THIN ENDOMETRIUM IN INFERTILE WOMEN

Dr.Roya Jahanmaedi

Royan institute

Embryo implantation success depends mainly on two conditions:

١) the degree of embryo development

٢)endometrial receptivity (ER).

ER refers to the ability of the endometrium to allow the embryo to contact, localize,and implant at a specific time, referred to as he window of implantation (WOI)

The WOI, when the embryo is most likely to implant days 20–24 of the normal menstrual cycle days 7–10 of the LH peak

Yidi Wang, Zunhao Tang and Xiuxiang Teng New advances in the treatment of thin endometrium٢٠٢٤

TE definition:

- ET≤7mm on HCG day by ultrasonography however, the definition of ‘thin’ varies from ≤6–8mm on HCG day
- ASRM:ET < 7mm on HCG day
- HSHRE:ET<7mm on HCG or day

- Eftekhar, M.; Tabibnejad, N.; Tabatabaie, A.A. The Thin Endometrium in Assisted Reproductive Technology: An Ongoing Challenge. Middle East Fertil. Soc. J. 2018,

- Liu KE, Hartman have found that low EMT is associated with a decrease
- in clinical pregnancy rate (CPR) and live birth (LBR):

- <8mm at fresh embryo transfer
- <7mmat frozen-thawed embryo transfer (FET)

In contrast, LBR increases at fresh embryo transfer, EMT reaches 10–12mm in FET cycles, EMT increases to 7–10mm

Liu KE, Hartman M, Hartman A, Luo ZC, Mahutte N. The impact of a thin endometrial lining on fresh and frozen–thaw IVF outcomes: an analysis of over 40 000 embryo transfers. Hum Reprod. (2018)

ASRM vs ESHRE: Definition and Management of Thin Endometrium

Aspect	ASRM	ESHRE
Definition	< 7 mm on hCG	< 7 mm on hCG
Threshold of Concern	< 6 mm associated with poor outcomes	6-7 mm may warrant cycle cancellation
Considerations	Thickness, pattern, vascularity	Thickness, pattern, vascularity
Preferred Management	Optimize estrogen, consider adjuncts	Stepwise: estrogen → adjuvants → cancellation
Experimental Therapies	PRP, G-CSF, Sildenafil (limited evidence)	PRP, G-CSF, stem cells (case-specific)
Cycle Decision	Cancel if <6 mm after optimization	Cancel if <6–7 mm despite intervention
Personalization	Strong emphasis on individualization	Strong emphasis on tailoring to patient

Prevalence:

TE prevalence increases with age, reaching 25% in natural cycles among women over age 40 years.

TE incidence in infertility treatment cycles (ART) is :2–3% yidi wang 2024

2.4% nalini-mahajan 2016

1-2.5% Kimberly E.2019

Measurment of Endometrial thickness

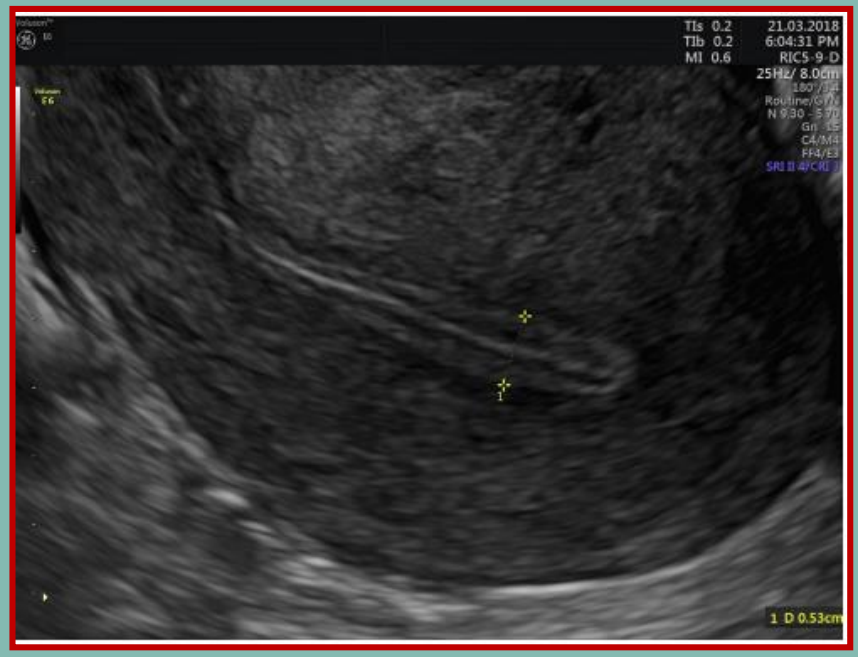
1)trans vaginal sonography (TVS)

2)Sono hystrograohy (SIS)

3)3D sonography

3)MRI

4)Hystroscopy



mafediRetal.Imaging in endometrial Disease /int Jgynecol Obstet 2016

Etiology:

- inflammatory
- medical
- idiopathic
- aging
- Anatomically, acquired uterine abnormalities:
- uterine adhesions
- endometrial polyps
- endometriosis
- fibroids

