarly, estrogen deprivation through gonadotropin-releasing hormone (GnRH) analog or letrozole treatment results in reduced BM-MSC engraftment in the endometriotic lesions.[49] Estrogens are involved in the migration of BM-MSCs to endometrium and endometriosis, and medications used to treat endometriosis function, at least in part, by interfering with stem cell recruitment. Taken together, these data supports the role of stem cells in the pathogenesis of endometriosis.

Stem cells as a therapeutic intervention to reproductive and non-reproductive system pathologies

Stem cell plasticity has garnered significant attention within the realm of regenerative medicine. BM-MSCs have been widely used in regenerative medicine and are also proving useful in the field of reproductive medicine. Endometrial stem cells also show clinical potential as both autologous and allogeneic sources of adult stem cells, due to their comparatively robust differentiation capability (multipotency), convenient accessibility, abundance, and ethical (regulatory) considerations.[50] The growing body of data from preclinical research and early clinical trials indicates that endometrial stem cells may have a wide range of therapeutic uses similar to BM-MSC.

Endometrial conditions involved in the etiology of reproductive failure include but are not limited to, endometriosis, thin endometrium, Asherman's syndrome, recurrent implantation failure, recurrent pregnancy loss, and reduced ovarian reproductive capacity in patients with premature ovarian insufficiency. These conditions can be targeted with stem cell therapeutic interventions, utilizing eMSCs and BM-MSCs (Figure 1).

The process of endometrial regeneration involves both endometrial progenitor stem cells and the migration of exogenous BM-MSCs.[51] Asherman's syndrome (AS) is a condition characterized by intrauterine adhesions/scarring due to damage to the endometrial basalis layer which contains the majority of progenitor cells. AS leads to infertility and adverse pregnancy outcomes, including miscarriage. In a mouse model of AS, BM-derived stem cell transplantation increased fertility rates as a result of the functional role BM-MSCs play in uterine repair after recruitment into the endometrium.[16] Similarly, in murine models of AS or thin endometrium, intrauterine administration of CXCL12 resulted in increased recruitment and engraftment of BM-MSCs in the uterus. This facilitated uterine remodeling by modulating vascularization, cellular proliferation, and immune responses, preventing fibrosis, ultimately restoring fertility, and increasing the rate of successful pregnancies.[16,23,52] In contrast, blocking the action of CXCL12 on its receptor CXCR4 with the antagonist ADM3100, resulted in the inhibition of recruitment of BM-MSCs to the injured endometrium in the AS-induced murine model, leading to decreased pregnancy success.[52]

This indicates the potential to use CXCL12 or CXCR4 agonists/antagonists as a therapeutic approach to address infertility associated with endometriosis, AS, and defects in endometrial receptivity.[53] In infertile women with defective thin endometrium, inoculation of eMSCs subendometrially or BM-MSCs through the uterine artery led to improvements in endometrial thickness, as well as increased clinical pregnancy rates and live birth rates.[54,55] While randomized controlled clinical trials are needed to confirm these findings, stem cell therapy may have a beneficial role in the treatment of infertility.

Additionally, through the induction of heightened bioactivity of CXCL12, DPP4 inhibitors have been shown to play a role in regulating endometrial decidual cells in women experiencing recurrent pregnancy loss, possibly by recruiting additional stem cells to the uterus.[23,56] This treatment was observed to enhance endometrial thickness and improve pregnancy outcomes over a 12-month period in a double-blind, randomized, placebo-controlled trial.[56]

MSC-based cellular therapies have been identified as a means to restore ovarian function in patients with premature ovarian insufficiency (POI), a condition marked by a reduction or loss of ovarian function before the age of 40. In murine models of chemotherapy-induced POI, treatment with GFP-tagged uterine cell suspensions containing eMSCs resulted

