DISCLAIMER: Results of database and or Internet searches are subject to the limitations of both the database(s) searched, and by your search request. It is the responsibility of the requestor to determine the accuracy, validity and interpretation of the results.

Date: 26 September 2018
Sources Searched: Embase, Medline.

Management of Persistently Thin Endometrium

1. 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.

Author(s): Sharma, Sunita; Rani, Geetha; Bose, Gunja; Saha, Indranil; Bathwal, Sikha; Chakravarty, B N

Source: Journal of human reproductive sciences; 2018; vol. 11 (no. 1); p. 34-39

Publication Date: 2018
Publication Type(s): Journal Article
PubMedID: 29681714
Available at Journal of Human Reproductive Sciences - from ProQuest (Hospital Premium Collection) - NHS Version
Available at Journal of Human Reproductive Sciences - from Europe PubMed Central - Open Access

Abstract:AimGonadotropin stimulation is used as the second line of treatment in patients with thin endometrium following clomiphene citrate (CC) administration, which is associated with higher cost, multiple births, and ovarian hyperstimulation syndrome. Tamoxifen (TMX), a selective estrogen receptor modulator, acts as an agonist on the endometrium. The objective of the present study was to compare the efficacy of low-dose CC, TMX, and gonadotropins in women with thin endometrium (<7 mm) following Clomiphene in intrauterine insemination (IUI) cycles.

Settings and DesignA prospective observational study between December 2011 and June 2013 was carried out in a tertiary infertility center.

MethodsWomen (n = 502) undergoing IUI with endometrium <7 mm after 100 mg CC were included in the study and divided into three treatment groups. Women in Group A (n = 182, cycles = 364) received clomiphene (50 mg/day from day 3 to 7), Group B (n = 179, cycles = 342) received TMX (40 mg/day from day 3 to 7), and Group C (n = 141, cycles = 226) received continuous urine-derived follicle-stimulating hormone 75-150 IU from day 3 onward until human chorionic gonadotropin injection. Endometrial thickness (ET), pregnancy rate, and live birth rate were considered as main outcome measures.

Statistical AnalysisMultiple comparisons using one-way ANOVA and Schiff’s test were performed.

ResultsPregnancy and live birth rate were significantly higher (P < 0.004) in TMX and gonadotropin groups compared to clomiphene. A number of follicles in the TMX group were found to be lower (P < 0.001) compared to other two groups. In polycystic ovary syndrome patients, ovulation induction with TMX resulted in inadequate response in more than half of the cycles.

ConclusionsTMX can improve ET and live birth rate in patients with thin endometrium after clomiphene.

Database: Medline
2. How to improve thin endometrium in cases of female infertility

**Author(s):** Sahoo G.; Agrawal V.; Garg R.; Malhotra N.

**Source:** Journal of SAFOG; 2018; vol. 10 (no. 2); p. 81-83

**Publication Date:** 2018

**Publication Type(s):** Editorial

**Abstract:** Thin endometrium is frequently encountered during the treatment of female infertility. It is associated with lower implantation and pregnancy rates. Adequate growth is an integral step in endometrial receptivity and embryo implantation. Several modalities have been studied and include extended estrogen, pentoxifylline, tocopherol, low-dose aspirin, acupuncture, neuromuscular stimulation, L-arginine, vaginal sildenafil, granulocyte colony-stimulating factor (G-CSF), and stem cell therapy. Studies show that vaginal sildenafil appears to be the first-line therapy option, G-CSF appears to be a potential second option, while stem cell therapy appears a new promising treatment modality. Copyright © 2018, Jaypee Brothers Medical Publishers (P) Ltd. All rights reserved.

**Database:** EMBASE

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3. Has the time come to include low-level laser photobiomodulation as an adjuvant therapy in the treatment of impaired endometrial receptivity?

**Author(s):** El Faham D.A.; Azmy O.M.; Elnoury M.A.H.; Morsy M.I.; El Shaer M.A.; Nour Eldin G.M.

**Source:** Lasers in Medical Science; Jul 2018; vol. 33 (no. 5); p. 1105-1114

**Publication Date:** Jul 2018

**Publication Type(s):** Article

**PubMedID:** 29546619

**Available at Lasers in Medical Science - from SpringerLink**

**Abstract:** Low-level laser therapy (LLLT) has been used in photobiomodulation to promote healing, regenerate, and restore tissue function. Women with persistent thin endometrium were assumed to encounter diminished activity in the regenerative and functional capacity of their endometrium. The aim of this study was to examine the ability of LLLT in 635 nm wavelength to enhance the proliferation and gene expression of in vitro cultured endometrial cells. Single (SE) versus multiple exposures (ME) to LLLT were examined in the study groups and compared to controls. A fluence dose of 4.27 J/cm² for 16 min was given once in the SE or divided in three equal sessions in days 2, 4, and 6 of the culture in ME. Cellular response was evaluated by measuring viable cell numbers and surface area. Pattern of MUC1, ITGA5, ITGB3, LIF, and PTEN gene expression was assessed using the qRT-PCR. Greater numbers of cells were found in both study groups (P < 0.001) as compared to controls. The surface area of cells at the end of culture phase was highly significant (P < 0.001) in ME when compared to SE and controls. A statistically significant difference was found in terms of gene expression in both irradiated groups (P < 0.001) as compared to controls, although greater difference in PTEN tumour suppressor gene (Phosphatase and tensin homolog) expression was toward ME. The introduction of LLLT to the armamentarium of infertility will serve as a new adjuvant therapy in this field. The current study proved that LLLT was able to increase the proliferative and functional capacity of cultured endometrial cells. Copyright © 2018, Springer-Verlag London Ltd., part of Springer Nature.

**Database:** EMBASE
4. The Effect of Tamoxifen on Thin Endometrium in Patients Undergoing Frozen-Thawed Embryo Transfer.

**Author(s):** Ke, Hanni; Jiang, Jingjing; Xia, Mingdi; Tang, Rong; Qin, Yingying; Chen, Zi-Jiang

**Source:** Reproductive sciences (Thousand Oaks, Calif.); Jun 2018; vol. 25 (no. 6); p. 861-866

**Publication Date:** Jun 2018

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 28345485

**Abstract:** Tamoxifen has played a vital role in endocrine therapy for the treatment of estrogen receptor-positive breast cancer. We examined the effect of tamoxifen in patients with a thin endometrium in frozen-thawed embryo transfer (FET) cycles and compared the improvement in endometrial thickness (EMT) and pregnancy outcomes stratified by different etiologies of thin endometrium. A total of 226 women were recruited for a new tamoxifen protocol; all had an EMT of less than 7.5 mm in previous cycles, including natural cycle (NC), hormone replacement treatment (HRT), and ovulation induction (OI) cycles. Compared with previous cycles, tamoxifen cycles showed a significantly increased EMT (from 6.11 ± 0.98 mm to 7.87 ± 1.48 mm in the NC group, from 6.24 ± 1.01 mm to 8.22 ± 1.67 mm in the HRT group, and from 6.34 ± 1.03 mm to 8.05 ± 1.58 mm in the OI group; all P < .001). Patients were further divided into 3 groups based on the causes of their thin endometrium: (1) history of intrauterine adhesion (n = 34), (2) history of uterine curettage (n = 141), and (3) polycystic ovary syndrome (PCOS; n = 51). Patients with PCOS obtained the thickest EMT (9.31 ± 1.55 mm), the lowest cycle cancellation rate (11.76%), and the highest rate of clinical pregnancy (60%) and live birth (55.56%) per transfer (P < .001). Multivariable regression analysis showed that EMT was related to live birth (odds ratio: 1.487; 95% confidence interval: 1.172-1.887).

A tamoxifen protocol improves EMT in patients after NC, HRT, and OI cycles during FET. Patients with PCOS show the most benefit from tamoxifen and achieve better pregnancy outcomes.