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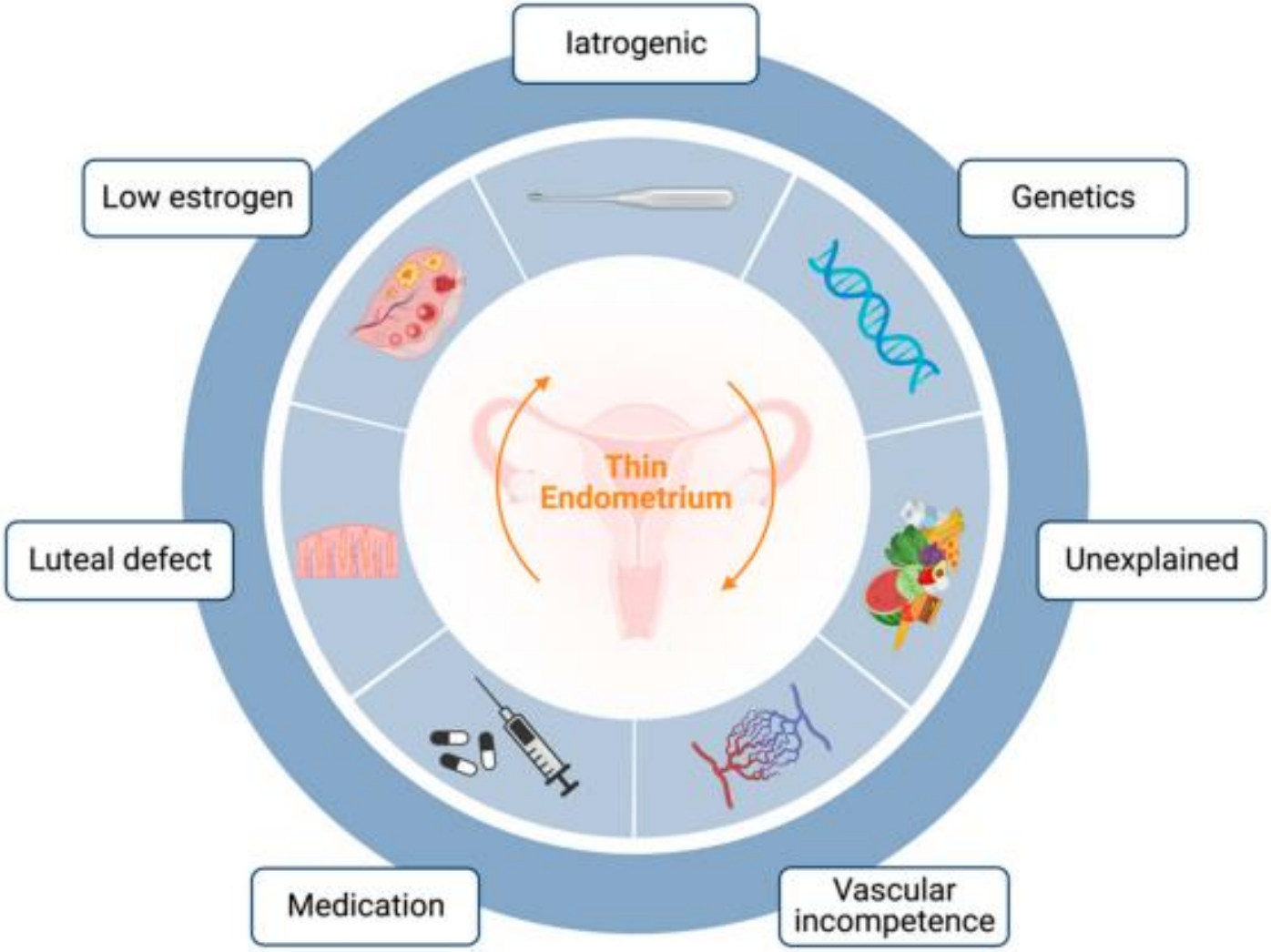

Figure 1. Schematic image of representative etiologies of thin endometrium (created using Biorender).

Yiqun Tang, Caroline Frisendahl Parameswaran Grace LalitkumarReview An Update on Experimental Therapeutic Strategies for Thin Endometrium 2023

complication:

Although the etiologies of endometrial thinning vary, they lead to similar outcomes:

- ✓reduced embryo implantation
- ✓pregnancy rates
- ✓increased miscarriage risks
- ✓intrauterine growth restriction(IUGR)
- ✓low birth weight
- ✓preterm labor
- ✓ hypertensive disorders of pregnancy
- ✓placenta previa,
- ✓ cesarean section

1)Liu X, Wang J,. Thin endometrium is associated with the risk of hypertensive disorders of pregnancy in fresh IVF/ICSIembryo transfer cycles: a retrospective cohort study of 9,266 singletonbirths. Reprod Biol Endocrinol 2021;

2) Mouhayar Y, Obstetrical complications of thin endometrium in assisted reproductive technologies: a systematic review. J Assist Reprod Genet 2019;

study conducted by Miwa et al.
it was found that vascular endothelial growth factor (VEGF) was under expressed in a thin endometrium (<8 mm), leading to poor vascularization of the endometrium and impaired placentation.

Miwa I, Tamura H, Takasaki A, Yamagata Y, Shimamura K, Sugino N. Path-ophysiologic features of "thin" endometrium. Fertil Steril 2009;

Although a thin endometrial lining is not the only factor influencing obstetric and neonatal outcomes in IVF, there is a large body of evidence that suggests that EMT plays a significant role; interventions for increasing EMT should be attempted when a thin endometrium is encountered.

Mouhayar Y, Franasiak JM, Sharara FI. Obstetrical complications of thin endometrium in assisted reproductive technologies: a systematic review. J Assist Reprod Genet 2019;

SYSTEMATIC REVIEW article

Front. Endocrinol., 11 February 2022

Sec. Reproduction

Volume 12 - 2021 |

https://doi.org/10.3389/fendo.2021.814648

This article is part of the Research Topic

Safety and Child Health of Assisted Reproduction Technology (ART)

View all 28 articles >

The Effect of Endometrial Thickness on Pregnancy, Maternal, and Perinatal Outcomes of Women in Fresh Cycles After IVF/ICSI: A Systematic Review and Meta-Analysis

Zhiqi Liao[1]  Chang Liu[2*] Lei Cai[1] Lin Shen[1]

Results:

: A total of 22 pieces of literature were included for the final meta-analysis. A decreased trend towards pregnancy outcomes was observed, such as live birth rate (LBR), clinical pregnancy rate (CPR), and implantation rate (IR) in the thin endometrium groups (EMT <7 mm).

In contrast, thick endometrium (EMT >14 mm) had no effect on pregnancy outcomes compared to medium EMT groups (EMT 7–14 mm). Moreover, thin endometrium (EMT <7.5 mm) enhanced the incidence of hypertensive disorders of pregnancy (HDP) and small-for-gestational-age (SGA) infants, and decreased the Birth weight (BW) of babies

ScienceDirect

Reproductive BioMedicine Online

Volume 40, Issue 1, January 2020, Pages 124-133

Article

Endometrial thickness and IVF cycle outcomes: a meta-analysis

Ge Gao, Xianfeng Cui, Shuang Li, Pan Ding, Shuai Zhang, Yunshan Zhang

Results :

Nine prospective and 21 retrospective studies, including a total of 88,056 cycles, were retrieved. The summary odds ratios indicated that women with lower EMT were associated with lower pregnancy rates than those with higher EMT (n = 30, OR 0.61; 95% CI 0.52 to 0.70; P < 0.001). Moreover, the implantation rate in women with lower EMT was significantly reduced (n = 9, OR 0.49; 95% CI 0.32 to 0.74; P = 0.001). Furthermore, no significant association was found between EMT and the miscarriage rate (n = 12).