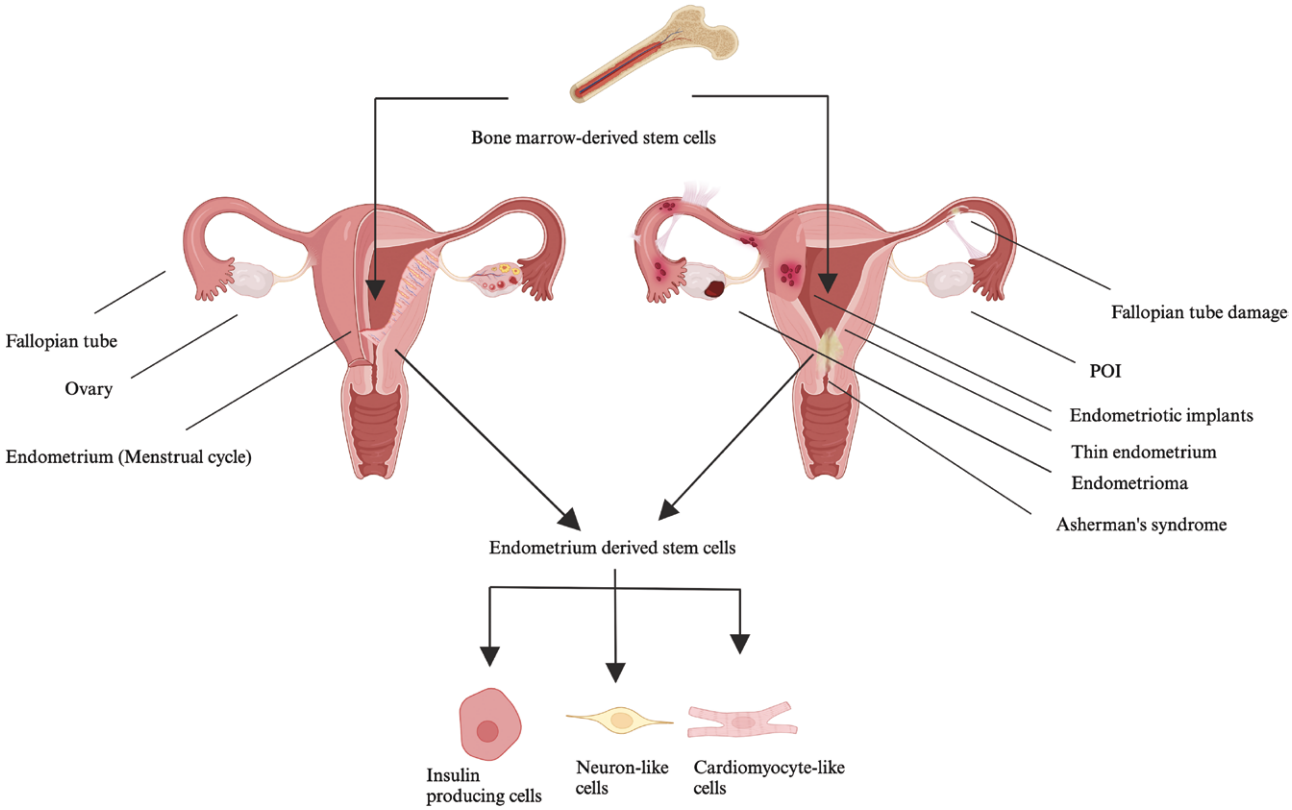

Figure 1. The involvement of bone marrow-derived mesenchymal stem cells (BM-MSCs) and endometrial progenitor cells in the cyclic self-renewal of the endometrium, preparing it for embryo implantation and pregnancy (Left). In contrast, both BM-MSCs and endometrium-derived mesenchymal stem cells (eMSCs) can migrate and integrate into endometriotic lesions leading to disease. Identification of the role of stem cells in reproductive system has led to novel insights into disease pathophysiology and uncovered novel therapeutic opportunities (Right); Finally, following isolation from the endometrium under appropriate conditions, eMSCs differentiate into diverse mature cell types, including insulin-producing cells, neuron-like cells, and cardiomyocyte-like cells, offering potential for therapeutic use (Bottom). Abbreviation: POI: Premature ovarian insufficiency.

