

# *Research Advances in New Therapies for Thin Endometrium*

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**Abstract:** Human assisted reproduction techniques are becoming increasingly sophisticated, but clinical observations suggest that patients with thin endometrium have poor clinical pregnancy outcomes. A variety of treatments have been reported in the literature, but the results remain unsatisfactory. New therapies include granulocyte colony-stimulating factor and regenerative medicine. Granulocyte colony-stimulating factor (G-CSF), a novel measure used in recent years to repair the endometrium and improve endometrial tolerance, was first reported in 2012 for the treatment of thin endometrium. Stem cells have the ability to infinitely self-renew and proliferate and differentiate into multiple cell types that can be targeted and induced into endometrial cells, and the current advantages of stem cell transplantation therapy are two fold: firstly, it can improve the endometrial thickness of thin endometrium, and secondly, it can improve endometrial tolerance, which has great promise and potential for application in the treatment of thin endometrium.

## 1. Introduction

The thickness of the endometrium plays an important role in assisted reproductive technology. The main function of the endometrium is to provide a place for the embryo to adhere and a source of nutrients[1].It has been shown that the probability of developing a thin endometrium in an assisted reproduction cycle is approximately 2.4%[2], with a lower live birth rate and pregnancy rate in this group of patients.Thin endometrium is defined as a thickness of the endometrium that is below the threshold thickness that enables successful embryo implantation[3],however, there are no clinically agreed diagnostic criteria for thickness cut-offs,It has been shown that the endometrial thickness in the mid-luteal phase is  $\leq 7$  mm,the pregnancy rates have decreased [4], and studies have used an endometrial thickness of  $\leq 8$  mm as the standard diagnosis for a thin endometrium [5].Endometrial receptivity (ER) refers to a combination of states in which the endometrium is receptive to embryonic implantation [6],i.e. the ability to allow embryos to position, adhere and invade in the uterine cavity,the thickness of the endometrium is also an important reference indicator of tolerability [7].A thin endometrium is one in which the effectiveness of estrogen and

progesterone decreases during the normal menstrual cycle, preventing adequate proliferation and conversion to a secretory phase, and where reduced tolerance prevents embryo implantation and development, which seriously affects the reproductive and psychological health of patients, and in vitro fertilisation-embryo transfer (IVF-ET) is one of the most difficult clinical problems to solve. This is why it is important to investigate the causes of thin endometrium while pursuing more effective treatment options. This paper proposes to review the treatment strategies for thin endometrium with new therapies in the hope of providing direction and ideas for clinical work.

## **2. Etiology of thin Endometrium**

The cause of thin endometrium has not been clarified in modern medicine. Studies have shown that the causes of thin endometrium formation are mainly related to age, medication, infection and uterine manipulation.

### **2.1 The Age Factor**

The age factor is an independent factor contributing to thinning of the endometrium. Some studies have shown that a thin endometrium is more common in women of advanced age. It has also been shown [8] that as women age, the blood flow to the endometrium slows and the receptors for oestrogen and progesterone decrease, the DNA content in the stromal cells is significantly reduced, but the collagen content is increased, ultimately leading to a reduction in the thickness of the endometrium. Bazyuta et al. showed [9] that the thickness of the endometrium was negatively correlated with age. This is due to the fact that in elderly patients, the bioactive substances that regulate immune function are gradually reduced, limiting the proliferation and differentiation of endometrial cells.

### **2.2 Medication Factors**

Long-term use of compounded oral contraceptives can lead to a thinning of the endometrium. Kodama et al [10] showed a decrease in endometrial thickness from 7 mm to 3.9 mm after taking oral contraceptives for more than 5 years, due to prolonged exposure to progesterone, which reduces the endometrial response to oestrogen [11], further leading to the development of a thin endometrium in a low-responsive uterus. It has also been shown that ovulation drugs and protocols can affect the development and reduce the thickness of the endometrium. The effect of letrozole or clomiphene on endometrial thickness is reduced by affecting oestrogen synthesis or anti-oestrogen action, and the effect of long, antagonist and short ovulation regimens on endometrial thickness deepens in that order [12], which may be related to the absence of competitive antagonism of oestrogen receptors by ovulation-promoting drugs or, in some studies, by affecting mitotic cell division to the detriment of endometrial proliferation [13].

### **2.3 Infection Factors**

Uterine infections include bacterial infections, mycoplasma infections, chlamydia, and pelvic tuberculosis (genital tuberculosis, GTB), all of which can occur in the endometrium [14] and all of which can damage the adhesions of the basal layer of the endometrium, causing difficulties in regeneration of the endometrium. As the condition persists leading to ulceration of the endometrium and even necrotic tissue, scarring of the endometrial tissue can affect the endometrial blood supply and cell proliferation, resulting in a thin endometrium and even infertility.

## 2.4 Uterine Operations

During various uterine operations such as curettage, endometrial ablation, diagnostic curettage, hysteroscopic removal of endometrial polyps and myomectomy, excessive force or fragile endometrial tissues can damage the endometrial basal layer and reduce endometrial tolerance, resulting in endometrial thinning and cavity adhesions. Chen Y et al [15] found by electron microscopy that mechanically damaged endometrium and mitochondria of endometrial cells showed hypoxic changes and atresia of interstitial microvascular necrosis, which affected embryo implantation and development and eventually led to female infertility.

