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Review Article

Research on Recent Progress in the Treatment of Thin Endometrium

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Abstract

Objective: The endometrium is an important part of the uterus. The human endometrium is a complex and dynamic tissue that goes through phases of growth and regression during any menstrual cycle. In this review, we review the literature on thin endometrium and discuss recent therapeutic tools and recent progress of thin endometrium to inform clinicians on better treatment options.

Methods: We conducted a narrative review aimed at clarifying several treatments (granulocyte colony-stimulating factor, sildenafil, low-dose aspirin, stem cell therapy, acupuncture, and physical therapy) in treating thin endometrium.

Results: Several treatments have been developed, such as granulocyte colony-stimulating factor, sildenafil, low-dose aspirin, stem cell therapy, acupuncture and physical therapy, among others. Overall, some of the newer therapies, including granulocyte colony-stimulating factor and stem cell therapy, may enjoy many advantages over conventional therapies.

Conclusions: There is still room for improvement in these therapies and much research is needed to maximize the potential of emerging new therapies. Finally, as the feasibility of acupuncture and physical therapy for thin endometrium is proven, these therapies should likewise receive adequate attention.

Keywords: Thin Endometrium; Stem cells; Granulocyte colony-stimulating factor; Acupuncture treatment; Physical therapy.

Introduction

Successful implantation of the embryo requires appropriate embryonic development and also requires that the mother has a well-conditioned endometrium. In humans, the uterus becomes receptive to implantation in the mid-luteal phase of the menstrual cycle, which is often referred to as the window of implantation. Implantation is a complex process that is subject to complex molecular regulatory mechanisms such as hormones, growth factors and cytokines (Figure 1). The initial step of the implantation process is the apposition and contact of the blastocyst with the endometrial epithelium, followed by the invasive activity of trophoblast cells between the epithelial cells. It has been reported in the literature that inadequate tolerance of the uterus will lead to about half of the implantations are abnormal and pregnancy failure [1-3]. Although assisted reproductive technologies have helped humans overcome most infertility problems, successful embryo implantation remains an important step for successful in vitro fertilization.

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The endometrium is composed of two cellular components, namely surface epithelial cells and mesenchymal cells. The endometrium is not stable and unchanging, but is a dynamic tissue that undergoes several changes during the menstrual cycle including morphological histology, biochemistry and molecular biology, which are essential elements for a successful embryo implantation process. Estrogen and progesterone stimulate the endometrium, with estrogen causing proliferation and thickening of the endometrium, and progesterone causing secretory changes, metaplasia, puffiness and thickening of the endometrium. Together, these two hormones promote the growth of the endometrium and induce differentiation of endometrial mesenchymal cells into metaphase, which ultimately provides an acceptable site for implantation of the blastocyst.

In assisted reproductive techniques, the development of the mother's endometrium is usually observed by transvaginal ultrasound. An accepted marker of uterine capacitance is the thickness of the endometrium [4]. For successful embryo transfer, the recommended minimum endometrial thickness is 7 mm, even though there is no standard value for diagnosing a thin endometrium [5]. In addition, higher implantation rates can be achieved with endometrial thicknesses greater than 9 mm. In contrast, a persistently thinner endometrium may be associated with a lower rate of implantation as well as a higher rate of miscarriage [6]. Therefore, many researchers around the world have tried to find some treatments that can improve endometrial tolerance and endometrial thickness. Although several treatments have been tried clinically (granulocyte colony-stimulating factor, sildenafil, low-dose aspirin, stem cell therapy, acupuncture, and physical therapy), clinical outcomes have been inconclusive. In this review, we review the literature on thin endometrium and discuss recent therapeutic tools and recent progress of thin endometrium to inform clinicians on better treatment options.