**Database:** Medline

5. Stem cell therapy in Asherman syndrome and thin endometrium: Stem cell-based therapy.

**Author(s):** Azizi, Ramyar; Aghebati-Maleki, Leili; Nouri, Mohammad; Marofi, Faroogh; Negargar, Sohrab; Yousefi, Mehdi

**Source:** Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie; Jun 2018; vol. 102 ; p. 333-343

**Publication Date:** Jun 2018

**Publication Type(s):** Journal Article Review

**PubMedID:** 29571018

**Abstract:** The endometrium is one of the essential components of the uterus. The endometrium of human is a complex and dynamic tissue, which undergoes periods of growth and turn over during any menstrual cycle. Stem cells are initially undifferentiated cells that display a wide range of differentiation potential with no distinct morphological features. Stem cell therapy method recently has become a novel procedure for treatment of tissue injury and fibrosis in response to damage. Currently, there is massive interest in stem cells as a novel treatment method for regenerative medicine and more specifically for the regeneration of human endometrium disorder like Asherman syndrome (AS) and thin endometrium. AS also known as intrauterine adhesion (IUA) is a uterine disorder with the aberrant creation of adhesions within the uterus and/or cervix. Patients with IUA are significantly associated with menstrual abnormalities and suffer from pelvic pain. In addition, IUA might prevent implantation of the blastocyst, impair the blood supply to the uterus and early fetus, and finally result in the recurrent miscarriage or infertility in the AS patients. It has been evidenced
that the transplantation of different stem cells with a diverse source in the endometrial zone had effects on endometrium such as declined the 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. This study presents a summary of the investigations that indicate the key role of stem cell therapy in regeneration and renovation of defective parts.

**Database:** Medline

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6. Effects of growth hormone on pregnancy rates of patients with thin endometrium.

**Author(s):** Cui, N; Li, A-M; Luo, Z-Y; Zhao, Z-M; Xu, Y-M; Zhang, J; Yang, A-M; Wang, L-L; Hao, G-M; Gao, B-L

**Source:** Journal of endocrinological investigation; Apr 2018

**Publication Date:** Apr 2018

**Publication Type(s):** Journal Article

**PubMedID:** 29671256

**Abstract:**

**PURPOSE**

To investigate whether growth hormone (GH) could improve pregnancy rates of patients with thin endometrium by clinical study and laboratory experiments.

**MATERIALS AND METHODS**

Ninety-three patients were randomized to either the GH-received group (40) or the routine exogenous administration of estrogens control group (53) for clinical study. The human endometrial carcinoma cell line RL95-2 was used for testing the role of GH with Western blot and real-time PCR by exposure to various concentrations of GH (0.1 nM, 1 nM, 10 nM, 100 nM).

**RESULTS**

Patients treated with GH had a significantly (P < 0.05) greater endometrium thickness on day 3 (7.87±0.72 vs 6.34±0.86), higher implantation rates (24.4% vs 10.5%) and greater clinical pregnancy rates (42.5% vs 18.9%) compared with the control group. No adverse events were associated with the use of GH. Administration of GH significantly up-regulated the expression of VEGF, ItgB3 and IGF-I expression in RL95-2 cells at both mRNA and protein levels (P < 0.05). AG490, an inhibitor of JAK2, nearly completely inhibited the up-regulative effect of GH through the JAK2-STAT5 pathway, and GH-induced effects could be mediated through autocrine IGF-I together with its hepatic counterpart. IGF-I mRNA was detected in the RL95-2 cells.

**CONCLUSION**

GH may improve pregnancy outcomes of patients with thin endometrium who undergo frozen embryo transfer by acting on human endometrial cells to promote proliferation and vascularization and to up-regulate receptivity-related molecular expression.

**Database:** Medline
7. The thin endometrium in assisted reproductive technology: An ongoing challenge

Author(s): Eftekhar M.; Tabibnejad N.; Tabatabaie A.A.

Source: Middle East Fertility Society Journal; Mar 2018; vol. 23 (no. 1); p. 19-22

Publication Date: Mar 2018

Publication Type(s): Review

Abstract: Thin endometrium is identified to adversely affect reproductive success rates after assisted reproductive technology (ART). Several treatment modalities have been presented to patients with thin endometrium, to improve endometrial thickness and the subsequent endometrial receptivity. These approaches comprising hormonal management by estradiol, tamoxifen, human chorionic gonadotropin (hCG) and gonadotropin-releasing hormone (GnRH) agonist, vasoactive agents such as aspirin, vitamin E, pentoxifylline, nitroglycerin and sildenafil, intrauterine infusion of growth factor such as Granulocyte Colony Stimulating Factor (G-CSF) and the latest application of platelet-rich plasma, electrical stimulation, regenerative medicine and presentation of endometrial receptivity array. In spite of the large variety of treatment, most of the choices achieve only minor modification in the endometrium thickness and have not been validated so far. Treatment of thin endometrium remains a challenge and future enormous investigations are required to further clarification and ideal management of patients with thin endometrium. Copyright © 2017 Middle East Fertility Society

Database: EMBASE

8. Role of granulocyte colony-stimulating factor in human reproduction

Author(s): Eftekhar M.; Naghshineh E.; Khani P.

Source: Journal of Research in Medical Sciences; Jan 2018; vol. 23 (no. 1)

Publication Date: Jan 2018

Publication Type(s): Review

Abstract: As new research reveals, granulocyte colony-stimulating factor (G-CSF) plays an effective role in pregnancy success, considering that it not only affects the embryo implantation and ovarian function but also it promotes endometrial thickening and improves the pathophysiology of endometriosis, which all fundamentally lead to reducing pregnancy loss. In this review, we focus on the role of G-CSF in human reproduction. We summarized its role in ovulation, luteinized unruptured follicle syndrome, poor responders, improving repeated in vitro fertilization failure, endometrial receptivity and treatment of thin endometrium, and recurrent spontaneous abortion. Copyright © 2018 Journal of Research in Medical Sciences.

Database: EMBASE

Author(s): Nigam S.; Shankar K.; Varma T.R.

Source: International Journal of Infertility and Fetal Medicine; 2017; vol. 8 (no. 3); p. 101-105

Publication Date: 2017

Publication Type(s): Article

Abstract: Introduction: One of the most challenging problems in in vitro fertilization (IVF) is patient with thin endometrium. The objective of the study was to ascertain whether daily human chorionic gonadotropin (hCG) for 7 days with estrogen in hormone replacement frozen embryo transfer (FET) cycles during follicular phase can increase the endometrial thickness (ET) and reduce the cancellation of cycles. Materials and methods: Twenty-five infertile patients with resistant thin endometrium who had antagonist protocol and planned for frozen embryo replacement were recruited. These patients had prior attempts to thicken their endometrium which had failed. All the patients received estrogen daily from D2/3 of cycle. On day 8 or 9 of estrogen administration, 200 IU of hCG was given daily for 7 days. After 7 days on hCG priming (D14/15), ET was measured and progesterone was started accordingly. Identification of an intrauterine gestational sac with fetal heart beat by transvaginal ultrasonography constituted clinical pregnancy. Results: Mean ET increased significantly from 5.84 to 7.61 mm (p < 0.01). About 72% of patients had more than 20% improvement in their ET after hCG priming. About 76% achieved an ET more than 7 mm. Overall, 50% became pregnant. The ongoing pregnancy rate was 40%. Conclusion: A total of 200 IU hCG endometrial priming for 7 days in the proliferative phase of hormone replacement cycles for FET is a highly promising approach to thicken thin endometrium with failed prior attempts. Copyright © 2017, Jaypee Brothers Medical Publishers (P) Ltd. All rights reserved.

Database: EMBASE

10. Platelet-rich plasma administration has benefit for infertile women with thin endometrium in frozen blastocyst-stage embryos transfer program

Author(s): Chang Y.; Li J.; Li X.; Liang X.; Yang X.