in improved ovarian function indirectly. MSCs increased oocyte function, serum anti-Müllerian hormone (AMH) concentrations, and body mass after six weeks. There was no evidence of GFP expression in oocytes or pups, meaning this benefit was seen without the contribution of these stem cells to the oocyte pool.[57] In clinical trials, the transplantation of autologous BM-MSCs on collagen scaffolds into the ovaries of POI patients resulted in an improvement in overall ovarian function. This was evident through elevations in the concentrations of estradiol and AMH, enhanced follicular development, increased antral follicle counts, and successful clinical pregnancies. It appears that MSCs play a significant role in rejuvenating granulosa cells and revitalizing ovarian function, with this effect attributed to their anti-inflammatory and immunomodulatory properties.[58] Moreover, perivascular stem cells derived from the umbilical cord artery have demonstrated angiogenic capabilities in vitro.[59] They enhance blood supply and restore organ function in POI through cell-to-cell communication via the CD146/AKT/FHL1/Jagged1 signaling pathway and IL6 paracrine activity in mouse models.[60]

The fallopian tube plays a crucial role in various fertility-related processes, such as sperm transport and capacitation, egg retrieval and transportation, fertilization, and embryo nutrition and transportation. When scar formation or adhesions occur from infections or surgical interventions, they can lead to occlusion of the fallopian tubes, resulting in infertility.[61] In a rat model, BM-MSCs exhibited reparative effects on fallopian tubes. They promoted the activity of resident stem cells in the distal parts of the fallopian tubes, causing an increase in proliferation, the expression of VEGF, and reduced apoptosis.[62]

Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) are frequently used to treat tissue injury, including those of the myocardium, liver, lung, kidney, skin, vascular endothelium, endometrium, and ovary. Following the use of hUC-MSCs in an endometrial damage model, several positive outcomes were observed.[63] These included the promotion of endometrial regeneration and epithelial recovery, collagen remodeling, increased expression of ER-α and progesterone receptors, as well as an enhancement in endometrial embryo receptivity. The topical application of hUC-MSCs in patients with severe intrauterine adhesions resulted in reduced re-adhesion rates and improved pregnancy outcomes.[63] After transplanting UC-MSCs into the uterine cavity of patients with recurrent intrauterine adhesions (IUA), there was an increase in endometrial thickness and a decrease in adhesion score compared to pre-treatment levels. Additionally, the levels of Erα, vimentin, Ki67, and vWF were upregulated, while the expression of ΔNP63 was downregulated, indicating improvements in endometrial proliferation, differentiation, and neovascularization following the treatment.[64]

Endometrial MSCs may have applications beyond reproduction. In addition to regenerative potential in the reproductive system, eMSCs, due to their multipotent mesenchymal properties, have been useful therapies in models of myocardial infarction, stroke, liver disease, acute lung injury, Duchenne

muscular dystrophy, and diabetes through differentiation into mesodermal and ectodermal cell lineages[65] (Figure 1). Human endometrial stromal stem cells have been differentiated into insulin-secreting cells in-vitro. Their resemblance to pancreatic beta cells was confirmed by expression of PAX4, PDX1, and insulin production in response to elevated glucose levels.[66] When these differentiated cells were injected into the kidney capsules of diabetic mice, human insulin was detected in their serum. Within 5 weeks, blood glucose levels were stabilized, and multiple complications associated with diabetes were prevented. This underscores the compelling potential of endometrial stem cells as a robust therapeutic intervention for individuals grappling with diabetes. Similarly, in a murine model of renal ischemia-perfusion injury, eMSC therapy promoted renal tubular regeneration, angiogenesis, and an overall improvement in kidney function.[67] Following the stem cell transplant, serum creatinine levels decreased within 48 hours, and survival was increased compared to controls. Finally, eMSCs hold promise for neurodegenerative disease. Parkinson's disease (PD) is characterized by the gradual loss of dopaminergic neurons in the substantia nigra in the brain, causing motor and non-motor symptoms. Upon intracerebral transplantation into mice, undifferentiated eMSCs successfully migrated to and engrafted in the substantia nigra. These cells spontaneously transformed into dopaminergic neurons, leading to an increase in dopamine concentrations.[68] In a primate model of PD, following intracerebral injection, eMSCs displayed neuron-like morphology and expressed tyrosine hydroxylase (TH), a rate-limiting step in dopamine synthesis. This led to an increased number of TH cells and higher dopamine concentrations on the transplanted side.[68] After homing, these cells were also found to release neurotrophic factors, which expedited the endogenous repair process.