Granulocyte colony-stimulating factor (G-CSF)

G-CSF is a hematopoietic growth factor, a factor that has positive effects on non-hematopoietic cells, including the endometrium [7]. In a prospective cohort study conducted by Gleicher et al. in 2011, the authors' team used G-CSF for transvaginal endometrial perfusion to treat thin endometrium. The results showed that four patients previously resistant to estrogen and vasodilator therapy had successful endometrial expansion to a minimum thickness of at least 7 mm after uterine perfusion with G-CSF, suggesting that intrauterine G-CSF may have a direct role in promoting endometrial growth [8]. A preliminary cohort study [9] showed an increase in endometrial thickness from 6.4 mm to 9.3 mm ($P < 0.001$) at an interval of 5.2 days between G-CSF infusion and embryo transfer. The mean change was 2.9 mm and did not change between conception and non-conception cycles. This is sufficient to demonstrate the utility of G-CSF in the treatment of chronic thin endometrium and that this treatment would result in a good overall clinical pregnancy rate (19.1%). Lucena et al[10] found that uterine infusion of G-CSF rapidly increased the thickness of the endometrium, thus ensuring a higher chance of successful pregnancy and a healthy birth rate of the baby. These results suggest that G-CSF is a factor involved in endometrial remodeling, which enhances the synchronization between the uterine environment and embryonic development.

Li et al [11] evaluated the effectiveness of G-CSF in a frozen embryo transfer program for infertile women with thin endometrium. The G-CSF group had a higher rate of induced cycles and a lower rate of natural cycles compared to the control group and showed a trend towards better implantation and clinical pregnancy rates. Similarly, Kunicki et al. reached similar conclusions [12]. Kunicki's team did a follow-up visit of 37 subjects with thin and unresponsive endometrium on the day of ovulation triggering. In all subjects, endometrial thickness was 6.74 mm beofre G-CSF infusion and increased significantly to 8.42 mm after infusion [12]. In another non-randomized interventional clinical trial, Eftekhar et al [13] compared the effects of in utero G-CSF treatment and direct embryo transfer in patients with endometrium (<7 mm). All patients were treated with oral estradiol and transvaginal sildenafil and on day 12 or 13, patients in the G-CSF group would receive intrauterine G-CSF therapy. While this study failed to demonstrate the potential of G-CSF to improve endometrial thickness, G-CSF treatment has the potential to improve clinical pregnancy rates in infertile women with thin endometrium in frozen-thaw embryo transfer cycles. Tehraninejad et al [14] performed intrauterine G-CSF infusion in 15 patients who underwent embryo transfer and were cancelled due to thin endometrium. The endometrial thickness of these patients increased from 3.59 mm to 7.120 mm with a clinical pregnancy rate of 20%.

However, negative results were also obtained by some research teams. Barad et al [15] conducted a randomized parallel double-blind controlled clinical trial to determine whether G-CSG affects endometrial thickness, implantation rate and clinical pregnancy rate. The results showed no statistically significant difference in increased endometrial thickness between the G-CSF group and the control group. However, this study was obtained in an older patient population, so they may not necessarily be applicable to younger women. In another prospective study, Miralaei et al [16] found a significant change in endometrial thickness after G-CSF treatment ($p<0.001$); however, nine patients (45%) did not reach an endometrial thickness of 7 mm and therefore the embryo transfer was cancelled. The above evidence allows people to know that although intrauterine infusion of G-CSF has a potential role in increasing endometrial thickness in patients, the rate of transfer failure remains high and events of poor pregnancy outcome are observed.

In 2016, Lee and his team explored the efficacy of intrauterine infusion of G-CSF in infertile women with thin endometrium on trigger day or the day of egg retrieval [17]. The overall clinical pregnancy rate was 22.0%, the implantation rate was 15.9%, and the ongoing pregnancy rate was 20%. Interestingly, there was a trend towards higher implantation, clinical pregnancy rates and sustained pregnancy rates with G-CSF infusion on the trigger day [17]. This provides a clinical rationale for the timing of intrauterine G-CSF infusion.