Source: Fertility and Sterility; Sep 2017; vol. 108 (no. 3)

Publication Date: Sep 2017

Publication Type(s): Conference Abstract

Abstract: OBJECTIVE: The purpose of this study was to evaluate the effectiveness of platelet-rich plasma (PRP) in women with thin endometrium in frozen embryo transfer program (FET) DESIGN: A prospective cohort study MATERIALS AND METHODS: PRP, as a portion of plasma fraction from autologous blood, contains a variety of growth factors including VEGF, TGF, PDGF and EGF, which can promote tissue regeneration and healing. Approximately 15 ml of venous blood was collected in a syringe prefilled with 5 ml anticoagulant solution (ACD-A), and a double-step centrifuge technique, with 300 x g and 700 x g of RCF respectively, was utilized to prepare PRP in our study. Patients undergoing FET were enrolled from the Reproductive Medicine Center, Sixth Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China) from July 2015 to July 2016. The inclusive criterias included: (1) age younger than 40 years, and FSH<10IU/L, (2) had a history of cycle cancellation due to thin endometrium, which was defined as endometrial thickness <7mm. All patients were treated with HRT protocol. For patients in PRP group, PRP was infused per intrauterine catheter on the 10th day in HRT cycle and progesterone administration day. All patients were transferred two good-quality blastocyst-stage embryos. The primary outcome were endometrial thickness, implantation rate and clinical pregnancy rate. Independent samples t-test, Chi-squared test and Fisher's exact test
were used for data analysis. P <0.05 was considered statistically significant. RESULTS: In total, PRP group included 42 cycles of 34 patients, while the control group including 51 cycles of 30 patients. After PRP infusion, the average endometrium thickness on day of progesterone administration in PRP group was 7.65±0.22mm, which was significantly thicker than control group (6.52±0.31mm). Furthermore, PRP group had lower cycle cancellation rate when compared to control group (19.05% vs. 41.18%, P<0.01). Most importantly, the implantation rate and clinical pregnancy rate in PRP group were significantly higher than control group (27.94% vs. 11.67%, P<0.05; 44.12% vs. 20%, P<0.05, respectively). The benefits of PRP for these infertile women with thin endometrium may due to the 4 times higher platelets and significant greater amounts of growth factors as PDGF-AB, PDGF-BB and TGF-b inPRP than peripheral blood(P<0.01). CONCLUSIONS: PRP plays an active role in promoting endometrium proliferation, improving embryo implantation rate and clinical pregnancy rate for women with thin endometrium.

Database: EMBASE

11. Efficacy of intrauterine perfusion of granulocyte colony-stimulating factor (G-CSF) for Infertile women with thin endometrium: A systematic review and meta-analysis.
Author(s): Xie, Yiran; Zhang, Tao; Tian, Zhengping; Zhang, Jiamiao; Wang, Wanxue; Zhang, Hong; Zeng, Yong; Ou, Jianping; Yang, Yihua
Source: American journal of reproductive immunology (New York, N.Y. : 1989); Aug 2017; vol. 78 (no. 2)
Publication Date: Aug 2017
Publication Type(s): Research Support, Non-u.s. Gov't Meta-analysis Journal Article Review
PubMedID: 28497881
Available at American Journal of Reproductive Immunology - from Wiley Online Library Science, Technology and Medicine Collection 2017
Abstract:This meta-analysis aimed to explore the efficiency of intrauterine perfusion of granulocyte colony-stimulating factor (G-CSF) on infertile women with thin endometrium. Following PRISMA protocol, we conducted a comprehensive search of academic literatures on various databases including PubMed, EMbase, and Cochrane Library. Studies published in English before July 1, 2016 were included for primary screening. Data on the thickness of endometrium, cycle cancelation rate,clinical pregnancy rate, and embryo implantation rate were extracted and analyzed, respectively. Eleven eligible studies involving 683 patients were included in this meta-analysis. Compared with control group, G-CSF perfusion could significantly improve endometrial thickness (mean difference [MD]=1.79, 95% confidence interval (CI): 0.92-2.67), clinical pregnancy rate (risk ratio [RR]=2.52, 95% CI: 1.39-4.55), and embryo implantation rate (RR=2.35, 95% CI: 1.20-4.60), while it could decrease cycle cancelation rate (RR=0.38, 95% CI: 0.25-0.58). Funnel plots revealed that there was no evidence of publication bias. The current data indicate that intrauterine perfusion of G-CSF can improve endometrial thickness, clinical pregnancy rate, and embryo implantation rate, but decrease the cycle cancelation rate in women with thin endometrium.
Database: Medline
12. Use of granulocyte-colony stimulating factor in assisted reproductive technology: A systematic review and meta-analysis.

**Author(s):** Kamath, Mohan S; Chittawar, Priya Bhave; Kirubakaran, Richard; Mascarenhas, Mariano

**Source:** European journal of obstetrics, gynecology, and reproductive biology; Jul 2017; vol. 214; p. 16-24

**Publication Date:** Jul 2017

**Publication Type(s):** Meta-analysis Journal Article Review

**PubMedID:** 28458165

**Abstract:** Granulocyte-colony stimulating factor (G-CSF), a glycoprotein, has been used in women undergoing Assisted Reproductive Technology (ART). We decided to undertake a systematic review to evaluate the effectiveness of G-CSF in women with thin endometrium and recurrent implantation failure (RIF) undergoing ART. The outcomes included an increase in endometrial thickness, live birth, clinical pregnancy rates and adverse effects. We included two trials evaluating women with thin endometrium and another two trials evaluating women with RIF. The pooled data did not reveal statistically significant increase in endometrial thickness following G-CSF in women with thin endometrium (mean difference 0.47, 95% CI -1.36-2.31; I² 82%). However significantly higher clinical pregnancy rate was noted (RR 2.43, 95% CI 1.09-5.40; I² 0%) following G-CSF compared to no intervention and quality of evidence for both these outcomes was very low. In RIF population, the administration of G-CSF was associated with a significantly higher clinical pregnancy rate compared to no intervention with pooled risk ratio of 2.51 (95% CI 1.36-4.63; I² 0%) and quality of evidence being low. Findings of current review suggest a possible benefit of G-CSF in women with thin endometrium undergoing ART and RIF. However these findings need to be further validated in larger trials before G-CSF can be used in routine clinical practice.

**Database:** Medline

13. The effect of G-CSF on infertile women undergoing IVF treatment: A meta-analysis

**Author(s):** Li J.; Mo S.; Chen Y.

**Source:** Systems Biology in Reproductive Medicine; Jul 2017; vol. 63 (no. 4); p. 239-247

**Publication Date:** Jul 2017

**Publication Type(s):** Article

**PubMedID:** 28632452

**Abstract:** Evidence for the effect of granulocyte colony stimulating factor (G-CSF) on infertile women undergoing in vitro fertilization (IVF) remains inconsistent. This study aimed to evaluate the effectiveness of G-CSF on infertile women undergoing IVF. PubMed and EMBASE databases were searched before August 2016. Comparing the transvaginal perfusion of G-CSF and placebo or no treatment, the available studies were considered. The pooled risk ratio (RR) with 95% confidence intervals (CIs) was used in the analysis and six studies were included. Transvaginal perfusion of G-CSF was significantly associated with a higher clinical pregnancy rate versus the placebo (RR=1.563, 95%CI: 1.122, 2.176), especially for the Asian population. Among patients with a thin endometrium or repeated IVF failure, the implantation and biochemical pregnancy rates were also significantly increased in patients with the use of G-CSF (implantation rate: RR = 1.887, 95% CI: 1.256, 2.833; biochemical pregnancy rate: RR = 2.385, 95% CI: 1.414, 4.023). However, no statistical significance in increasing endometrial thickness was detected. Transvaginal perfusion of G-CSF for infertile women may play a critical role in assisting human reproduction, especially for patients with a thin endometrium or repeated IVF failure in the Asian population. Copyright © 2017 Taylor & Francis.

**Database:** EMBASE
14. G-CSF and stem cell therapy for the treatment of refractory thin lining in assisted reproductive technology

Author(s): Mouhayar Y.; Sharara F.I.
Source: Journal of Assisted Reproduction and Genetics; Jul 2017; vol. 34 (no. 7); p. 831-837
Publication Date: Jul 2017
Publication Type(s): Review
PubMedID: 28405864
Available at Journal of Assisted Reproduction and Genetics - from ProQuest (Hospital Premium Collection) - NHS Version
Available at Journal of Assisted Reproduction and Genetics - from Europe PubMed Central - Open Access

Abstract: Purpose: The study aims to describe two promising therapeutic options for resistant "thin" endometrium in fertility treatment: granulocyte colony-stimulating factor (G-CSF) and stem cell therapy. Methods: A review of the scientific literature related to patients with thin endometrium undergoing fertility treatment. Results: Sufficient endometrial growth is fundamental for embryo implantation. Whether idiopathic or resulting from an underlying pathology, a thin endometrium of <7 mm is associated with lower probability of pregnancy; however, no specific thickness excludes the occurrence of pregnancy. We specifically reviewed two relatively new treatment options for resistant thin lining: intrauterine G-CSF and stem cell therapy. The majority of the reviewed trials showed a significant benefit for intrauterine G-CSF infusion in improving endometrial thickness and pregnancy rates. Early results of stem cell therapy trials seem promising. Conclusions: EMT <7 mm is linked to lower probability of pregnancy in assisted reproductive technology. Intrauterine G-CSF infusion appears to be a potentially successful treatment option for resistant cases, while stem cell therapy seems to be a promising new treatment modality in severely refractory cases. Copyright © 2017, Springer Science+Business Media New York.