EMSCs have even been found in low numbers in menstrual blood, allowing for a non-invasive source of MSCs. Human menstrual fluid-derived stem cells have been differentiated into beating cardiomyocyte-like cells and demonstrated functional improvement was observed when injected into infarcted zones in the heart using a murine model.[69] EMSCs offer a promising path in the realm of regenerative medicine when dealing with a spectrum of pathologies affecting both reproductive and non-reproductive systems. Their attributes, including easy accessibility, low immunogenicity, minimal immune rejection, multipotency, and high proliferative capacity contribute to their potential therapeutic significance.

While transplanted MSCs have a clear role in regenerative medicine, their signaling to resident cells is also critical to their function. BM-MSCs exert a significant and diverse paracrine influence on endometrial homeostasis through the transfer of specific micro RNAs via exosomes, boosting proliferative and regenerative potential while inhibiting terminal differentiation, thereby facilitating tissue growth and repair.[70] MSC-derived extracellular vesicles (EVs) are promising candidates for cell-free therapies in regenerative medicine due to their stability in extracellular biofluids, high biocompatibility, and minimal toxicity and immunogenicity.[71] Additionally, EVs have the capability to cross the blood-brain barrier, offering an advantage over conventional MSC-based therapies.[70]

Conclusions

Stem cells play a role in female physiological processes including menstruation and pregnancy. Endometrial progenitor stem cells are involved in endometrial regeneration and repair, and their role in regeneration after menstruation seems to be of importance. BM-MSCs are also essential to pregnancy and post-partum repair of the uterus. As we better understand these physiologic processes, we are learning more about defective stem cell recruitment and engraftment in reproductive pathophysiology. BM-MSCs appear to play a role in some reproductive diseases including endometriosis, an understanding of which offers new therapeutic avenues for reducing the impact of this common and debilitating condition. Stem cells also offer therapeutic solutions to many reproductive and non-reproductive pathologies. Early studies exploring the regenerative potential of eMSCs and MSC-derived EVs for the treatment of reproductive diseases including improving pregnancy outcomes or treating infertility, are yielding positive results. BM-MSCs also show promise in reversing pathologies of the uterine endometrial lining in the treatment of infertility and implantation failure. BM-MSCs can even be mobilized by altering the CXCL12/CXCR4 axis, allowing for targeted engraftment of endogenous stem cells to areas of pathology. Further, eMSCs and MSC-derived EVs hold promise for potential treatments for diabetes, kidney disease, PD, and cardiac injury; their ease of collection with minimally invasive techniques makes them the most readily available adult stem cell. Ongoing trials are examining eMSCs' ability to aid women dealing with both multiple reproductive and non-reproductive tract pathologies. As the safety and efficacy of stem cell interventions become clearer, a broader acceptance and integration of this treatment modality into clinical practice will certainly follow.

Conflicts of interest

None declared.

Author contributions

E. Cansu Cevik (Data curation, Writing—original draft). Ramanaiah Mamillapalli (Writing—review & editing). Hugh S. Taylor (Conceptualization, Writing—original draft, Writing—review & editing)

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Data availability

This is a review article and does not contain any original data. No new data were generated or analyzed in the preparation of this manuscript.

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