In addition, women with lower EMT were associated with reduced live birth or ongoing pregnancy rate (11 studies, OR 0.60; 95% CI 0.48 to 0.73; P < 0.001).

Finally, the incidence of ectopic pregnancy rate between lower and higher EMT showed no statistically significant association (n = 3).

Treatments:

1) Drug therapies

Endocrine therapies

- Estrogen
- Growth hormone
- Human chorionic gonadotropin
- Gonadotropin-releasing hormone agonist
- Tamoxifen

Increased endometrial blood perfusion

- Low-dose aspirin
- Sildenafil citrate
- Botulinum toxin A
- Vitamin E

2) Stem cells and their derivatives

A)MSCs

- BMDMSCs
- MenSCs
- Adipose-derived stem cells and adipose-derived regenerative cells
- UC-MSCs

B)Human embryonic stem cells

C)Extracellular vesicles and exosomes

3) Intrauterine growth factor-granulocyte colony-stimulating factor infusion (GCS –F)

4)Autologous platelet-rich plasma

5)Complementary and alternative therapies

6)surgary

Estrogen

Estrogen secretion increases during the follicular phase of the normal menstrual cycle and binds to estrogen receptors to promote proliferation and regeneration of endometrial epithelial cells (EECs).

Estrogen affects embryo implantation via endometrial estrogen receptor a and cytokines such as leukocyte inhibitory factor (LIF) and IL-6

Shen MS, Wang CW, Chen CH, Tzeng CR. New horizon on successful management for a woman with repeated implantation failure due to unresponsive thin endometrium: Use of extended estrogen supplementation.

The concentration, duration of action, and route of supplementation of estrogen may also be related to endometrial tolerance.

Regarding dosage, patients with TE are not sensitive enough to respond to normal physiologic doses of estrogen because of their relatively low number, and dysfunction, of estrogen receptors

Liu SM, Zhou YZ, Wang HB, Sun ZY, Zhen JR, Shen K, et al. Factors associated with effectiveness of treatment and reproductive outcomes in patients with thin endometrium undergoing estrogen treatment. Chin Med J (Engl). (2015)

Strategy:

The simplest solution is often the best.

- Plan A:

- extend the course of estrogen :
(extending by a week should not have any detrimental effect, and many women will achieve a more optimal thickness by this simple intervention)

Emily A. Jacobs, M.D.,aBrad Van Voorhis, M.D.,b Jennifer F. Kawwass M.D., M.H.C.I., Ph.D. Endometrial thickness: How thin is too thin? Fertility&sterlity 2022

- increase the dose of estrogen administered

- The route of estrogen administration can also be altered, : oral, vaginal, transdermal, or intramuscular formulations

- Plan B:
- end this attempt at endometrial preparation and starting new cycle with changes in the dose and route of estrogen administration from the start.

Emily A. Jacobs, M.D.,aBrad Van Voorhis, M.D.,b Jennifer F. Kawwass M.D., M.H.C.I., Ph.D. Endometrial thickness: How thin is too thin? Fertility&sterlity 2022

❑Plan C:

❑Natural cycle preparation for embryo transfer, which allows for normal endogenous estrogen production, is an option that is gaining favor among ovulatory women

❑ use of gonadotropin stimulation of endogenous estrogen production

❑minimal stimulation cycle with low doses of gonadotropins can reduce the cost to the patient while still achieving adequate EMT to proceed with the transfer

Emily A. Jacobs, M.D.,aBrad Van Voorhis, M.D.,b Jennifer F. Kawwass M.D., M.H.C.I., Ph.D. Endometrial thickness: How thin is too thin? Fertility&sterlity 2022

A prospective randomized controlled study by Yi et al. found similar endometrial growth in patients with uterine adhesions after one cycle of oral estradiol valerate tablets versus transdermal gel treatment after hysteroscopy.

Yi T, Zhang X, Gupta V, Li L, Zhong Q. Transdermal estrogen gel vs oral estrogen after hysteroscopy for intrauterine adhesion separation: A prospective randomized study. Front Endocrinol (Lausanne). (2023)

The highest serum drug concentrations and endometrial proliferation rates are obtained with transvaginal estrogen .

administration, which is recommended after other modes have failed.

Almeida-Francia CC, Keator CS, Mah K, Holden L, Hergert C, Slayden OD.Localization and hormonal regulation of endometrial matrix metalloproteinase-26 in the rhesus macaque. Hum Reprod. (2012)

However, when using estrogen to treat TE, the risk of endometrial pathology remains an important consideration (e.g., endometrial cancer, thrombosis)

These may result from prolonged, high-dose estrogen use, and the endometrium should also be protected by regular progestin use, except for contraindications.

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New advances in the treatment of thin endometrium٢٠٢٤

Growth hormone

GH is a peptide hormone secreted by the pituitary gland, the receptors for which are found on the human endometrium.

✓ mechanisms such as:

✓ increased endometrial blood perfusion
✓ increased expression of genes and proteins associated with endometrial tolerance
✓ induction of insulin growth like factor-1 (IGF-1) production

Hosseini Aghdam S, Ghasemzadeh A, Farzadi L, Hamdi K, Baradaran-Binazir M, Nouri M, et al. Growth hormone: A potential treatment of patients with refractory th endometrium: A clinical trial study. Int J Fertil Steril. (2022)

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Volume 28, Issue 6
November-December 2022

JOURNAL ARTICLE

Administration of growth hormone improves endometrial function in women undergoing *in vitro* fertilization: a systematic review and meta-analysis

FREE

Yujie Shang ✉ , Minghua Wu , Ruohan He , Yuanyuan Ye , Xiumei Sun

Human Reproduction Update, Volume 28, Issue 6, November-December 2022, Pages 838–857, https://doi.org/10.1093/humupd/dmac028

Adjuvant application of GH increase the LBR, CPR, and IR, it also improved EMT. Based on subgroup analysis, a dose- and time-dependent relation between GH combination therapy and CPR was also found. Administration of GH daily from the follicular phase of previous cycle until the hCG trigger with < 5 IU/day led to a thicker endometrium and a greater chance of becoming pregnant,
while 5-10 IU/day or administration from the luteal phase of the previous cycle until the hCG trigger resulted in higher oocyte and embryo quality the optimal recommendation for improving CPR was consistent with that for EMT,rather than for oocytes and embryos

Thus, GH may promote fertility by improving endometrial quality.
(increased EMT& promoted endometrial morphology)

Human chorionic gonadotropin

HCG is a glycoprotein hormone synthesized by gestational trophoblasts and is commonly used as a trigger drug in ovulation promotion.

