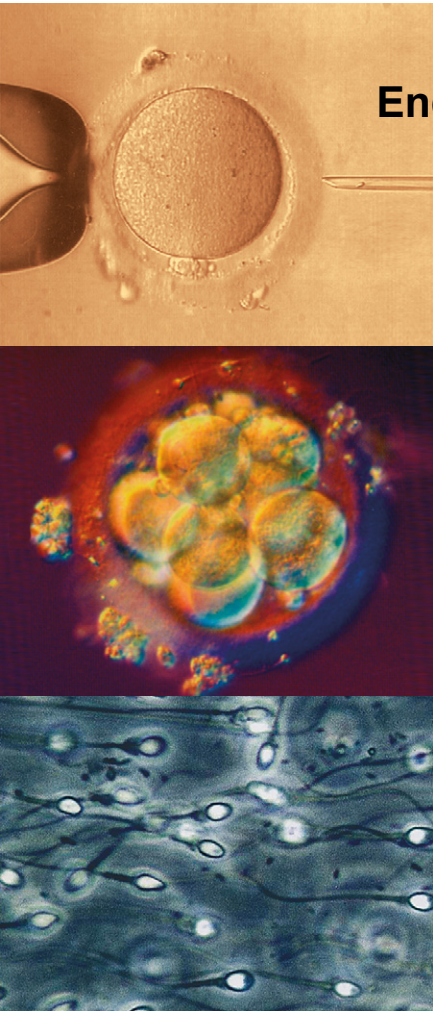


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Endocrine Aspects of Endometrial Stem Cell Function in Reproductive-Age Women

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Endocrine Aspects of Endometrial Stem Cell Function in Reproductive-Age Women

M. Götte, L. Kiesel

Besides the ovary, the endometrium is one of the most prominent fertility-determining tissues in women. Under the cyclic influence of gonadotropins and steroid hormones, the endometrium is characterized by an enormous regenerative capacity during the female reproductive period. Current evidence suggests that adult stem cells contribute to endometrial regeneration. These cells are characterized by defined stemness-associated marker gene expression patterns, high proliferative potential, long-term culturing properties, and multilineage differentiation potential. Whereas a dysregulated endometrial stem cell function has been linked to the pathogenesis of endometriosis, the therapeutic application of stem cells derived from menstrual blood or transcervical biopsies holds some promise for the therapy of fertility-associated conditions such as Asherman's syndrome. While the release of endothelial progenitor cells into the circulation is influenced by menstrual-cycle-dependent changes in steroid hormone levels, steroid-receptor negative tissue-resident endometrial stem cells appear to be indirectly stimulated by hormone-receptor positive cells within the endometrial stem cell niche. **J Reproduktionsmed**

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■ The Human Endometrium – Portrait of a Highly Regenerative Tissue

Apart from the ovary, the endometrium plays a pivotal role in human reproduction. Histologically, the inner lining of the uterus is composed of endometrial glands, a supportive stroma populated by diverse leukocyte subpopulations, characteristic blood vessels and lymphoid aggregates. Under the influence of cyclic hormonal changes, the endometrium presents as a highly regenerative tissue in reproductive-age women [1]. Following shedding of the functional layer during menstruation, regenerative processes originating in the basal layer allow for growth of the endometrium from 0.5–1 mm to 5–7 mm in thickness during one menstrual cycle [2]. The progesterone-dominated luteal phase of the cycle is characterized by transformation of endometrial glands into a secretory state, and by formation of spiral arteries, serving to prepare the decidualized endometrium for embryo implantation [3]. Increasing evidence suggests that the tremendous regenerative capacity of the human endometrium is based on the activity of adult stem cells [4]. Stem cells are undifferentiated cells showing the ability to self-renew and to generate differentiated daughter cells via the process of asymmetric cell division. In contrast to embryonic stem cells (ES cells) and induced pluripotent stem cells