Stem cell therapy

Among many types of cellular therapies, stem cell therapy is considered to be an effective treatment [18]. Stem cells are capable of differentiating into pluripotent stem cells, and several studies have been conducted to enumerate the advantages and disadvantages associated with stem cell therapy [19]. A recent review published in the journal Cell in 2021 writes that stem

cells are now increasingly considered as promising alternative therapies for translational research in regenerative medicine. Considering the less ethical issues and easy access to abundant resources, induced pluripotent stem cells and mesenchymal stem cells have been extensively studied within the field of infertility to understand their potential applications in reproductive medicine.

Similar to most treatments, stem cell therapy can come with side effects. For example, before stem cells are used, they are harvested from embryos and cultured for several months. When stem cells are harvested from the adult body, especially from the bone marrow, it can put the patient through many painful procedures. In addition, stem cell therapy has the potential to cause a certain percentage of rejection [20].

Mesenchymal stem cells

MSCs are adult stem cells that can be obtained from a variety of tissues, including bone marrow, umbilical cords, menstrual blood, endometrial tissue, and adipose tissue. Given their ability to self-renew and differentiate, MSCs are considered by some studies to be the most attractive cell therapy candidates in regenerative medicine [21]. This property can reflect the origin of the tissue, as MSCs isolated from different tissues show different sensitivities to inducible bioactive molecules in the culture medium. A well-known example is adult bone marrow-derived MSCs, which are often used as the standard type of MSCs. The conditions of induction of bone marrow-derived MSCs differ from those of adipose-derived MSCs, which may be attributed to the existence of a different microenvironment in the vascular system where the cells are located [22]. In addition, several in vitro experiments have demonstrated the excellent in vitro regenerative potential of MSCs. The protective role played by bone marrow MSCs after allogeneic transplantation has been reported in several models of injury, such as damaged nerve, myocardium, liver, cartilage and bone tissue, among others [23].

It is currently believed that the therapeutic effects of MSCs are mainly due to their immunomodulatory function, which is associated with anti-inflammatory effects through the regulation of the adaptive and innate immune system lymphocytes. In addition, MSCs have been shown to modulate the immune response in a variety of diseases [24]. Besides, MSCs are able to regulate T cell function and proliferation, balance Th2 and Th1 activity, upregulate Tregs function, inhibit B and NK cell function, and prevent dendritic cell activation and maturation [25]. Additionally, MSCs stimulate the proliferation and cytokine secretion of innate lymph-like cells, a new family of lymph-like cells that play an important role in innate defense against pathogens.

The effectiveness of MSCs in treating thin endometrium has also been confirmed by several studies. Zhao et al [26] established a rat model of thin endometrium by injecting ethanol into the uterine cavity in order to investigate whether direct transplantation of MSCs into the uterine cavity could improve endometrial thickness. The results showed that the endometrium of rats in the intrauterine cavity transplanted with MSCs group was significantly thickened, and the expression of cytokeratin, wave protein, integrin αγβ3 and leukemia inhibitory factor was higher than that of the control group. The expression of some pro-inflammatory cytokines such as tumor necrosis factor and interleukin 1 was significantly downregulated, while the expression of anti-inflammatory cytokines such as basic fibroblast growth factor and interleukin 6 was significantly upregulated. The authors concluded that uterine perfusion of MSCs represents a promising new therapeutic tool to address the currently intractable problem of endometrial thinning. In another study, Jing and his team explored whether bone marrow MSC treatment could promote endometrial regeneration and improve endometrial tolerance [27]. They implemented a randomized controlled animal study in which bone marrow MSC transplantation was performed by tail vein injection. The results showed that the endometrium of the experimental group was significantly thickened and the expression of cytokeratin, wave protein, integrin αγβ3, and leukemia inhibitory factor was significantly enhanced compared to the control group. The above evidence could suggest that MSCs are beneficial to thin endometrium, which may act through the migration and immunomodulation of MSCs.