HCG receptor expression is also present on the endometrium during the endometrial secretory phase.

- maternal–fetal immune tolerance,
- upregulating endometrial thickness
- Improving pregnancy outcomes.

Fogle RH, Li A, Paulson RJ. Modulation of HOXA10 and other markers of endometrial receptivity by age and human chorionic gonadotropin in an endometrial explant model. Fertil Steril. (2010)

Gonadotropin-releasing hormone agonist

After the first application of GnRH-a, it binds to the GnRH receptor in the pituitary gland and instantly stimulates the release of gonadotropins (follicle stimulating hormone and luteinizing hormone) from pituitary cells, resulting in a ‘flare-up’ effect, which raises the serum estrogen level and stimulates the body to produce the cytokines necessary for implantation, hus improving the EMT and increasing endometrial tleraonce

Liu Y, Ma L, Zhu M, M. STROBE-GnRHa pretreatment in frozen-embryo transfer cycles improves clinical outcomes for patients with persistent thin endometrium: A case-control study. Med (Baltimore). (2022)

› Reprod Biomed Online. 2023 Mar;46(3):527-535. doi: 10.1016/j.rbmo.2022.12.003. Epub 2022 Dec 7.

Agonist long protocol improves outcomes of vitrified–warmed embryo transfer in repeatedly thin endometrium

Peiyu Wang [1], Haiyan Yang [1], Zhuo Chen [1], Ya Chen [1], Congcong Jin [1], Rong Yu [1], Jia Lin [1], Qianqian Chen [1], Xuefeng Huang [2]

Affiliations + expand

PMID: 36604214 DOI: 10.1016/j.rbmo.2022.12.003

Results: EMT became significantly greater (7.18 ± 1.14 mm versus 6.13 ± 0.63 mm, $P < 0.001$) using GnRH agonist + HMG compared with previous IOA cycles, but this was not related to serum oestrogen concentrations. A total of 213 cycles after the GnRH agonist + HMG protocol proceeded with FET, showing a significantly increased clinical pregnancy rate, implantation rate and live birth rate compared with those after IOA. (using oral and vaginal oestradiol for more than 21 days (IOA protocol).

Tamoxifen

TMX is a selective estrogen receptor modulator. As an antitumor drug, it has both anti-estrogenic and estrogen-like effects, and plays different roles in different target organs, inhibiting breast tumors while promoting endometrial hyperplasia.

> Front Endocrinol (Lausanne). 2023 Mar 1:14:1102706. doi: 10.3389/fendo.2023.1102706. eCollection 2023.

Hormone replacement therapy alone or in combination with tamoxifen in women with thin endometrium undergoing frozen-thawed embryo transfer: A retrospective study

Qingqing Shi [1 2 3], Chenyang Huang [1 2 3], Jingyu Liu [1 2 3], Yifan Li [1 2 3], Na Kong [1 2 3], Jie Mei [1 2 3], Xiaoyue Shen [1 2 3], Yanxin Sun [1 2 3], Feifei Lu [1 2 3], Haixiang Sun [1 2 3], Guijun Yan [1 2 3]

Affiliations + expand

PMID: 36936160 PMCID: PMC10014925 DOI: 10.3389/fendo.2023.1102706

Combination TMX+hormone replacement therapy (HRT) in patients with infertility with TE (EMT <8mm) increased EMT more than HRT alone however, NO differences in clinical pregnancy outcomes (CPR, embryo IR, early miscarriage rate, LBR)

Publication of Indian Society of Assisted Reproduction
Journal of Human Reproductive Sciences

J Hum Reprod Sci. 2018 Jan-Mar;11(1):34–39. doi: 10.4103/jhrs.JHRS_9_17

Tamoxifen is Better than Low-Dose Clomiphene or Gonadotropins in Women with Thin Endometrium (<7 mm) after Clomiphene in Intrauterine Insemination Cycles: A Prospective Study

Sunita Sharma [1,✉], Geetha Rani [1], Gunja Bose [1], Indranil Saha [1], Sikha Bathwal [1], B N Chakravarty [1]

Clinical studies by Sharma Shave found that TMX somewhat improves EMT and LBR and reduces the likelihood of multiple pregnancies in patients with TE who are treated with clomiphene; however, in patients with polycystic ovary syndrome, the ovulation induction by TMX may be inadequate

It is also clear that current use of TMX in reproduction is beyond its scope of application, and its safety remains unclear

Low-dose aspirin

- Aspirin, a cyclooxygenase inhibitor, does not directly increase EMT, but may improve pregnancy outcomes by improving
- endometrial morphology
- perfusion
- tolerance
- the combination of low-dose aspirin in patients treated with high-dose estrogens may also help reduce the risk of blood clots

INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 45: 1351-1360, 2020

Aspirin inhibits endometrial fibrosis by suppressing the TGF-β1-Smad2/Smad3 pathway in intrauterine adhesions

ZIHUI ZHANG[1,2*], SHUANG LI[1,2*], JIE DENG[1,2], SHAORONG YANG[3], ZIWU XIANG[3], HONGYAN GUO[1], HONGLI XI[1], MING SANG[1] and WEI ZHANG[1]

[1]Department of Obstetrics and Gynaecology, [2]Laboratory of Gynaecological Oncology and Reproductive Health, [3]Department of Pathology, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, Xiangyang, Hubei 441000, P.R. China

Received August 28, 2019; Accepted January 24, 2020

DOI: 10.3892/ijmm.2020.4506

At present, the first-line treatment strategies for IUAs in the clinical practice are hysteroscopic transuterine resection of adhesion and postoperative adjuvant therapy, including oestrogen..

In this study have demonstrated that aspirin combined with estrogen may significantly prevent the postoperative disease recurrence rate, improve endometrial receptivity and improve the conception rate by increasing endometrial blood supply and angiogenesis more effectively.

The TGF-β1-Smad2/Smad3 pathway is one of the important mechanisms involved in endometrial fibrosis. However, whether aspirin can inhibit endometrial fibrosis through the TGF-β1-Smad2/Smad3 pathway to prevent postoperative

Sildenafil citrate

- Sildenafil citrate is a specific phosphodiesterase inhibitor type 5 that enhances the vasodilatory effect of nitric oxide on vascular smooth muscle by preventing cGMP degradation

- mechanism : impedance to high blood flow in uterine arteries.