(iPS cells), which are pluripotent (i.e. capable of differentiating into cells of all three germ layers), adult stem cells are either multipotent, i.e. capable of differentiating into multiple cell types of a given lineage, or unipotent, thus generating only one differentiated cell type [4–7]. Upon asymmetric division, the adult stem cell generates more differentiated, so-called committed progenitor cells, which display comparably high proliferation rates. Progressive acquisition of differentiation markers by these cells ultimately leads to the generation of terminally differentiated cells, such as glandular epithelial cells, endometrial stroma cells or endothelial cells [8]. The existence of a putative endometrial stem cell activity has been postulated already in the 1940s, based on the observation of regeneration of functional endometrial tissue after complete endometrial ablation in nonhuman primates and humans [9–11]. Additional indirect evidence was provided by kinetic studies on replacement of differentiated endometrial cells both in glands and stroma (reviewed in [4]), investigations of altered methylation patterns in endometrial glands [12], and by demonstration of a clonal origin of these glands based on markers such as X-chromosome inactivation pattern of the androgen receptor gene and PTEN null mutations [13, 14]. The ability of hysterectomy-derived endometrial stroma and epithelial cells to form colonies when plated at clonal density in cell cul-

ture was first demonstrated by Caroline Gargett's group, suggesting a stem cell activity both in the endometrial stroma and in endometrial glands [15, 16]. The colony-forming potential of endometrial stroma-derived putative stem cells could later be demonstrated in endometrial tissue derived from minimally invasive transcervical biopsies [17].

■ Characteristics of Endometrial Stem Cells

Apart from the indirect evidence reported in the previous section, the expression of marker genes is widely used to phenotypically characterize adult stem cells, as these cells have no easily recognizable morphological characteristics. Specific combinations of marker genes and proteins can be detected by flow cytometric analysis [18], conventional PCR or real-time PCR-based technologies, enzyme activity assays (e.g. for telomerase) and immunostainings. Compared to most adult tissues, increased expression and activity of the stemness-associated enzyme telomerase, which ensures the unlimited proliferation potential of stem cells, has been detected in the human endometrium [19, 20]. In addition, cells showing the side population phenotype, a surrogate marker of stemness, could be detected in the endometrium [21, 22]. These cells can be analyzed by flow cytometry, based on their ability to exclude the fluorescent

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dye Hoechst 33343 as a result of increased expression levels of multidrug resistance proteins in stem cells [18]. According to a study by Masuda et al. [23], about 2% of the endometrium show the side population phenotype. Endometrial side population cells are telomerase-positive [24] and express a variety of stem cell markers. Among numerous publications describing stemness-associated marker expression for endometrium-derived putative stem cells, two general characteristics emerge:

1. Endometrial stem cells apparently express a panel of markers which are mainly typical for mesenchymal stem cells [25], CD105 (endoglin), CD90, CD73 (ecto-5'-nucleotidase), CD44 (the hyaluronan receptor [26], and CD29 (integrin β 1), in addition to CD146 (MCAM) and CD140b (PDGFR β) [17, 22–24, 27]. Moreover, they do not express leukocyte markers such as CD45. While some studies have also detected vascular progenitor cell markers such as CD31, CD34 and KDR in endometrial stem cell populations [22, 23], the majority of studies has failed to detect these markers, which may be attributable to different isolation and characterization protocols.
2. In addition to mesenchymal stem cell-like markers, endometrial stem cells apparently express markers of pluripotency, including Oct4, Sox2, nanog and KLF4 [24, 28, 29]. Notably, differentiated somatic cell such as fibroblasts can be converted into a pluripotent state via transduction with these factors [7, 30], thus generating iPS cells. The high expression levels of these pluripotency markers compared to other adult tissues is considered the underlying cause for the finding that endometrium-derived cells are more amenable to reprogramming into iPS cells compared to skin fibroblasts [31]. Finally, components of the stemness-associated notch- [20] and wnt-signaling pathways [32] have been identified as possible endometrial stem cell determinants.