Mesenchymal stem cell-derived extracellular vesicles (MSC-EVS)

Recent studies have also focused on the study of exosomes secreted by mesenchymal stem cells. Exosomes are active paracrine components with a high potential to repair damaged tissues. Exosomes include many paracrine factors responsible for regeneration and angiogenesis [28]. MSC-EVS is a lipid bilayer complex that acts as a mediator by transferring multiple molecules (e.g., proteins, microRNAs, lipids, and cytokines) to the recipient cells. The basic mechanisms of action of MSC-EVS have been agreed upon and include promotion of angiogenesis, antifibrosis, immunomodulation and anti-oxidative stress levels.

However, many issues need to be fully substantiated before MSC-EVS can be used in the clinic, including standardized purification and identification methods, suitable storage and transport systems, large-scale production facilities, and safety issues. In addition, limited yield is one of the major issues limiting the widespread use of MSC-EVS. Overall, MSC-EVS shows great potential in regenerative medicine compared to MSCs, not only because it is derived from parent cells, but also because it has higher biological stability and lower immunogenicity [29].

Human amniotic epithelial cells (hAECs)

As a potential source of stem cells, hAECs are isolated from the amniotic membrane, which is in contact with amniotic fluid and is the layer of tissue closest to the fetus. Many studies have reported the immunomodulatory effects of hAECs on acquired immune cells and innate immune cells. In addition, hAECs can differentiate into many cells of mesodermal and ectodermal origin, including neuronal cells, pancreatic cells, hepatocytes, adipocytes, cardiomyocytes and myocytes. Besides, hAECs are able to inhibit the proliferation of B cells and suppress the migration and proliferation of neutrophils and macrophages [30]. Additionally, hAECs inhibited the activation of CD4+ T cells and reduced the production of pro-inflammatory cytokines by CD4+ T cells. According to the literature, hAECs significantly enhance proliferating cell nuclear antigen (PCNA), which is essential for accurate DNA replication [31]. Punyadeera et al [32] analyzed the mRNA expression levels of all known vascular endothelial growth factor ligands and receptors in human endometrium collected during the menstrual and proliferative phases of the menstrual cycle. The results showed that PCNA was most abundant in both epithelial and mesenchymal tissues in the proliferative phase. However, the expression of hAECs was reduced in the endometrium of mice during the secretory phase, suggesting that hAECs may have a role in promoting endometrial proliferation. Vascular endothelial growth factor was mainly ex-

pressed during the proliferative and menstrual phases, which is associated with the maintenance and formation of micro vessels and the reconstruction of endometrial tissue.

Chen et al [33] verified that intrauterine adhesion release combined with hormone replacement therapy significantly increased endometrial vascular endothelial growth factor expression and microvascular density in patients with severe uterine adhesions. Besides, patients with better outcome did have more VEGF expression and denser microvasculature compared to those with poor treatment response. hAECs were found to increase VEGF expression in a model of intrauterine adhesions by Zhou et al [34], suggesting that hAECs have the potential to promote angiogenesis in the injured endometrium. The estrogen receptor, a nuclear transcription factor, binds to estrogen to promote endometrial cell proliferation and metabolism. In one study, umbilical cord-derived mesenchymal stromal cells were loaded onto a collagen scaffold and transplanted into the uterine cavity after a uterine adhesion separation procedure [35]. 3 months later after surgery, patients had an increase in mean maximum endometrial thickness and a decrease in uterine adhesion scores compared to pre-treatment. Histological studies showed upregulated levels of estrogen receptor, wave protein and vascular hemophilia factor expression, suggesting improved endometrial proliferation, differentiation and neovascularization after treatment. Another study came to a similar conclusion that hAECs significantly improved the uterine architecture after uterine adhesions. hAECs treatment resulted in thickened endometrium, increased number of endometrial glands, and reduced fibrosis, which in turn produced more micro vessels. Expression levels of vascular endothelial growth factor, PCNA and estrogen receptor were increased in hAECs-treated endometrium, indicating improved angiogenesis and stromal cell proliferation. Finally, hAECs also increased pregnancy outcome, pregnancy rate and fetal number in mice with uterine adhesions [36].