Li X, Luan T, Zhao C, Zhang M, Dong L, Su Y, et al. Effect of sildenafil citrate on treatment of infertility in women with a thin endometrium: a systematic review and meta-analysis. J Int Med Res. (2020)

Journal of International Medical Research

J Int Med Res. 2020 Nov 12;48(11):0300060520969584. doi: 10.1177/0300060520969584

Effect of sildenafil citrate on treatment of infertility in women with a thin endometrium: a systematic review and meta-analysis

Xin Li [1], Ting Luan [2], Chun Zhao [1], Mianqiu Zhang [1], Li Dong [1], Yan Su [1], Xiufeng Ling [1,✉]

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PMCID: PMC7673063 PMID: 33176524

Nine studies involving 1452 patients were included for analysis in our study. We found that endometrial thickness in patients who received sildenafil citrate was significantly higher thanthat in the control group (placebo or no treatment) (weighted mean difference: 1.22; 95% confidence interval [CI]: 1.07–1.38). and the clinical pregnancy rate (risk ratio:1.31; 95% CI: 1.11–1.53) and biochemical pregnancy rate (risk ratio: 1.45; 95% CI: 1.11–1.89) were significantly higher in the sildenafil citrate group compared with the control group.

Vitamin E

Vitamin E is a fat-soluble vitamin, the hydrolysis product of which is tocopherol, which

1) increases estrogen levels and improves fertility.

.2) antioxidant that acts to limit reactive oxygen species (ROS) during oxidative stress.

3)reduces free radical-induced chromosome damage by inhibiting ROS formation and nucleic acid endonuclease activation

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New advances in the treatment of thin endometrium٢٠٢٤

Pentoxifylline (PTX)

Pentoxifylline (PTX) is a methylxanthine derivative used in the treatment of vascular diseases; it is an antioxidant and promotes vasodilation.

Original Articles

Efficacy of tocopherol and pentoxifylline combined therapy for women undergoing assisted reproductive treatment with poor endometrial development: a retrospective cohort study on 143 patients

Fabien Krief, Cynthia Simon, Rebecca Goldstein, Laura Prat Ellenberg & Nathalie Ledee

Pages 367-375 | Received 14 Aug 2018, Accepted 07 Jul 2019, Published online: 10 Oct 2019

In a retrospective study of 143 patients with EMT <7mm and repeated implantation failures, combination tocoherpol and PTX treatment (for at least 2 months)significantly improved endometrial volume (EV) thresholds and EMT

2) Stem cells and their derivatives

A)MSCs

- BMDMSCs
- MenSCs
- Adipose-derived stem cells and adipose-derived regenerative cells
- UC-MSCs

B)Human embryonic stem cells

C)Extracellular vesicles and exosomes

➢BMDMSCs: bone marrow-derived MSC

- ➢Novel option for patients with Asherman syndrome and recalcitrant TE
- ➢ requires bone marrow biopsy and subsequent cell sorting
- ➢Interventional radiation to gain small uterine artery access
- ➢this treatment expensive and potentially harmful.
- ➢The differentiation ability of BMDMSCs is also related to patient age
- ➢research is needed to guide clinical practice and potential applications of this therapy.

Chen, H.; Liu, O.; Chen, S.; Zhou, Y. Aging and Mesenchymal Stem Cells: Therapeutic Opportunities and Challenges in the Older Group. Gerontology 2022,

MenSCs menstrual-derived stem cell

- MenSCs have multi-directional differentiation abilities.
- noninvasive process of obtaining them
- The limitation of this approach is mainly related to difficulty with implementation among amenorrheic women. (Tan, J.; Li, P.2016)

Adipose-derived stem cells(ADSCs)

- ADSCs can be obtained and isolated from subcutaneous adipose tissue (e.g., from human thighs, abdominal wall).
- ADSCs have the ability of multidirectional differentiation,
- thry are relatively available and easy to obtain,
- have high proliferative activity in in vitro cultures
- Despite the additional cosmetic effects of liposuction, the overall cost of this treatment remains high
- its clinical efficacy has not yet to be validated in trials with larger samples

Mazini, L.; Rochette, L.; Amine, M.; Malka, G. Regenerative Capacity of Adipose Derived Stem Cells (ADSCs), Comparison with Mesenchymal Stem Cells (MSCs). Int. J. Mol. Sci. 2019,

UC-MSCs umbilical cord-derived MSCs

UC-MSCs are derived from discarded neonatal umbilical cord tissue, which are :

their low immunogenicity(undetectable HLA class I expression: without the need for immunosuppression

- ❑ short proliferation cycle
- ❑ long survival time.
- ❑painless collection procedure

Christodoulou, I.; Goulielmaki, M.; Devetzi, M.; Panagiotidis, M.; Koliakos, G.; Zoumpourlis, V. Mesenchymal Stem Cells in Preclinical Cancer Cytotherapy: A Systematic Review. Stem Cell Res. Ther. 2018,

Extracellular vesicles and exosomes

EVs are membrane-bound vesicles found in biological fluids, which carry and transfer regulatory molecules such as microRNA and proteins, and may mediate intercellular communication between cells and tissues

EVs, they can be divided into three categories:

Exo	40-60nm
microvesicles (MVs)	100-1000 nm
apoptotic bodies.	1~5mm

Jin X, Xin L, Zhang S. Effect of extracellular vesicles on improving endometrial receptivity and the research status. Chin J Pract Gynecology Obstetrics. (2022)

EVs are produced in different tissues or cells such as endometrium ,decidua, embryos, semen, and fallopian tubes during implantation windows

Current stem cell therapy limitations include the

- ❑abovementioned immune problems
- ❑ ethical issues
- ❑tumorigenicity
- ❑ the low retention rate of stem cells at the transplant site caused by the shape of the uterus.