Besides clonality and expression of characteristic marker profiles, additional criteria have been defined for adult stem cells [25]. For example, in vitro, endometrium- and menstrual

blood-derived stem cells show a high proliferative potential [15–17, 27], and long-term culturing properties [17, 27, 33, 34] in the absence of chromosomal aberrations. Perhaps the most relevant functional characteristic of adult stem cells is their multilineage differentiation potential. Clonal endometrial stem cell cultures have been differentiated into smooth muscle cells, adipocytes, chondrocytes, and osteoblasts [17, 27, 35], whereas endometrial side population cells could be differentiated into adipocytes and osteocytes [24, 36], as well as endometrial gland (CD9+)- and stroma (CD13+)-like cells [21]. Furthermore, the in vitro-differentiation into a variety of therapeutically relevant cell types such as cardiomyocytes [37], dopaminergic-neuron-like cells [38] and insulin-producing cells [39, 40] has been successfully achieved. In addition to the demonstration of a multilineage differentiation potential of endometrial stem cells in vitro, their capability to generate endometrial tissue in vivo has been shown in several studies. Cervello et al. [24], for example, were able to generate endometrial-like tissue by injecting human endometrial side population cell lines into the kidney capsule of immunodeficient mice. Moreover, a study by Taylor [41] on bone marrow-transplantations between allogeneic donors and recipients demonstrated that bone-marrow derived stem cells from HLA-mismatched donors could regenerate endometrial tissue in the recipient, a finding that was later corroborated in two studies using the Y-chromosome as a marker for the donor [42, 43]. The finding that bone-marrow-derived cells may be responsible for endometrial regenerative processes raises the question of the source and location of endometrial stem cells. As the endometrial basal layer is not shed during menstruation, it was postulated quite early that this endometrial layer harbours endometrial stem cells [10, 44]. This concept is intuitively appealing, and is supported by several findings, including zonal differences in endometrial cell proliferation (reviewed in [4]), preferential expression of components of the notch- and wnt-signaling pathways in the basal vs the functional layer of the endo-

metrium [20, 32]. Nevertheless, endometrial stem cell activity has also been demonstrated in the functional layer of the endometrium, as evidenced by the demonstration of mesenchymal-like stem cells obtained by transcervical biopsy [17], isolation of endometrial side population cells derived from Pipelle biopsies [24] and by the isolation of endometrial stem cells from menstrual blood [33, 34, 37], with important implications both for diagnostic and clinical use of these cells (see [17] and [45] for discussion).

■ Dysregulated Stem Cell Function in Endometriosis

Endometriosis presents as a steroid hormone-dependent benign disease characterized by the ectopic growth of endometrium-like glands and stroma outside the uterine cavity [46–48]. Endometriosis is frequently associated with a severe and chronic suffering accompanied by pelvic or abdominal pain, dysmenorrhoea or dyspareunia [47, 48], and has a measurable impact on endometrial receptivity: It is estimated that 6–10% of women in general and 35–50% of women with pelvic pain or infertility suffer from endometriosis [47, 49]. While the etiology of endometriosis is still enigmatic, it is noteworthy that the major current concepts for its pathogenesis would be in accordance with a dysregulated endometrial stem cell function: Following the widely accepted classical concept of implantation of endometrial tissue fragments into ectopic locations after retrograde menstruation [46], one could imagine that a displacement of menstrual-blood-derived endometrial stem cells [33, 37] would facilitate the growth of ectopic lesions based on the unlimited proliferative potential and high developmental plasticity of these cells. Dysregulated developmental processes caused by aberrant stem cell function would be conform to the concept of coelomic metaplasia, which states that coelomic tissue could be transformed into endometrium in the presence of external stimuli such as a proinflammatory environment [50, 51]. Moreover, endometrial stem cells could be ectopically distributed via the process of lymphovascular metastasis [52], a postulated contributing factor to en-