Acupuncture and physical therapy

Acupuncture is a representative of traditional Chinese medicine and has accumulated much clinical experience in the treatment of gynecologic infertility. For thin endometrium, acupuncture therapy has shown the same great potential for clinical application. Acupuncture is an important part of traditional Chinese medicine, which applies mechanical stimulation through the use of needles at specific acupuncture points, thereby regulating the body's functions.

Several studies have shown that acupuncture treatment for patients can effectively improve the clinical pregnancy rate and increase ovarian-uterine blood perfusion at embryo implantation [37]. Performing transcutaneous acupoint electrical stimulation during the pre-implantation phase can promote increased expression of endometrial angiogenesis and stromal cell proliferation-related factors, resulting in a significant improvement in endometrial tolerance [38]. Mechanistic studies have shown that progesterone levels were significantly increased after transcutaneous acupoint electrical stimulation treatment, and integrin family proteins and leukemia inhibitory factors were significantly increased and positively correlated with the increase in progesterone. Li Yu et al. randomly divided 90 patients who failed to conceive due to unexplained endometrial dysplasia into two groups. The experimental group was treated with transcutaneous electrical acupoint stimulation from the 5th day of menstruation, supported by progesterone after ovulation and embryo transfer three days after ovulation; the control group was given conventional estradiol valerate and progesterone support. The results showed that the pre-transfer thickness and endometrial type improved significantly in the experimental group compared with the control group. Among the subendometrial blood flow parameters, the resistance index and fluctuation index of the experimental group were significantly lower than those of the control group, and the difference was statistically significant ($P<0.05$). In terms of clinical pregnancy rate, the experimental group was higher than the control group, and the difference was statistically significant.

Zhang et al [39] evaluated the effect of transcutaneous electrical acupoint stimulation on pregnancy rates in women. This was a prospective, randomized, single-blind placebo-controlled clinical trial that included patients who underwent cryopreserved embryo transfer or fresh cycle in vitro fertilization with or without intracytoplasmic single sperm injection. The results showed that one day before transplantation, administration of transcutaneous electrical stimulation of acupuncture points for 30 min increased clinical pregnancy rate by 13%, and administration of 2 transcutaneous electrical stimulation of acupuncture points 1 day before transplantation and 2 times after transplantation increased clinical pregnancy rate by 20%. Low-frequency electrical stimulation at 2 Hz was superior to high-frequency electrical stimulation at 100 Hz, and acupuncture points on the abdominal dorsum (Gui Lai, Zi Gong, Guan Yuan, and Shen Yu) were more beneficial than acupuncture points on the extremities (Xue Hai, Di Ji, Zu San Li, and Tai Xi) in terms of fertility and clinical pregnancy rate [39]. Meng Qingyu et al [40] observed the effect of electroacupuncture combined with bone marrow mesenchymal stem cell injection on estrogen and progesterone receptors in thin endometrium of rats. The results showed that the uterine coefficient and the expression of Ki67, estrogen receptor, and progesterone receptor were significantly higher in the electroacupuncture combined with bone marrow MSC injection group compared with the control group, and this effect was superior to that of bone marrow MSC injection alone. Similar conclusions were reached by You et al. who found that high-frequency electroacupuncture was effective in improving blastocyst implantation in rats with impaired endometrial tolerance. High-frequency electroacupuncture significantly increased endometrial thickness and number of pinnae. This effect may be achieved by enhancing the LIF/STAT3 signaling pathway in rats [41]. The above evidence demonstrates that acupuncture therapy promotes endometrial growth, improves endometrial tolerance, and ultimately promotes embryo implantation and clinical pregnancy.