Database: EMBASE

15. Effect of intra-uterine G-CSF on endomerial thickness in patients with persistently thin endometrium: A retrospective study of 244 thawed embryo transfer cycles

Author(s): Singh S.; Ashraf M.; Laddad D.
Source: Human Reproduction; Jul 2017; vol. 32
Publication Date: Jul 2017
Publication Type(s): Conference Abstract

Abstract: Study question: Does intra-uterine G-CSF infusion increase endometrial thickness in women with earlier cancelled embryo transfer cycles due to thin endometrium despite using estradiol valerate, pentoxiphylline, vitamin E and Sildenafil citrate? Summary answer: Use of intra uterine G-CSF results in significant improvement in endometrial thickness from 7.19 +/- 0.52 mm to more than 8.10 +/- 1.09 mm. What is known already: Persistently thin endometrium represents a therapeutic challenge for the physicians. It leads embryo transfer in suboptimal conditions, cancelled transfer and transfer to gestational surrogates; leading to emotional and financial burden. The mainstream treatment for improving endometrial thickness is estrogen supplementation. However few patients are refractory to estrogen supplementation and require other modalities. Inconsistent response has been seen with sildenafil citrate, low dose aspirin, pentoxifylline, and tocopherol etc, with no established roles. Earlier case reports have been published showing significant improvement in
endometrial thickness after intrauterine instillation of granulocyte colony stimulating factor. Study design, size, duration: This is a historical case control study of 192 women with persistently thin endometrium in previous 2 estrogen replacement therapy (ERT). All cases were recruited at Craft Hospital and Research Centre over a period of 3 years from January 2013 to December 2015. All women had endometrial thickness less than 7 mm at day 20 of previous 2 estrogen replacement cycle and it failed to improve even with addition of above mentioned adjuvants.

Participants/materials, setting, methods: After initial failed attempt all women were started on ERT (8 mg/day) from day 2 of period and serial ultrasound monitoring was performed from 10th day onwards at interval of 3-5 days. Intra uterine instillation of 300 mcg/1 ml of G-CSF (Endokine, Filgrastim, INTAS) was done if endometrial thickness was less than 7 mm after 18 days of high dose ERT. Main results and the role of chance: Before infusion of G-CSF the mean ET of the cohort was 7.19 +/- 0.52 on day 18.1 +/- 3.7 of high dose ERT. After 48 hours of infusion the mean endometrial thickness of the cohort increased by 0.57 mm and reached 7.76 +/- 0.96 mm. At second review after 4.9 +/- 2.7 days of G-CSF infusion the mean endometrial thickness of the cohort reached 8.10 +/- 1.09 mm showing increase of 0.91 mm. Out of 244 cycles, 115 cycles (47%) showed improvement in endometrial thickness upt0 and beyond 8.0 mm. The average increase in endometrium seen in these 115 cycles was 1.75 +/- 0.62 mm on last day of ERT. In other 119 cycles the improvement in endometrial thickness was less than 1 mm and did not reach threshold for embryo transfer. There were 10 more cycles where reduction in endometrial thickness was noted after G-CSF infusion. Total 127 frozen-thawed embryo transfer was performed i.e. 52% of treated cycles. The implantation rate, clinical pregnancy and live birth rate per transfer procedure were 27.5%, 44% and 29.9% respectively for these women. Limitations, reasons for caution: This is a retrospective study with small sample size. The women acted as their own controls. Wider implications of the findings: This study supports the use of intrauterine -G-CSF for patient with persistently thin endometrium. But overall improvement in endometrial thickness is less than 1.75 mm. Further robust data in terms of large multicentric randomised controlled trials are needed to substantiate the findings.

Database: EMBASE

16. Clinical pregnancy outcome after double dose intrauterine instillation of granulocyte colony-stimulating factor(G-CSF) in the unresponsive thin endometrium in frozen embryo transfer

Author(s): Sen U.; Khastgir G.

Source: Human Reproduction; Jul 2017; vol. 32

Publication Date: Jul 2017

Publication Type(s): Conference Abstract

Abstract: Study question: Does double dose intrauterine instillation of G-CSF in patients with unresponsive thin endometrium improve clinical pregnancy outcome following frozen embryo transfer. Summary answer: Double dose intrauterine G-CSF instillation results in higher clinical pregnancy rates in patients with unresponsive thin endometrium undergoing frozen embryo transfer. What is known already: G-CSF, a biologic response modifier has the beneficial effect on clinical pregnancy outcome in Assisted Reproductive Technology (ART). However, some studies failed to demonstrate such benefit. Possible reasons for this, as concluded in a recent meta-analysis are the use of the relatively low dose of G-CSF and one-time administration. They also concluded that cohort studies are required to investigate the appropriate route and dose of G-CSF administration. Study design, size, duration: A prospective observational cohort study over 6 months, carried out on 200 patients undergoing FET, aged between 23- 40 years. All patients had two cancelled cycles due to thin endometrium (<5 mm on day 12/13 of cycle) after receiving conventional treatment with oral and topical oestrogen. 3 patients were lost to follow up. 197 patients underwent 300 microgram intrauterine G-CSF instillation (97 patients received second
Primary and secondary outcome measures were endometrial thickness and clinical pregnancy. Participants/materials, setting, methods: All patients received oral and topical oestrogen from day 2/3 of cycle, endometrial thickness (ET) was reassessed on day 12/13 by transvaginal ultrasonography. Subjects having ET 4-5 mm received intrauterine instillation of 300 microgram G-CSF. After 72 hours patients having an ET increase of 1.5mm or more underwent FET; others received 2nd dose of G-CSF after another 72 hours. Those with 1.5mm ET increase from day 12/13, underwent FET, others having cycle cancelled. Main results and the role of chance: Out of 197 subjects, 100 (50.76%) had ET increase more than 1.5mm after 72 hours of the 1st dose of G-CSF (mean 6.17 mm +/- SD 0.81), significantly higher than value after conventional treatment (p value<0.001). Out of 97, receiving the 2nd dose of G-CSF, 70 (72.16%) had minimum ET increase of 1.5mm after another 72 hours (mean 6.5mm+SD 0.74), significantly higher than value after conventional therapy (p value<0.001). 27 out of 197(13.70%) had their cycles canceled. Out of 100 patients undergoing FET after 1st dose of G-CSF 49(49%) had clinical pregnancy documented by transvaginal ultrasonography. Rest 97 received the 2nd dose of G-CSF of which 70 underwent FET. Out of this 97 receiving the second dose,23(23.71%) had the clinical pregnancy. Overall 197 patients with unresponsive thin endometrium receiving either 1 or 2 doses of G-CSF 72(36.55%)attained clinical pregnancy. Limitations, reasons for caution: The absence of control, the safety of 2nd dose of G-CSF instillation. Wider implications of the findings: This study reaffirms utility of G-CSF instillation in unresponsive thin endometrium in ART. It opens the feasibility of using 2nd dose of G-CSF to enhance clinical pregnancy outcome in such cases. Furthermore, endometrial thickness of less than 5.5 mm may be considered for G-CSF administration to proceed to clinical pregnancy.

Database: EMBASE

17. Intrauterine infusion of human autologous peripheral blood mononuclear cells in patients with repeated failed attempts of optimum endometrial development in FET cycle: A Pilot study

Author(s): Chakravarty B.; Wasim S.; Ghosh S.; Goswami S.K.; Chakraborty S.; Kabir S.N.; Chattopadhyay R.