. He C, Zheng S, Luo Y, Wang B. Exosome theranostics: biology and translational medicine. Theranostics. (2018)

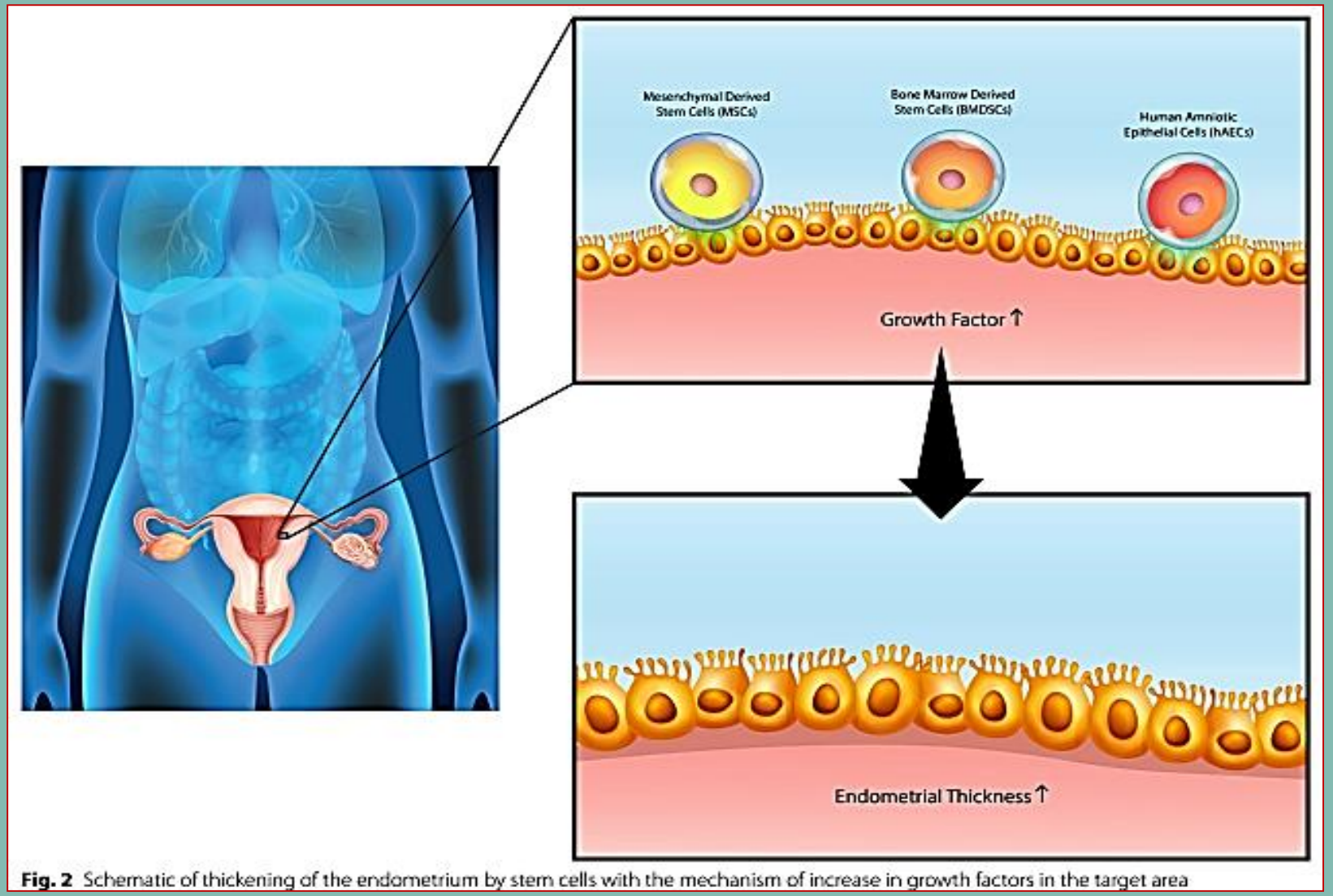

Fig. 2 Schematic of thickening of the endometrium by stem cells with the mechanism of increase in growth factors in the target area

SYSTEMATIC REVIEW article

Front. Immunol., 04 July 2022

Sec. Immunological Tolerance and Regulation

Volume 13 - 2022 | https://doi.org/10.3389/fimmu.2022.899666

Clinical Evaluation of Autologous and Allogeneic Stem Cell Therapy for Intrauterine Adhesions: A Systematic Review and Meta-Analysis

Jia-ming Chen[1] Qiao-yi Huang[1] Wei-hong Chen[1] Shu Lin[2,3*]

Results:

Our search returned 154 reports, 10 of which met the inclusion criteria, representing 116 patients. Of these, 44 patients in two studies were treated with allogeneic stem cells and 72 patients in eight studies were treated with autologous stem cells.. Endometrial thickness increased more after autologous stem cell IUA treatment and the pregnancy rate was also improved No obvious and serious adverse reactions were observed during stem cell therapy in either group.

Reference	Cell Source	Study Design	Administration Protocol	Control Group (n)	Intervention Group (n)	Outcome
Zhang et al., 2021	UC-MSCs	Self-controlld Prospective study	Asuspension of(2 mL) UC-MSCs oncollagen scaffolds, transplanted into the uterinecavity	/	16	Average EMT Increased 3/15 CP, 2/3 LB
Lee et al., 2020	Autologous adipose-derived cells	Prospective Case series	Transcervical instillationof autologous AD-SVFfrom adipose tissue	/	6	EMT increased; resume of menstruation in2/5 patients,1/5 pregnancies after EMT

Reference	Cell Source	Study Design	Administration Protocol	Control Group (n)	Intervention Group (n)	Outcome
Sudoma et al., 2019	Autologous ADSCs	Prospective case series	subendometrial injection every 5–7days 3 times	/	25	EMT increased; 13/25 pregnancies, 9/25 live births
Tan et al., 2016	Autologous MenSCs	Prospective case series	Instillation of 0.5 mL MenSCs suspension on cd16	/	7	EMT increased; 2/4 CP; one spontaneous pregnancy after MenSCs transplantation