Several physical therapies including pulsed electromagnetic fields and massage have also had a positive impact on improving endometrial tolerance and increasing endometrial thickness. Merhi Z et al. combined transcutaneous ozone therapy with pulsed electromagnetic field therapy to treat patients with thin endometrium. The results showed that ozone with pulsed EMF therapy had vasodilatory, anti-inflammatory and antioxidant effects and successfully improved endometrial lining thickness in all patients, with two-thirds of patients becoming pregnant after single embryo transfer [42]. Yang et al. investigated the effect of pelvic floor neuromuscular electrical stimulation therapy in improving endometrial thickness. The mean endometrial thickness before and after the treatment group was 5.60 mm and 7.93 mm, respectively, compared with 5.50 mm and 6.78 mm in the control group, with statistically significant differences, so neuromuscular electrical stimulation therapy may be effective in patients with thin endometrium [43]. Electro-ultrasound is

a new type of physical therapy currently available, which combines transcutaneous acupoint electrical stimulation technique, pelvic floor neuromuscular electrical stimulation technique and acupoint ultrasound technique. Acupuncture point ultrasound is a new acupuncture technique that uses the technique of ultrasound to simulate acupuncture to achieve a non-invasive acupuncture effect. Zhang et al. [44] 2021 studied 80 patients with thin endometrial infertility, in which 40 patients in the control group were treated with estradiol valerate and 40 patients in the observation group were treated with estradiol valerate in combination with electro-ultrasound. The results indicated that the endometrial thickness, morphology and volume improved in both groups, and the difference was more obvious in the observation group (P<0.05). After treatment, the uterine artery resistance index (RI) and type I flow ratio were significantly reduced and type III flow ratio was significantly increased in the observation group, and the endometrial and subendometrial vascularization index (VI), blood flow index (FI) and vascularized flow index (VFI) were significantly improved in the observation group, and the differences were statistically significant (P<0.001). The clinical pregnancy rate in the observation group was higher than that in the control group, and the difference was statistically significant (P<0.01). In addition, a study found that pelvic floor muscle massage can effectively improve the clinical pregnancy rate. The mechanism is to induce muscle contraction, increase intra-abdominal pressure, accelerate pelvic blood flow, reduce uterine artery blood flow resistance, and increase subendometrial blood flow and perfusion, which improves the thickness and structure of the endometrium and improves the active function and hormone levels of the uterus and ovaries [45].

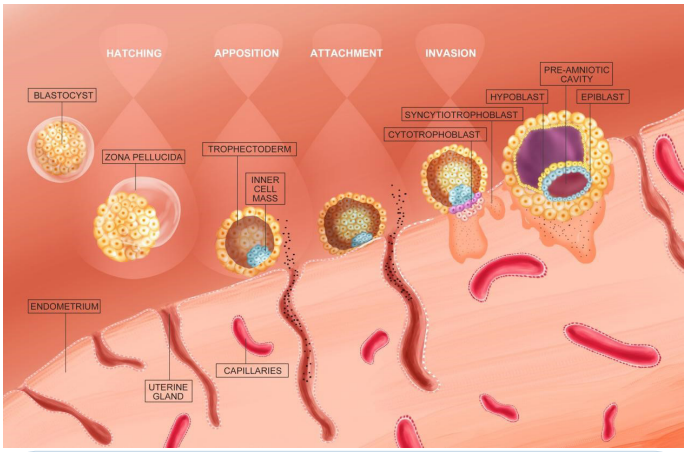

Figure 1: Embryo implantation process under normal physiological conditions.

Conclusion

As a global disease, infertility affects a large number of women and is both a social and a medical problem. Given the important role of the endometrium in maternal health and reproduction, it is crucial to maintain its physiological structure, eliminate its defects and promptly recover after damage. Several treatments have been developed, such as granulocyte colony-stimulating factor, sildenafil, low-dose aspirin, stem cell therapy, acupuncture and physical therapy, among others. Overall, some of the newer therapies, including granulocyte colony-stimulating factor and stem cell therapy, may enjoy many advantages over conventional therapies. However, there is still room for improvement in these therapies and much research is needed to maximize the potential of emerging new therapies. Finally, as the feasibility of acupuncture and physical therapy for thin endometrium is proven, these therapies should likewise receive adequate attention.

Declarations

Authors' contributions: XT and KN wrote this manuscript; XT prepared all the figures improved the language of the manuscript; KN conceived the structure and revised the manuscript; all authors read and approved the final manuscript.

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