## 2.5 Thin Endometrium of Unknown Origin

Clinical observations suggest that not all patients with a thin endometrium have physiological or pathological risk factors, and that hysteroscopy shows a normal uterine cavity without adhesions or scarring, but only a thin endometrium. In these patients, a decrease in coronary RI, an upregulation of VEGF expression and a significant improvement in endometrial thickness were observed after administration of drugs to improve endometrial blood flow, suggesting that reduced endometrial blood flow is a factor in unexplained endometrial thinning [16]. Yuan et al. [17] explored the etiology of idiopathic thin endometrium from a molecular biology perspective, and investigated the relationship between thin endometrium and estrogen receptor  $\alpha$  (ER $\alpha$ ) gene polymorphisms, the expression of ER $\alpha$  was lower in the thin endometrium group compared to the control group, thus suggesting that one of the causes of unexplained thin endometrium may be related to genetic polymorphisms of ER $\alpha$ .

## 3. New Therapeutic Treatments

### 3.1 Granulocyte Colony-Stimulating Factor

Granulocyte colony-stimulating factor (G-CSF) is a proliferative factor for bone marrow haematopoietic cells that promotes cell proliferation and differentiation, and it is presumed to be used to promote endometrial growth because of the large number of G-CSF mRNAs and their receptors on the surface of the endometrium [18]. Zhao et al [19] demonstrated that G-CSF promotes targeted differentiation of stem cells at the site of injury and repair of endometrial cells as well as regeneration, induces high expression of cytokeratin and vitamins, and thus improves the thickness of thin endometrium. In 2011, Gleicher et al [20] used G-CSF for the first time to treat infertile patients with thin endometrium and successfully achieved pregnancy, and then expanded the sample size for a pilot study, the study reaffirms the proliferative effect of G-CSF on thin endometrium, the mean endometrial thickness increased from  $(6.4 \pm 1.4)$  mm to  $(9.3 \pm 2.1)$  mm before treatment ( $P < 0.001$ ), with a mean endometrial growth of  $(2.9 \pm 2.0)$  mm, and obtained a 19.1% continuation of pregnancy rate [21]. Li et al [22] found that G-CSF treatment increased embryo implantation rates and clinical pregnancy rates. The use of G-CSF in the treatment of thin endometrium offers a new direction, but the study of its appropriate regimen needs to be further refined and confirmed.

### 3.2 Regenerative Medicine

Stem cells are a class of cells with undifferentiated and pluripotent properties that are now used in the treatment of neurological disorders. Bone marrow stem cells include haematopoietic stem cells and mesenchymal stem cells (BMSCs). Du et al [23] found that uterine ischaemia/reperfusion

injury leads to an increase in the number of BMSCs in the endometrium, which can differentiate into endothelial epithelial and mesenchymal cells and participate in the repair of the endometrium after injury. Zhao et al [24] injected BMSCs into the uterine cavity of SD rats with thin endometrium and found that the rat endometrium was thickened, presumably because BMSCs could differentiate directly into endometrial cells or through uterine regulation of immune-related cytokines that could stimulate endometrial cell proliferation. Markers of endometrial tolerance were detected after transplantation of BMSCs, indicating that stem cell infusion not only increased the regenerative capacity of the endometrium but also improved endometrial tolerance, creating conditions for embryo implantation.

Human umbilical cord-derived MSCs (UC-MSCs) have the characteristics of self-renewal, multidirectional differentiation, short proliferation time and low immunogenicity, which can promote endometrial cell damage repair, improve endometrial function, reduce endometrial scar formation and facilitate embryo implantation and pregnancy, It is now the seed cell of choice for transplantation [25]. He Sang et al [26] showed that human umbilical cord MSCs improve endometrial tolerance through induction and immunomodulatory properties. Zhang et al[27] showed that collagen scaffold/human umbilical cord MSCs facilitate endometrial proliferation and angiogenesis, enhance endometrial response to estrogen and progesterone, and are a promising and promising method for the treatment of unresponsive thin endometrium caused by Asherman syndrome[28].

Menstrual blood-derived stem cells (MenSCs) are novel mesenchymal stem cells obtained from female menstrual blood that express the stemness marker OCT-4 and stage-specific surface antigen 3/4 (SSEA-3/4)[29] and are widely used in basic research because of their multidirectional differentiation, high proliferation, simplicity and easy accessibility. Wang Hongyan [30] et al. showed that compared with the model group, the endometrial thickness of rats in the MenSCs group and the estrogen group increased significantly, while the endometrium of rats in the MenSCs group was thicker, suggesting that MenSCs transplantation also had a better therapeutic effect on thin endometrium. However, the effect of MenSCs transplantation on the function of thin endometrium has not yet been clearly elucidated, and it is thought that there may be several mechanisms: ① Mesenchymal stem cells have a differentiation and implantation role. In cases of endometrial injury, MSCs can migrate through the body circulation to the site of endometrial injury to help repair the endometrium by regulating inflammation at the site of injury, and their differentiation potential can also induce thin endometrial stem cells to differentiate into endometrium-like cells for self-repair [31,32]; ② Mesenchymal stem cells have paracrine functions and can secrete protective cytokines, such as vascular endothelial growth factor and insulin-like growth factor, which can induce cell proliferation and angiogenesis to improve endometrial function and reduce endometrial damage [33].

At present, research into the value of stem cell therapy in thin endometrium is still in the exploratory stage and requires extensive experimental validation and research due to the multi-differentiation potential and the powerful proliferative capacity of stem cells, which may have adverse effects on the organism.

#### 4. Conclusion

Thin endometrium is still an unsolved problem in the field of reproduction and is an important factor in clinical pregnancy rates. In recent years, granulocyte colony-stimulating factor and regenerative medicine have gained the attention of clinicians and are now new ideas in the treatment of thin endometrium, with new therapeutic treatments focusing on a wide range of applications for damaged endometrium.

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