



Stem cells and thin endometrium

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Definition of thin endometrium

- ▶ It is apparent that an endometrial thickness <6 mm is associated with a trend toward lower probability of pregnancy.
- ▶ Miwa demonstrated that thin endometrial were characterized by poor growth of glandular epithelium, high uterine blood flow impedance, decreased vascular endothelial growth factor (VEGF) expression, and poor vascular development.

Miwa et al., 2009

A thin endometrium is seen more often in older women probably because of decreased vascularity.

Thin endometrium and successful pregnancy

- ▶ Physiological angiogenesis does not occur in most organs in the adult. However, endometrium is the site where normal angiogenesis take place, and it is a fundamental process in the menstrual cycle as well as in embryo implantation.
- ▶ On ultrasound endometrial thickness and a trilaminar endometrium on the day of ovulation trigger is associated with an increased probability of pregnancy while a hyperechoic character signals failure.
- ▶ The clinical PR (CPRs) increase and miscarriage rates (MRs) will be decrease with endometrium ≥ 7 and it is marker of endometrial receptivity (ER).

Etiology of thin endometrium

- ▶ Inflammatory causes: Acute or chronic infection can lead to the destruction of the basal layer of the endometrium.
- ▶ Iatrogenic:
 - ▶ -Surgical – repeated or vigorous curettage damages the basal layer of endometrium. Hysteroscopic myomectomy, polypectomy, or laparoscopic myomectomy where the cavity is opened may lead to IU adhesions.
 - Medical – indiscriminate use of drugs such as clomiphene citrate
- ▶ Idiopathic: Thin endometrium may not necessarily be secondary to a disease process. It can result from individual uterine architecture or the intrinsic properties of endometrium that affect its growth.

Dain L et al, Fertil Steril. 2013

MODALITIES TO IMPROVE REFRACTORY ENDOMETRIUM

- * **granulocyte colony-stimulating factor**

G-CSF can increase mesenchymal and hematopoietic stem cells in the bone marrow. G-CSF may stimulate ESCs or mobilize bone marrow stem cells promoting endometrial development

Gargett CE, Ye L ,Fertil Steril. 2012 Jul;

- * **Extended estrogen support**

Chen MJ, J Assist Reprod Genet. 2006

- * **Human chorionic gonadotropin priming in the follicular phase**

Papanikolaou EG, J Assist Reprod Genet. 2013

Drugs that increase endometrial blood flow have been administered individually or in combination to improve Eth

- ▶ Pentoxifylline 800 mg/day and tocopherol 1000 mg/day given over several months and low dose aspirin 75 mg/day. None of these therapies have met with much success.

Acharya S, *Hum Fertil (Camb)* 2009

- ▶ Sildenafil 100 mg/day given as vaginal pessary and L-arginine 6 g/day


Takasaki A, *Fertil Steril.* 2010 Apr; 93(6):1851-8

MISCELLANEOUS TREATMENTS

Occasional reports of IU autologous platelet rich plasma infusion, IU administration of bone marrow stem/progenitor cells, luteal phase support with GnRH agonist, pelvic floor Neuromuscular electrical stimulation for improving Eth are found in literature, but none of the treatments have been substantiated


How does stem cell could resolve thin endometrium

- ▶ Regenerative medicine – numerous research units are working on the use of stem cell therapy for regeneration of the endometrium. So far, it remains a research protocol and has not been cleared for routine clinical use.
- ▶ Endometrial stem cells are present in both the basalis and functional layers of the human endometrium, and it is thought that these stem cells play a role in regenerating the endometrial lining during each estrous cycle.


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- ▶ Non-endometrial stem cells seem to have a role in endometrial regeneration as well; in fact, hematopoietic and non-hematopoietic bone marrow-derived stem cells (BMDSCs) are recruited to the endometrium in response to injury as shown by Taylor and colleagues.


Taylor HS, JAMA. 2004

- ▶ Uterine ischemia/reperfusion injury results in a twofold increase in bone marrow-derived stem cell recruitment to the endometrium, which is independent of G-CSF and only serves in uterine repair after injury rather than monthly cyclic regeneration of the endometrium.


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- ▶ The first human application was in 2011, when a patient with AS and refractory thin endometrium (3.6 mm) was treated with intrauterine autologous endometrial angiogenic stem cells . The infusion was followed by high-dose estradiol valerate, aspirin (75 mg PO daily), and four cycles of cyclical estrogen and progesterone therapy until the EMT reached 7.1 mm. Three donor oocyte embryos were subsequently transferred resulting in a single viable intrauterine pregnancy . Similar findings were noted (2014) in a case series of six patients with refractory AS who were treated with autologous mononuclear stem cells.

Singh N, *J Hum Reprod Sci.* 2014

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- ▶ In a promising early human trial, patients with AS and refractory thin endometrium had significant improvement in their endometrial thickness that lasted up to 6 months after autologous bone marrow-derived stem cells were infused via the uterine arterioles, with excellent pregnancy rates .

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- ▶ Patients with AS and refractory thin endometrium had significant improvement in their endometrial thickness in the Santamaria study , that lasted up to 6 months after autologous bone marrow-derived stem cells were infused via the uterine arterioles, with excellent pregnancy rates .

Santamaria X, *Hum Reprod.* 2016

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- ▶ Stem cell therapy method recently has become a novel procedure for treatment of tissue injury and fibrosis in response to damage. Reducing fibrotic area, an elevated number of glands, stimulated angiogenesis, the enhanced thickness of the endometrium, better formed tissue construction, protected gestation, and improved pregnancy rate.

Thank you