Source: Human Reproduction; Jul 2017; vol. 32

Publication Date: Jul 2017

Publication Type(s): Conference Abstract

Abstract: Study question: Does autologous peripheral blood mononuclear cells (PBMC) help in optimum endometrial development in patients with several failed FET cycles due to inadequate endometrial thickness and vascularity? Summary answer: Intrauterine infusion of PBMC resulted improvement of endometrial development in 27 amongst 37 patients studied, with 5 pregnancies following 15 transfer results declared so far. What is known already: Autologous PBMC is one of the most convenient source for stem cells generation. This process is non-invasive, cost effective and causes minimal discomfort to the patient. PBMC has been shown as a source of pluripotent stem cells for regeneration of blood cells, nerve cells, epithelial cells, myofibroblast, muscle cells, bone cells and endometrial cells. There are studies depicting the role of PBMC with or without hCG priming for increasing the invasive potential of embryos as a therapeutic modality in recurrent implantation failure. There is a case report of regeneration of endometrium using PBMC in case of Asherman syndrome. Study design, size, duration: Prospective study, with sample size of 37 patients, from August 2016 and continuing till date of submission of this abstract. The study was designed to evaluate possible improvement in endometrial thickness and vascularity following intrauterine autologous PBMC compared to the mean of their previous records in failed IVF attempts (min. 3 and max. 10) due to inadequate endometrial development. Mononuclear cells were isolated from patient's peripheral blood by density gradient centrifugation using commercially available lymphoprep. Participants/materials, setting, methods: Setting: Institute of Reproductive Medicine,
Kolkata, India Patients received oestradiol valerate 6.0 mg daily from day2 till endometrial thickness reached >=6.5mm with significant increase in blood flow, when progesterone was administered. End diastolic velocity(EDV) was considered as the main marker of endometrial vascularity. On day5, isolated mononuclear cells suspended in 500 muL normal saline were infused into uterine cavity and embryo transfer was performed around day25. Inadequate endometrial response (thickness/vascularity) resulted in cancelation of embryo transfer. Main results and the role of chance: The patients were categorized in 4 groups with regard to their response to therapy; a) Significant increase in thickness (6.2 +/- 0.8 vs 7.3 +/- 0.9, P = 0.003) and vascularity (8.55 +/- 1.79 vs 10.05 +/- 1.66, P = 0.04) in 12 patients (44.44%) b) significant increase in vascularity (7.68 +/- 1.62 vs 9.24 +/- 1.66, P = 0.02) but not in thickness (6.8 +/- 0.7 vs 7.2 +/- 0.7, NS) in 2 patients (7.4%) c) significant increase in thickness (6.7 +/- 1.2 vs 7.9 +/- 1.3, P = 0.02) but not vascularity (7.84 +/- 1.32 vs 8.68 +/- 1.47, NS) in 13 patients (48.14%) d) no significant increase either in thickness (6.5 +/- 0.8 vs 7.2 +/- 1.1, NS) or in vascularity (7.45 +/- 1.13 vs 8.22 +/- 1.31, NS) in the rest 10 patients. 5 pregnancies were achieved out of 15 embryo transfer results declared so far. 4 pregnancies occurred when both thickness and vascularity improved and in one, than vascularity rather thickness showed improvement. No pregnancies were recorded in other two groups. The probability of events happening due to chance is low although effect of catheter insertion and invoking cytokine production accelerating the endometrial development in presence of estrogen supplementation cannot be ruled out. It is still premature to ascertain the increase in endometrial thickness and vascularity due to PBMC because some other factor like catheter insertion might have resulted in identical endometrial changes. Limitations, reasons for caution: Number of patients studied till now is not adequate to make a valid conclusion. But results achieved already appear promising. However, there were patients whose cycles were cancelled implying that some unknown patient or endometrial characteristics may exist which may influence in achieving optimum endometrial preparation for successful blastocyst implantation. Wider implications of the findings: Till date other than surrogacy, there is no proven treatment of repeated thin endometrium in FET cycles. It is cost effective and minimally invasive procedure and can result in pregnancy without taking recourse to surrogacy.

Database: EMBASE
A randomized controlled clinical trial: The treatment of tamoxifen with patients of thin endometrium undergoing frozen-thawed embryo transfer

Author(s): Sun Q.; Li H.; Xu J.; Yao B.; Chen L.

Source: Human Reproduction; Jul 2017; vol. 32

Publication Date: Jul 2017

Publication Type(s): Conference Abstract

Abstract: Study question: Endometrial thickness <7 mm is always a criterion for fresh IVF cycle cancellation and all embryos will be cryopreserved. However, improving endometrial growth in such patients is very difficult. Summary answer: Tamoxifen compared with letrozole drugs in patients of thin endometrium undergoing frozen-thawed embryo transfer (FET) can increase endometrial thickness and improve implantation rate. What is known already: Up to now, there are no standard treatment guidelines for thin endometrium. Tamoxifen, Some research supported that tamoxifen (TAM) compared with clomiphene for ovulation induction can significantly improve the endometrial thickness, but there are few reports about the use of tamoxifen with patients having thin endometrium in frozen-thawed embryo transfer. Study design, size, duration: A total of 133 women with thin endometrium scheduled for FET (January 2014-June 2016) were enrolled in an open-label randomized clinical trial to ovarian stimulation with letrozole per oral (n = 72, 2.5 mg/day from Day 3-7) or tamoxifen per oral (n = 61, 40 mg/day from Day 3-7). Participants/materials, setting, methods: We studied subfertile couples undergoing FET. Further inclusion criteria were female age <=40 years, number of embryos transferred <=2 and at least one of good quality, failure of growth of endometrium in hormone replacement therapy. The primary end-point was clinical pregnancy. Main results and the role of chance: The serum estradiol level of LE group both on HCG and transfer day [(1193.80 +/- 629.64)ng/L vs (2776.30 +/- 157.34)ng/L, (1195.90 +/- 820.30)ng/L vs (2129.40 +/- 1208.71)ng/L, p = 0.000] were statistically lower, serum luteinizing hormone level were statistically higher than TAM group [(20.48 +/- 15.50)IU/L vs (10.59 +/- 8.34)IU/L, p < 0.05]; implantation rate of LE group were statistically lower than TAM (39.32% vs 45.83%, p = 0.001). The endometrial thickness and serum E2 and P levels in TAM cycles were significantly higher compared with those in hormone replacement therapy cycle [(8.49 +/- 1.36)mm vs (6.43 +/- 0.96)mm, p = 0.018]. Limitations, reasons for caution: Since the sample size is small, this conclusion needs confirmation with large one. Wider implications of the findings: Tam compared with LE for patients of thin endometrium undergoing FET can increase endometrial thickness and improve implantation rate, thus providing a new solution.

Database: EMBASE
Collagen mixed with epidermal growth factor promotes the endometrial HOXA10 expression as well as endometrial growth in patients with thin endometrium