dometriosis. Finally, an aberrant distribution or function of hematopoietic precursor cells including natural killer cell progenitors, endothelial progenitor cells, or neuronal stem cells may have a profound effect on several endometriosis-associated processes, including altered inflammation, angiogenesis, and neurogenesis [6, 27, 53–55]. Keeping these considerations in mind, it is not surprising that a dysregulated expression and distribution of endometrial stem cell markers has been observed in endometriosis. For example, the number of putative stem cells expressing the adult stem cell marker Musashi-1 (Msi1), a regulator of the stemness-associated notch pathway is increased in endometriotic tissue compared to normal secretory endometrium [20]. Similarly, differential expression of the pluripotency markers Sox2 [29], Oct4 [56], and of the transcription factor SALL4 [57] has been reported in endometriosis. In line with these findings, Chan et al. [58] demonstrated that cell clones derived from ovarian endometrioma contain a subset of cells with somatic stem cell properties, including multilineage differentiation potential and expression of the stemness-associated markers SALL4, CD133, and Musashi-1. Further support for a stem cell involvement is provided by the outcome of *in vivo* experiments in animal models. The ability of endometrial side population cells to generate endometrial tissue in mouse models [23, 24] is a clear sign of their developmental plasticity, with the potential to differentiate into ectopic endometrial lesions. Of note, compared to endometrial mesenchymal stem cells isolated from eutopic endometrium, cells from ectopic endometrial lesions showed greater cell migration and invasion capacity *in vitro* and in an immunodeficient mouse model, where increased angiogenesis was additionally observed [59]. An angiogenesis-promoting effect and increased vascular endothelial progenitor cell numbers were also observed in two additional animal models of endometriosis; a study demonstrating that endothelial progenitor cells contribute to the vascularization of endometriotic lesions [60] and an independent study showing up-regulation of circulating endothelial progenitor cells in a mouse model of endometriosis [61]. In summary, these findings demonstrate at least a partial contribution of stem cells to the patho-

genesis of endometriosis, as an underlying cause of reduced fertility in women. Future studies need to address the full diagnostic potential of studying aberrant endometrial stem cell marker expression in large patient collectives [20, 29], as well as exploring the therapeutic concept of inducing differentiation of pathologically altered endometrial stem cells [62].

■ Endocrine Aspects of Endometrial Stem Cell Function

The endometrium of reproductive-age women is constantly regenerated during successive menstrual cycles. The menstrual cycle is characterized by steadily increasing levels of the gonadotropins follicle-stimulating hormone and luteinizing hormone, resulting in increased ovarian production and release of the steroid hormone estrogen [1]. Peak levels of these hormones trigger ovulation and formation of the corpus luteum, which produces progesterone, thus steering the endometrial changes during the luteal phase. In the absence of fertilization, degeneration of the corpus luteum and the associated drop in progesterone and estrogen levels trigger menstruation. There are some indications that changes in the endocrine milieu during the menstrual cycle affect en-

dometrial stem cell function. Several studies have demonstrated that endothelial progenitor cell numbers are affected by the menstrual cycle. Lemieux et al. [63] could demonstrate that several circulating CD133+ endothelial progenitor cell populations fluctuate throughout the cycle synchronously with circulating 17 β -estradiol levels, and that maturation towards advanced CD144+ endothelial progenitor cell subpopulations was reduced at the mid-luteal phase. Additional studies have revealed an attenuation of a glucose-induced increase in circulating CD133+ endothelial progenitor cells in amenorrhoeic patients [64], and a significantly higher amount of Lin-/7AAD-/CD34+/CD133+/KDR+ circulating endothelial progenitor cells in women with regular menstrual cycles compared to menopausal women [65]. Apart from the hormone-dependent release of circulating endothelial progenitor cells, a menstrual-cycle-dependent fluctuation of adult progenitor cell numbers has been observed within endometrial tissue. For example, our group could demonstrate significantly increased numbers of putative endometrial stem cell populations characterized by Msi1 [20] and Sox2 [29] expression in the proliferative compared to the secretory phase of the menstrual cycle, consistent with the proliferative effect of estradiol in the preovulatory phase. In