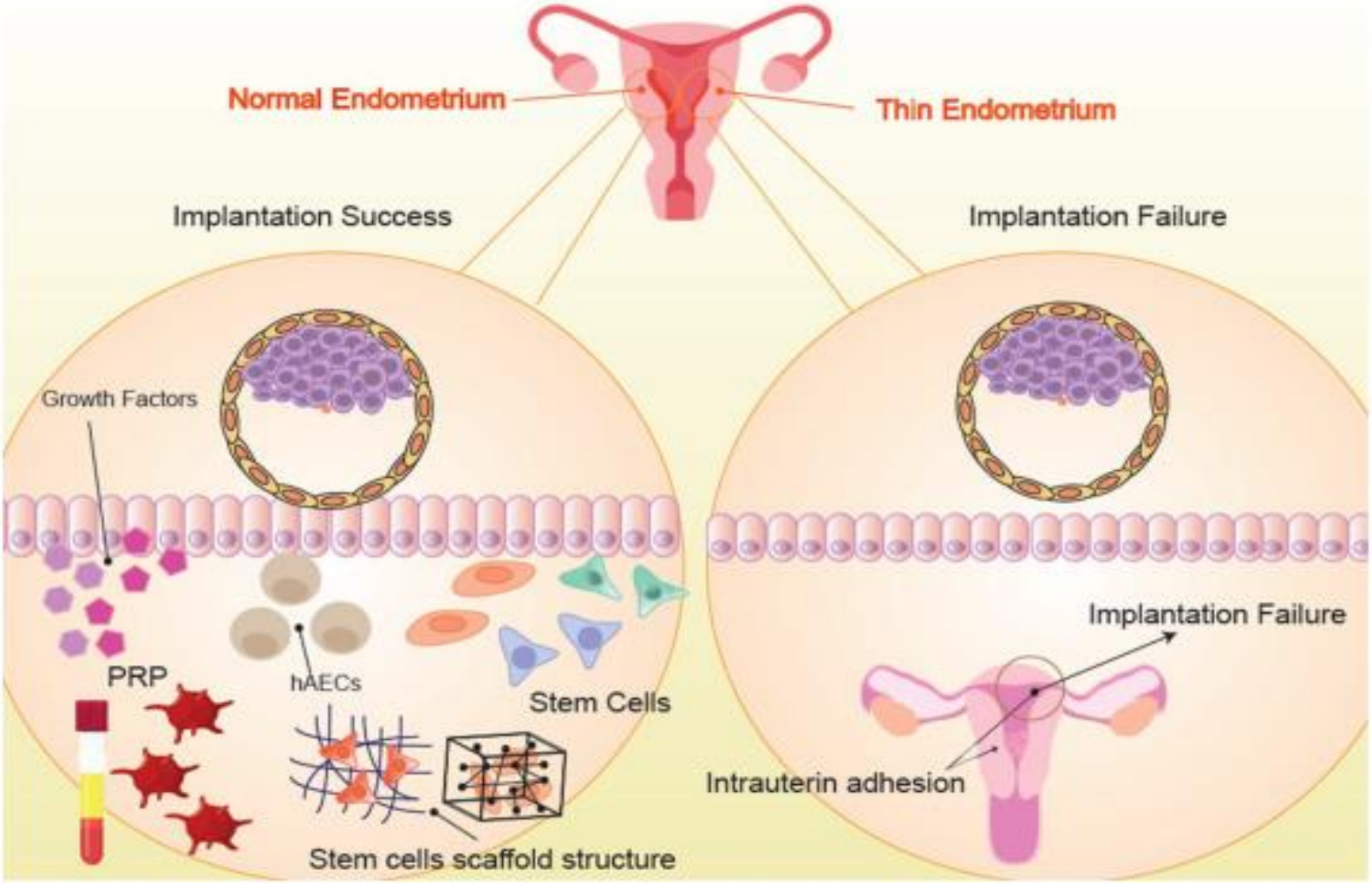

Fig. 1 On the right side of the figure, a patient with a thin endometrium is illustrated who has had implantation failure. On the left side of the figure, different types of cell therapy, which lead to the thickness of the patient's endometrium and subsequently success in pregnancy, are shown

Granulocyte colony-stimulating factor

Granulocyte colony-stimulating factor is known to be widely expressed in the female reproductive system, including the endometrium

Epithelial cells are amajor source of biologically active G-CSF in the human endometrium.

- follicular growth and development
- ovulation
- Pregnancy
- has a bidirectional regulatory role in maternal–embryonic exchange.

Isik G, Oktem M, Guler I, al. The impact of granulocyte colony-stimulating factor (G-CSF) on thin endometrium of an animal model with rats. Gynecol Endocrinol. (2021)

Efficacy of Granulocyte Colony Stimulating Factor (G-CSF) for Improving Endometrial Thickness in IVF/ICSI Patients with thin Endometrium: A Meta-Analysis and Systematic Review

Amr Sobhy Sweed[1], Ahmed Sherif Abdel hamid[1], Maram Salaeldeen Mahmoud[2], Hanan Shehata[1], Suzy Abdel Aziz[3] and Mohamed I. Taema[1]

Department of Obstetrics and Gynecology, Faculty of Medicine, [1]Ain Shams University, [2]Fayoum University, [3]Cairo University, Egypt

Received: 15 October 2024, Accepted: 11 December 2024

Results:

Eight research investigations totaling 673 candidates were enrolled in this meta-analysis, comprising two nonrandomized controlled investigations and six randomized controlled trials.
The results of the meta-analysis disclosed that G-CSF significantly increased the clinical pregnancy rate (RR = 1.73, 95% CI (1.22, 2.45), p = 0.002) and the embryo implantation rate (RR = 1.91, 95% CI (1.26, 2.91), in contrast to the placebo group. The endometrial thickness in the G-CSF arm had an insignificant rise in comparison to that of the placebo arm (mean difference (MD) = 0.81, 95% CI (–0.04, 1.67), p = 0.06.

Warning

in reproductive medicine, G-CSF is most commonly administered either subcutaneously or intrauterine. Of the13 trials included in the Cochrane review, only 4 trials collected data on adverse outcomes (none of them reported major adverse events), leaving the safety of G-CSF administration (particularly intrauterine infusion) in question.

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Autologous platelet-rich plasma

PRP, defined as “the plasma component of autologous blood in which the platelet concentration is four to five times the normal level”, is obtained by centrifugation of autologous peripheral venous blood.

Reduces the risk of immune rejection
pathogen transmission
cancer development

Sharara, F.I.; Lelea, L.-L.L.; Rahman, S.; Klebanoff, J.S.; Moawad, G.N. Review- A Narrative Review of Platelet-Rich Plasma (PRP) in Reproductive Medicine. J. Assist. Reprod. Genet. 2021

The mechanism of PRP:

- promote cell proliferation
- improve the blood flow
- secret anti-inflammator y cytokine s
- it contains various growth factorssuch as:
  VEGF, PDGF, EGF, TGF, IGF1,
- which is essential for tissue regeneration and repair

In patiant that the root cause of refractory endometrium is endometrial injury or damage secondary to a procedure or disease process (i.e., dilation and curettage, endometritis, intrauterine adhesions, etc.)