**Author(s):** Kim C.; Jeung Y.; Kim S.H.; Chae H.D.; Kang B.M.; Moon J.W.

**Source:** Human Reproduction; Jul 2017; vol. 32

**Publication Date:** Jul 2017

**Publication Type(s):** Conference Abstract

**Abstract:**

Study question: Does collagen mixed with epidermal growth factor (EGF) increase the expression of endometrial HOXA-10 in the mid-luteal phase of infertile patients with thin endometrium, compared with EGF alone? Summary answer: EGF-loaded collagen stimulates the endometrial HOXA10 expression in the mid-luteal phase and improves the endometrial growth effect of EGF in infertile patients with thin endometrium. What is known already: Treatment of poorly developed thin endometrium is still challenging. Several growth factors and cytokines including EGF and granulocyte colony-stimulating factor (G-CSF) have been shown to stimulate the endometrial growth in patients with thin endometrium. In 2016, we have presented that collagen enables sustained release of EGF and improves the treatment effect of EGF on thin endometrium of infertile women. However, study on the effect of EGF-loaded collagen on endometrial receptivity markers including HOXA10 in patients with thin endometrium has not been reported. Study design, size, duration: We analyzed the results of a total of 87 consecutive infertile women with thin endometrium < 6 mm who underwent intrauterine treatment with either EGF-loaded collagen solution (study group, n = 50) or EGF alone solution (control group, n = 37) between March 2014 and November 2016 for this retrospective study. Endometrial tissue in the midluteal phase was obtained in 15 patients included in the study group and 12 patients included in the control group in the same period. Participants/materials, setting, methods: In the study group, slow intrauterine infusion of 0.8% collagen gel (Collabarrier, Dalimtissen. Co. Ltd., Seoul, Korea) in which 200 ng/ml EGF was loaded was performed every 2-3 days during the follicular phase of 4 to 5 menstrual cycles. In the control group, EGF alone solution with same concentration was used during same period. Endometrial biopsy was performed in the mid-luteal phase of last treatment cycle. Endometrial HOXA10 mRNA was analyzed by realtime RT-PCR. Main results and the role of chance: Study and control groups were similar with respect to patient's characteristics. The treatment duration and number were also comparable between the two groups. The peak endometrial thickness was significantly higher in the study group of 7.51 +/- 0.68mm compared with 6.86 +/- 0.66 mm in the control group (p < 0.001) and resistance index (RI) of subendometrial artery (SEA) was also significantly lower in the study group (p < 0.001). Proportion of patients with blood flow of subendometrial artery (SEA) after treatment was also significantly higher in the study group (p = 0.021). Relative amount of HOXA-10 mRNA in the endometrium was significantly higher in the study group of 15.85 +/- 5.76 compared with 3.21 +/- 2.70 in the control group (p < 0.001) Limitations, reasons for caution: This study may have a limitation due to a small number of sample available. Inaddition, it is difficult to know whether the positive effect of EGF-loaded collagen on endometrial HOXA-10 expression is caused by the collagen itself or by the sustained release of EGF. Wider implications of the findings: This new treatment regimen may not only promote endometrial growth but also enhance embryo implantation by increasing endometrial HOXA-10 expression in infertile patients with thin endometrium.

**Database:** EMBASE
20. New aspects of thin endometrium in ART
Author(s): Eftekhar M.
Source: International Journal of Reproductive BioMedicine; Apr 2017; vol. 15 (no. 4); p. 14
Publication Date: Apr 2017
Publication Type(s): Conference Abstract
Abstract: Successful embryo implantation needs a good quality embryo, coincident with a receptive endometrium. Suboptimal endometrial growth is an important step in endometrial receptivity and embryo implantation. Thin endometrium less than 7 mm is correlated to a lower chance of pregnancy. Intrauterine adhesions due to infection or curettage, treatment by oral contraceptives or clomiphene citrate, congenital anomalies, or past history of radiotherapy can lead to thin endometrium. However, thin endometrium is reported in 2.4% of assisted reproductive technology cycles. A thin endometrium sometimes is reported in in vitro fertilization (IVF) cycles in spite of the absence of demonstrable causes. Several strategies to treat thin endometrium have been studied including extended estrogen, ovarian hyper-stimulation with gonadotropins, low dose aspirin, low-dose hCG, tamoxifen, pentoxifylline and vitamin E, l-arginine, sildenafil, acupuncture and neuromuscular electric stimulation, granulocyte colony-stimulating factor (G-CSF), stem cell therapy and autologous platelet-rich plasma. In spite of the many modality of treatment, most of the options lead to only minor change in the endometrium thickness and subsequent pregnancy, and when this modality fails, patients are eventually candidate to surrogacy.
Database: EMBASE

Author(s): Fetih, A N; Habib, D M; Abdelaal, I I; Hussein, M; Fetih, G N; Othman, E R
Source: Facts, views & vision in ObGyn; Mar 2017; vol. 9 (no. 1); p. 21-27
Publication Date: Mar 2017
Publication Type(s): Journal Article
PubMedID: 28721181
Available at Facts, Views & Vision in ObGyn - from PubMed Central
Abstract: We aimed to investigate the effect of adding sildenafil vaginal gel to clomiphene citrate (CC) in infertile women with prior CC failure. METHODOLOGY: This is a self-controlled clinical trial. Women with CC failure (in prior 5 cycles) and thin endometrium were recruited (N = 42). In their 6th (CC only) cycle, women continued on CC 100 mg/day for 5 days, and had measurement of endometrial thickness and Doppler assessment of uterine arteries on day of HCG administration. In the 7th cycle, women (N = 36) were given usual dose of CC supplemented with sildenafil vaginal gel (5 gm, containing 50 mg sildenafil) twice daily from cycle day 8 to day of HCG administration. Endometrial thickness and uterine artery Doppler were measured on the day of HCG administration. In the 7th cycle, endometrial thickness was significantly higher than in the 6th (CC only) cycle (9.3 mm +/- 3.1 mm versus 6.6 mm +/- 1.4 mm, respectively, P = < 0.001). Uterine artery pulsatility index dropped from 2.4 +/- 0.8 in 6th cycle to 1.6 +/- 1.3 in 7th cycle (P = 0.002). Clinical pregnancy rate increased but numbers were too small (only 3 pregnancies). CONCLUSIONS: Sildenafil vaginal gel significantly increased endometrial thickness and uterine blood flow, and may improve pregnancy rate in patients with CC failure due to thin endometrium. Mucoadhesive vaginal gel formulation allowed shorter duration of sildenafil application, and less frequent daily dosing.
Database: Medline
22. Thermosensitive bioadhesive gels for the vaginal delivery of sildenafil citrate: in vitro characterization and clinical evaluation in women using clomiphene citrate for induction of ovulation

**Author(s):** Soliman G.M.; Fetih G.; Abbas A.M.

**Source:** Drug Development and Industrial Pharmacy; Mar 2017; vol. 43 (no. 3); p. 399-408

**Publication Date:** Mar 2017

**Publication Type(s):** Article

**PubMedID:** 27783532

**Abstract:**

**Objective:** The objective of this study is to develop and characterize in situ thermosensitive gels for the vaginal administration of sildenafil as a potential treatment of endometrial thinning occurring as a result of using clomiphene citrate for ovulation induction in women with type II eugonadotrophic anovulation. While sildenafil has shown promising results in the treatment of infertility in women, the lack of vaginal pharmaceutical preparation and the side effects associated with oral sildenafil limit its clinical effectiveness. Methods: Sildenafil citrate in situ forming gels were prepared using different grades of Pluronic (PF-68 and PF-127). Mucoadhesive polymers as sodium alginate and hydroxyethyl cellulose were added to the gels in different concentrations and the effect on gel properties was studied. The formulations were evaluated in terms of viscosity, gelation temperature (Tsol-gel), mucoadhesion properties, and in vitro drug release characteristics. Selected formulations were evaluated in women with clomiphene citrate failure due to thin endometrium (Clinicaltrial.gov identifier NCT02766725). Results: The Tsol-gel decreased with increasing PF-127 concentration and it was modulated by addition of PF-68 to be within the acceptable range of 28-37 degreeC. Increasing Pluronic concentration increased gel viscosity and mucoadhesive force but decreased drug release rate. Clinical results showed that the in situ sildenafil vaginal gel significantly increased endometrial thickness and uterine blood flow with no reported side effects. Further, these results were achieved at lower frequency and duration of drug administration. Conclusion: Sildenafil thermosensitive vaginal gels might result in improved potential of pregnancy in anovulatory patients with clomiphene citrate failure due to thin endometrium. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.

**Database:** EMBASE

23. Modern management of thin lining

**Author(s):** Mouhayar Y.; Sharara F.I.

**Source:** Middle East Fertility Society Journal; Mar 2017; vol. 22 (no. 1); p. 1-12

**Publication Date:** Mar 2017

**Publication Type(s):** Review

**Available at Middle East Fertility Society Journal - from ScienceDirect**

**Abstract:**

**Objective** To define "thin" endometrium in fertility treatment, and to critically explore the available treatment options. Design A review of the scientific literature. Setting N/A. Methods An electronic literature search pertaining to patients with "thin" endometrium undergoing fertility treatment was performed through April 2016. Results Adequate endometrial growth is an integral step in endometrial receptivity and embryo implantation. Whether idiopathic or resulting from an underlying pathology, a thin endometrium of <7 mm is linked to a lower probability of pregnancy; however, no reported thickness excludes the occurrence of pregnancy. Several treatment modalities have been studied and include extended estrogen, gonadotropin therapy, low-dose hCG, tamoxifen,
pentoxifylline, tocopherol, L-arginine, low-dose aspirin, vaginal sildenafil, acupuncture and neuromuscular electric stimulation, intrauterine G-CSF, and stem cell therapy. All treatment modalities except vaginal sildenafil, intrauterine GCF, and stem cell therapy were inconsistent in showing significant improvement in pregnancy rates. Early results of stem cell therapy trials seem promising. Conclusions EMT <7 mm is associated with lower probability of pregnancy in ART. Vaginal sildenafil appears to be a reasonable first line therapy option, and G-CSF appears to be a potential second option, while stem cell therapy seems to be a promising new treatment modality.