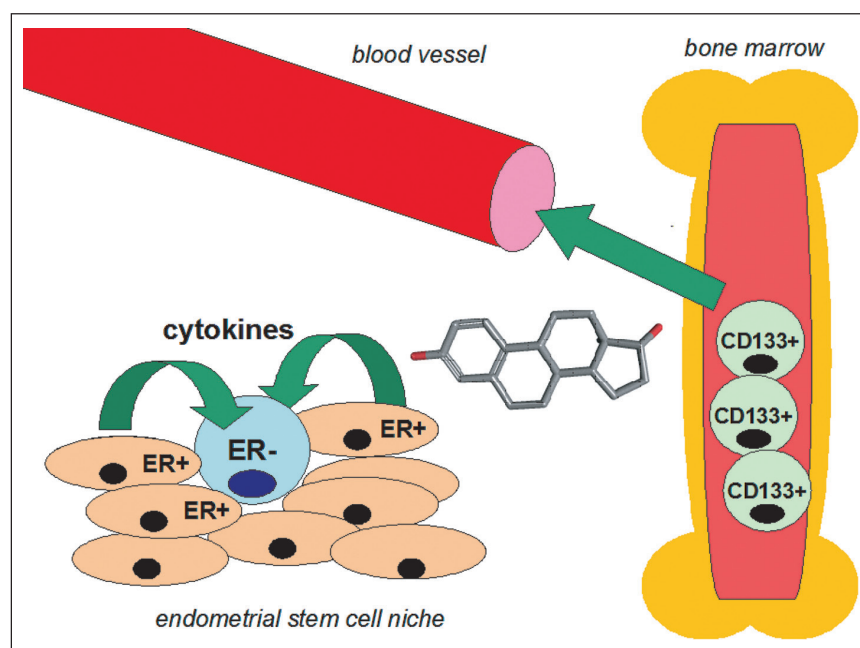


Figure 1. Effects of estrogen on adult stem cell recruitment. Estrogen stimulates cytokine secretion by ER+ cells within the endometrial stem cell niche, leading to an activation of ER- endometrial stem cells (lower left panel). In addition, estrogen modulates the release of bone-marrow-derived CD133+ endothelial progenitor cells into the circulation (right panel). See text for details.

addition, endometrial telomerase activity varies during the menstrual cycle [66]: Telomerase activity was found to be high during the proliferative phase but to be inhibited during the mid-secretory phase. Interestingly, telomerase expression coincided with the rise and fall of progesterone levels and the time period of maximal uterine receptivity for embryo implantation. Finally, it was demonstrated that estrogen, but not progesterone promoted endometrial recruitment of side population cells in a mouse model of LPS-induced endometrial injury, whereas ovariectomy abolished side population recruitment [67]. While these data suggest a clear endocrine influence on adult stem cell activity in the endometrium, a report by Caroline Gargett's group on label-retaining putative stem cells in the murine endometrium suggested that glandular endometrial stem cells may lack expression of estrogen receptor, whereas a small proportion of stromal label-retaining cells expressed estrogen receptor [68]. These findings were in accordance with their previous observation of a lack of variations in endometrial cell clonogenicity from the proliferative to the secretory stage of the menstrual cycle [16]. Additional experiments in a mouse model supported their hypothesis that estrogen receptor-negative endometrial stem cells may be activated by neighbouring estrogen receptor-positive cells residing in the stem cell niche, which may secrete cytokines upon estrogen stimulation. The stem cell niche is an anatomical microenvironment which either keeps stem cells in an undifferentiated state, or triggers asymmetric cell division and differentiation dependent on cues from neighbouring cells and the extracellular matrix [69]. In an extension of their previous work [68], estrogen-stimulated endometrial growth was studied in prepubertal and cycling mice subjected to a pulsed estrogen and BrdU injection in ovariectomised animals [70]. Proliferating and mitotic epithelial label-retaining putative stem cells were detected eight hours after estrogen treatment, whereas all epithelial label-retaining cells in cycling mice proliferated within two hours, in spite of a lack of estrogen receptor expression. The concept of an indirect steroid-dependent stimulation of endometrial stem cells, as developed in this mouse system, is supported by recent findings in human en-