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The common administration methods include:

- injection of the drug into the endometrium through an endoscopic needle under hysteroscopic visualization
- drip/ perfusion through a uterine catheter

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Liu *et al. BMC Pregnancy and Childbirth* (2024) 24:567
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BMC Pregnancy and Childbirth

RESEARCH Open Access

Efficacy of platelet-rich plasma in the treatment of thin endometrium: a meta-analysis of randomized controlled trials

Xinyuan Liu[1,2], Chengyu Qian[3], Xiaoyue Jiang[1,2], Yue Zhou[1,2], Xue Feng[4], Yinyin Ding[1,2], Jing Jin[2], Minghui Hu[1], Weiye Zhou[2], Bei Liu[2] and Huifang Zhou[2*]

Results Eight RCTs involving 678 patients with thin endometrium were included. Patients receiving PRP infusion demonstrated significantly superior outcomes compared to the control group in endometrial thickness, clinical pregnancy rate, live birth rate,ycle cancellation rate), and embryo implantation rate There were no statistically significance in spontaneous abortion rate ,chemical pregnancy rate and endometrial vascular improvement rate) between the two groups.

Reference	Study Design	PRP Injection Protocol	Control Group (n)	Intervention Group (n)	Outcome
Gangaraju et al., 2023	Prospective interventional study	0.8 mL lyophilized PRP infusion 2–3 days before FET	/	٩	EMT increased; positive pregnancy outcomes in 8/9
Dogra et al., 2022	Prospective interventional study	0.5–1 mL PRPinfusion on HRTday 8, repeated 2–3 times every48 h untilEMT > 7 mm	/	٢٠	EMT increased; IR, CPR, and LBR increased significantly in a fresh group

Reference	Study Design	PRP Injection Protocol	Control Group (n)	Intervention Group (n)	Outcome
Kusumi et al., 2020	comparedProspective cohort withtheprior cycle	1 mL PRP infusion on cd10 and cd12	/	٣٦	EMT increased; CPR 15.6%
Chang et al., 2019	Prospective cohort study	0.5–1 mL PRPinfusion on cd10, repeated every3 days untilEMT > 7 mm	٣٠	٣٤	EMT, IR, and CPR increased ($p < 0.05$)

Reference	Study Design	PRP Injection Protocol	Control Group (n)	Intervention Group (n)	Outcome
Eftekhar et al., 2018	RCT	0.5–1 mL PRPon/cd13, repeated after 48 h if EMT still <7 mm	۴۳	۴۰	EMT; IR increased; CPR/cycle increased OPR/cycle increased
Agarwal et al., 2020	Cross-sectional study	Hysteroscopic subendometrial injection with 4 mL PRP (1 mL per wall) 7–10 days after injecting leuprolide during the previouscycle		۳۲	EMT increased; CPR, ORP, and LBR increased

NOTE !!

drawing final conclusions about the potential benefits of PRP for patients with refractory endometrium is difficult because of:

1)poor study design (the lack of randomization and blinding)
2)the lack of treatment standardization (differences in preparation and infusion protocols)
3)the inclusion of multiple infertility diseases in trials (recurrent implantation failure, recurrent pregnancy loss, and refractory endometrium)

At this juncture, PRP for refractory endometrium is at best at the experimental stage, and clinicians should exercise caution if offering it as a therapeutic treatment option.

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Complementary and alternative therapies

- Chinese medicine
- acupuncture
- Massage

European Journal of Obstetrics & Gynecology and Reproductive Biology
Volume 277, October 2022, Pages 32-41

Full length article

Intracavitary physiotherapy combined with acupuncture mediated AMPK/mTOR signalling to improve endometrial receptivity in patients with thin endometrium

Yinghua Qi [a], Xiaoxuan Wang [a], Sen Hou [a], Zhijuan Wu [b], Xiaoyan Xu [a], Conghui Pang [a 1]

✓This study showed :
✓acupuncture significantly
✓increased EMT
✓decreased bilateral uterine artery PI, uterine RI
✓up-regulated the HOXA10 protein expression and mRNA in endometrial tissues,
✓ increased the rate of embryo implantation and clinical pregnancy in patients with TE.

Surgical Interventions to Optimize EMT

There is mixed evidence supporting the use of routine hysteroscopy to improve IVF outcomes in asymptomatic women

abnormal endometrial pathology has been estimated to be identified in approximately 18%–30% of patients with a history of a failed IVF cycle despite a normal transvaginal ultrasound result

The role of surgical interventions for refractory endometrium adds another complex layer, given that often, a thin endometrium results from a previous intrauterine operation and that the rate of intrauterine adhesion reformation is high

Zikopoulos A, Galani A,, et al. Is hysteroscopy prior to IVF associated with an increased probability of live births in patients with normal transvaginal scan findings after their first failed IVF trial? J Clin Med 2022

The most practical approach is via the reservation of operative hysteroscopy in patients who

- fail to achieve adequate EMT despite attempts using various endometrial preparation protocols to rule out previously undetected intrauterine adhesions

- in those with an abnormal transvaginal ultrasound result concerning for uterine pathology.

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Thin Endometrium In COH/IUI

A systematic review and meta-analysis (2017) of IUI cycles withCC, aromatase inhibitors, and gonadotropins showed that although CC was associated with a lower EMT, there was no difference in the EMTs between patients who conceived and those who did not conceive.

1)Weiss NS,, et al. Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis. HumReprod 2017

Randomized controlled trial (RCT)(2022) of 739 couples comparing gonadotropin with CC found that although the EMT was higher with gonadotropins (8.9 mm vs. 7.5 mm, respectively), there was no effect of EMT on pregnancy rates

in contrast to IVF,a thin endometrium does not appear to effect pregnancy rates in COS and IUI cycles.

Danhof NA, . Endometrial thickness as a biomarker for ongoing pregnancy in IUI for unexplained subfertility: a secondary analysis.
2020;

Conclusion

The endometrium plays a crucial role in embryo implantation.

TE reduces endometrial tolerance, which in turn affects embryo implantation and development, leading to pregnancy failure

In ART, poor pregnancy outcomes in patients with TE are a major clinical challenge.

- In most patients, TE is associated with medical factors like previous uterine operations. This requires obstetricians and gynecologists to focus on the concept of primary endometrial prevention while researching and formulating clinical treatment plans, avoiding unnecessary uterine operations, and reducing the occurrence of medically-related TE at the source.

- pregnancy outcomes among patients with TE remain unsatisfactory. When the effect of single treatment is inadequate, a combination of multiple treatment methods has been tried

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- change in the route of estrogen supplementation or performing minimally invasive diagnostic hysteroscopy might be all that is needed.
- Beyond this, additional therapies should take an individualized approach with appropriate counseling on the experimental nature of these treatments in addition to the potential for adverse events.
- if all else fails, one should consider embryo transfer despite not achieving adequate EMT (because some patients may just never achieve a thick endometrial lining)
- vs. the consideration of a gestational carrier.

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THANKS FOR YOUR ATTENTION