Database: EMBASE

Author(s): Zadehmodarres, Shahrzad; Salehpour, Saghar; Saharkhiz, Nasrin; Nazari, Leila
Source: JBRA assisted reproduction; Feb 2017; vol. 21 (no. 1); p. 54-56
Publication Date: Feb 2017
Publication Type(s): Case Reports
PubMedID: 28333034
Available at JBRA Assisted Reproduction - from Europe PubMed Central - Open Access

Abstract: Endometrium is one of the main factors in pregnancy. During assisted reproductive technology (ART) treatments, some cycles are cancelled due to inadequate endometrial growth. This study was conducted to evaluate the effectiveness of platelet-rich plasma (PRP) in the treatment of thin endometrium. Ten patients with history of inadequate endometrial growth in frozen-thawed embryo transfer (FET) cycles were recruited into the study. Intrauterine infusion of PRP was performed. Endometrial thickness was assessed. Chemical and clinical pregnancies were reported. In all patients, endometrial thickness increased after PRP and embryo transfer was done in all of them. Five patients were pregnant. According to this study, it seems that PRP was effective for endometrial growth in patient with thin endometrium.

Database: Medline

25. Granulocyte colony stimulating factor treatment of resistant thin endometrium in women with frozen-thawed blastocyst transfer.
Author(s): Kunicki, Michal; Łukaszuk, Krzysztof; Liss, Joanna; Skowrońska, Patrycja; Szczyptańska, Joanna
Source: Systems biology in reproductive medicine; Feb 2017; vol. 63 (no. 1); p. 49-57
Publication Date: Feb 2017
Publication Type(s): Controlled Clinical Trial Journal Article
PubMedID: 27874292

Abstract: The aim of the study was to assess the granulocyte-colony stimulating factor (G-CSF) effect on unresponsive thin (0.05). The live birth rate was 2/29 (6.89%) in the G-CSF group and 2/33 (6.06%) in the control group (p>0.05). We concluded that G-CSF infusion leads to an improvement in endometrium thickness but not to any improvement in the clinical pregnancy and live birth rates. Until more data is available G-CSF treatment should be considered to be of limited value in increasing pregnancy rate. ABBREVIATIONS: G-CSF: granulocyte colony-stimulating factor; M-CSF: macrophage colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; FET: frozen embryo transfer; IVF: in vitro fertilization.

**Author(s):** Le, A W; Wang, Z H; Dai, X Y; Xiao, T H; Zhuo, R; Zhang, B Z; Xiao, Z L; Fang, X J

**Source:** Genetics and molecular research : GMR; Jan 2017; vol. 16 (no. 1)

**Publication Date:** Jan 2017

**Publication Type(s):** Journal Article

**PubMedID:** 28128406

Available at Genetics and molecular research : GMR - from Free Medical Journals . com

**Abstract:** This study aimed to investigate the effect of icariin (ICA) on thin endometrium in a rat model. To this end, 6- to 8-week-old female Sprague Dawley rats (105) were randomly divided into 7 groups: untreated, vehicle-treated (lavage with NaCl), high-dose ICA (lavage with ICA at 200 mg·kg^-1·day^-1), medium-dose ICA (lavage ICA at 100 mg·kg^-1·day^-1), low-dose ICA (lavage with ICA at 50 mg·kg^-1·day^-1), sham model (injected with NaCl at uterus horn), and sample group. To induce thin endometrium, rats of all groups (except sham-model) were injected with 95% ethanol via the uterine horn. Each group underwent its respective treatment for 3 estrous cycles, after which 5 rats from each group were sacrificed, and endometrial thickness was measured. The expression of CD31, factor VIII, vascular endothelial growth factor (VEGF), cytokeratin (CK), and vimentin were detected via immunohistochemistry. The results showed that CD31, factor VIII, and VEGF were primarily expressed in the cytoplasm of endometrial and vascular epithelial cells. No difference in the expression of these factors was detected between the ICA lavage groups and the untreated groups. However, high dose ICA-treated group exhibited significantly higher expression of CD31, factor VIII, and VEGF compared to that in the low dose and vehicle-treated groups. CK and vimentin in the endometrial tissue were significantly higher in the untreated and treatment groups compared to the vehicle-treated group. This study demonstrated that ICA increases thickness of the endometrium, and it may modulate expression of VEGF, CD31, and factor VIII.

**Database:** Medline
27. Improvement of pelvic floor neuromuscular electrical stimulation (Nmes) on endometrial thickness and blood perfusion of infertile women with thin endometrium

**Author(s):** Luo Y.-P.; Xiao L.; Liang J.-H.; Lian W.

**Source:** International Journal of Clinical and Experimental Medicine; Jan 2017; vol. 10 (no. 1); p. 760-766

**Publication Date:** Jan 2017

**Publication Type(s):** Article

**Abstract:** Objective: Neuromuscular Electrical Stimulation (NMES) has been used in clinical treatment of problems related to gynaecology and obstetrics department, including stress urinary incontinence (SUI), low back pain, sexual dysfunction, pelvic pain, and constipation. However, its effect on endometrial thickness and blood perfusion in infertile women with thin endometria is still unknown. We aimed to evaluate the effect of pelvic floor neuromuscular electrical stimulation (NMES) therapy for improving endometrial thickness and blood perfusion in infertile women with thin endometria through different current intensity and duration of NMES current. Methods: 284 patients with infertility and thin endometria were recruited and divided into two groups, both of which were continuously monitored in regard to endometrial thickness and endometrial vascular resistance index (RI) during mature follicles days of two menstrual cycles. The control group of 134 patients was treated with estradiol valerate. The experimental group of 150 patients was treated with estradiol valerate and pelvic floor NMES. Endometrial thickness and RI were measured during the mature follicles days. Results: The mean endometrial thickness and RI were higher after NMES in the experimental group than in the control group; the difference was statistically significant (P<0.05). Further, the mean endometrial thickness, RI and luteinizing hormone (LH) were increased followed by the increased current intensity (P<0.05). Whereas the mean of endometrial thickness, RI and luteinizing hormone (LH) were unchanged when the patients were treated with different duration of NMES current. Also, we found that the endometrial thickness was related to the time of the electric stimulate P<0.05, and the longer is the treatment time, the thicker is the endometrial thickness. However, the intensity of the current is not associated with endometrial thickness, P>0.05. Conclusion: This study suggests that pelvic floor NMES not only increases endometrial thickness, but also improves endometrial perfusion. Therefore, NMES therapy may be effective for patients with thin endometria.

28. Failure to increase the thickness of thin endometria with intrauterine infusion of granulocyte colony stimulating factor (G-CSF).

**Author(s):** Check, J H; Choe, J K; Summers-Chase, D

**Source:** Clinical and experimental obstetrics & gynecology; 2016; vol. 43 (no. 3); p. 332-333

**Publication Date:** 2016

**Publication Type(s):** Journal Article

**PubMedID:** 27328485

**Abstract:** PURPOSE To corroborate or refute a previous study suggesting that intrauterine infusion of granulocyte colony stimulating factor (G-CSF) could significantly improve endometrial thickness into more fertile levels when the endometrial thickness was ≤ five mm. MATERIALS AND METHODS Three women whose endometrial thickness never exceeded five mm on the in vitro fertilization-embryo transfer (IVF-ET) cycle or subsequent attempted frozen ETs using graduated estradiol had intrauterine infusion of G-CSF to the estradiol regimen. RESULTS Not one of the three women improved the endometrial thickness beyond five mm and none conceived on the G-CSF cycle. One woman had a subsequent pregnancy following a frozen ET with only a four-mm thickness with no
infusion of G-CSF.

**CONCLUSION**

These data do not confirm the efficacy of intrauterine infusion of G-CSF for poor endometrial thickness. Perhaps only certain cases will respond. A larger series could take time to accumulate since other studies have shown that only 0.3% of women with ≤ five mm endometrial thickness in the late proliferative phase during an IVF-ET cycle will not improve the endometrial thickness > five mm using graduated estradiol protocols.