dometrial stem cells: Schüring et al. [17] demonstrated a downregulation of ER α and ER β , but not of progesterone receptor expression upon serial cloning of endometrial stroma cells – an experimental technique used for enrichment of endometrial progenitor cells. Furthermore, Cervello et al. [24] demonstrated a lack of ER α and progesterone receptor expression in endometrial side population-derived cells. In summary, Gargett's model of a niche-dependent indirect stimulation of endometrial stem cells by steroid hormones allows to integrate seemingly contradictory data on their endocrine regulation during the menstrual cycle (Fig. 1).

■ Therapeutic Potential of Endometrial Stem Cells

In contrast to ES and iPS cells, which harbour the potential risk of teratoma formation, and which are in part subject to ethical concerns [7], adult stem cells have been identified as an attractive source of regenerative therapies for a variety of diseases. In fact, endometrial and menstrual-blood derived stem cells have been successfully applied in a variety of experimental models of human disease. Therapeutic concepts include the direct application of purified endometrial or menstrual stem cells, or an *in vitro* predifferentiation of these cells into a desired therapeutic cell type aimed at replacing diseased or damaged tissue. Prominent examples of preclinical therapeutic applications include a protective function of endometrial stem cells in rodent models of myocardial infarction [37], stroke [71], Duchenne muscular dystrophy [72], critical limb ischemia [73], Parkinson's disease [38] and type 1 diabetes [39, 40]. Pilot studies in patients affected by multiple sclerosis indicate that therapeutic application of menstrual-blood derived stem cells appears to be safe [74] and potentially beneficial. Of note, the NIHs public database ClinicalTrials.org lists several announced (and partially recruiting) clinical trials aimed at testing the safety and therapeutic efficacy of endometrium- or menstrual blood-derived adult stem cells, including trials addressing endometriosis, type 1 diabetes, critical limb ischemia and liver cirrhosis. This development is clearly very encouraging and can be expected to lay down the groundwork for the treatment of patients suffer-

ing from infertility or subfertility. In this context, gaining a deeper knowledge on the involvement of stem cells in the pathogenesis of endometriosis will be one pivotal aspect. An additional perspective concerns the potential use of stem cells for the generation of uterine and endometrial tissue. For example, Cervello et al. [24] have proposed that endometrial stem cells capable of regenerating endometrial tissue could be used to regenerate endometrium in patients suffering from Asherman's syndrome, a disease characterized by complete obliteration of the uterine cavity with adhesions resulting in amenorrhea and infertility [75]. A recent case report on endometrial regeneration using autologous adult stem cells followed by conception by *in vitro* fertilization in a patient of severe Asherman's syndrome has gained considerable attention and seemed to provide proof-of-concept [76]. However, this study has also raised several questions concerning the nature of the transplanted cells and the putative activation of endogenous endometrial progenitor cells induced by the curettage procedure (see [77] for discussion). Clearly, additional, carefully designed studies are required to assess the full therapeutic potential of adult stem cells for infertility treatment.

■ Relevancy to Practice

- A dysregulated function of endometrial stem cells may contribute to the pathogenesis of endometriosis, potentially contributing to endocrine therapy resistance.
- Endometrial and menstrual-blood-derived stem cells may be a therapeutic cell source for the Asherman's syndrome in the near future.
- Induced differentiation of dysregulated endometrial stem cells may be a future therapeutic approach for endometriosis.

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■ Conflict of Interest

No potential conflict of interest to this article was reported.

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