**Database:** Medline

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**29. G-CSF effects on treatment-resistant thin endometrium in women with frozen transfer/h2**

**Author(s):** Lukaszuk K.; Kunicki M.; Liss J.; Skowronska P.; Szczypanska J.

**Source:** Journal of Assisted Reproduction and Genetics; Dec 2016; vol. 33 (no. 12); p. 1706

**Publication Date:** Dec 2016

**Publication Type(s):** Conference Abstract

Available at [Journal of assisted reproduction and genetics](https://example.com) - from ProQuest (Hospital Premium Collection) - NHS Version

Available at [Journal of assisted reproduction and genetics](https://example.com) - from Europe PubMed Central - Open Access

**Abstract:** Objective The aim of the study was to assess the G-CSF effects on unresponsive thin (7 mm) endometrium in women undergoing frozen-thawed embryo transfer of blastocyst (FBT). Design Prospective pilot study performed at the INVICTA Fertility and Reproduction Centre. Materials and methods Twenty women with thin unresponsive endometrium were included in the process of FBT. The patients also failed to achieve an adequate endometrial thickness in previous IVF cycles. Results Prior to G-CSF infusion, endometrial thickness was 6.3 +/- 1.4 mm, and after it expanded to 7.5 +/- 1.5 mm (p = 0.01). When we divided the group into two subgroups in the endometrium increased from 6.1 +/- 0.1 to 6.6 +/- 0.4 mm in the group which conceived (ns) and from 6.3 +/- 1.4 to 7.6 +/- 1.5 mm in the which did not (p = 0.001). There were no significant differences between the two subgroups in respect to the endometrial thickness both before (p = 0.802) and after infusion (p = 0.252). delta (p = 0.189). The clinical pregnancy rate was 15%. Conclusion We concluded that G-CSF infusion leads to the improvement of endometrium thickness but our data do not indicate any improvement in clinical pregnancy rate. Prospective randomized placebo controlled study should be performed to support the claim. Financial support Study was funded by INVICTA Fertility and Reproduction Centre.

**Database:** EMBASE
30. Effects of Granulocyte Colony-Stimulating Factor (GCSF) on Persistent Thin Endometrium in Frozen Embryo Transfer (FET) Cycles.

**Author(s):** Mishra, Vineet V; Choudhary, Sumesh; Sharma, Urmila; Aggarwal, Rohina; Agarwal, Ritu; Gandhi, Khushali; Goraniya, Nilesh

**Source:** Journal of obstetrics and gynaecology of India; Oct 2016; vol. 66 ; p. 407-411

**Publication Date:** Oct 2016

**Publication Type(s):** Journal Article

**PubMedID:** 27651638

Available at [The Journal of Obstetrics and Gynecology of India](https://www.ncbi.nlm.nih.gov/pubmed/27651638) - from Europe PubMed Central - Open Access

**Abstract:**

**OBJECTIVE:** To predict the effectiveness of granulocyte colony-stimulating factor (GCSF) in the treatment of persistent thin endometrium resistant to other treatments in frozen embryo transfer (FET) cycles.

**STUDY DESIGN:** This is a hospital-based prospective study.

**PATIENTS:** Thirty-five women with persistent thin endometrium (<7 mm) resistant to standard treatments were involved in this study.

**INTERVENTIONS:** Intravenous infusion of GCSF (300 mcg/1 ml) was done in patients with thin endometrium on day 14 of FET cycles, and their endometrial thicknesses were measured after 48 h of infusion.

**MAIN OUTCOME MEASURES:** The primary outcome was an increase in endometrial thickness and the secondary outcome measures were chemical and clinical pregnancies.

**RESULTS:** The endometrial thickness increased from 5.86 ± 0.58 to 6.58 ± 0.84 mm after GCSF infusion. In 19 of the 35 participants (54.28 %) endometrial thickness increased to ≥7 mm and they subsequently underwent embryo transfer. Of these, 3 (15.78 %) patients had chemical pregnancy, but there was no clinical pregnancy. In 16 participants, embryo transfer was canceled in view of insufficient endometrial thickness (<7 mm).

**CONCLUSION:** GCSF caused a small increase in endometrial thickness in women with persistent thin endometrium, but there was no improvement in their pregnancy rates.

**Database:** Medline

31. Platelets for endometrial regeneration: A novel approach

**Author(s):** Aghajanova L.; Houshdaran S.; Balayan S.; Irwin J.; Huddleston H.; Giudice L.

**Source:** Fertility and Sterility; Sep 2016; vol. 106

**Publication Date:** Sep 2016

**Publication Type(s):** Conference Abstract

**Abstract:**

**OBJECTIVE:** Asherman's syndrome and a thin lining refractory to available therapy present significant challenges in ART practice. Autologous platelet rich plasma (PRP) is used to support tissue repair and growth in orthopedics, dentistry and other specialties. Herein we tested the hypothesis that PRP stimulates cellular processes involved in endometrial regeneration relevant to management of a thin lining or intrauterine scarring.

**DESIGN:** Laboratory-based study.

**MATERIALS AND METHODS:** PRP and platelet-poor plasma (PPP) were prepared using a double-spin method and activated with thrombin and calcium chloride. Human primary endometrial epithelial cells (eEC), endometrial stromal fibroblasts (eSF), endometrial mesenchymal stem cells (eMSC), bone marrow-derived mesenchymal stem cells (BM-MSC) and Ishikawa endometrial adenocarcinoma cells (IC) were cultured with and without 5% activated PRP, non-activated PRP, activated PPP and non-activated PPP. Effects of treatments were evaluated using in vitro assays for cell proliferation (WST-1), wound healing migration, and chemotaxis Transwell migration. Occurrence of mesenchymal-to-epithelial transition (MET) was evaluated by cytokeratin and vimentin immunofluorescence.

**RESULTS:** Activated PRP promoted the migration of human eSF, eMSC, BM-MSC, IC and eEC.
compared to non-activated PRP, PPP and vehicle controls, in both wound healing and chemotaxis assays, in a time-dependent manner (p<0.05). The WST-1 assay showed increase in stromal and mesenchymal cell proliferation by activated PRP vs. non-activated PRP and PPP (p<0.05), while epithelial cell proliferation was affected by both activated, but not non-activated, PRP and PPP (p<0.05). Under the experimental conditions tested, PRP did not promote MET in eSF or eMSC as shown by expression of vimentin and absent cytokeratin immunoreactivity. CONCLUSIONS: This is the first study to evaluate the effect of PRP on different human endometrial cells and on BM-MSC involved in regeneration. PRP enhanced migration and proliferation of all cells studied. These data provide an initial ex vivo proof of principle for the use of autologous PRP to promote endometrial regeneration in Asherman's syndrome and a thin endometrial lining and warrant pre-clinical studies in animal models and subsequently in the clinical setting.

32. Significant improvement in endometrial thickness with use of tamoxifen citrate in case with persistently thin endometrium: A retrospective study of 52 patients

Author(s): Singh S.; Ashraf N.; Basheer R.; Ashraf M.

Source: Human Reproduction; Jul 2016; vol. 31

Publication Date: Jul 2016

Publication Type(s): Conference Abstract

Available at Human Reproduction - from Oxford Journals - Medicine

Abstract: Study question: Does tamoxifen citrate increase endometrial thickness in women with earlier multiple cancelled embryo transfer cycles due to thin endometrium despite using estradiol valerate, pentoxifyllin, vitamin E, Sildenafil citrate, and granulocyte colony stimulating factor? Summary answer: Use of tamoxifen results in significant improvement in endometrial thickness from 6.8 mm to more than 8 mm. What is known already: Persistently thin endometrium is a very difficult entity to treat and is responsible for embryo transfer cancellation in a substantial number of women. The available modalities of treatment like high dose of estradiol valerate, sildenafil citrate, pentoxifyllin, vitamin E and granulocyte colony stimulating factor have been useful in increasing the endometrial thickness only in few of these women. An earlier published small case series of 3 women with thin endometrium showed improvement in the thickness after using tamoxifen citrate. Study design, size, duration: This is a historical case control study of 52 women with persistently thin endometrium with normal hysteroscopy and failed 2-3 cycle of estrogen replacement. All cases were recruited between February 2014 and November 2015. All these women had failed to achieve an adequate endometrium of 8 mm after using estradiol valerate 12 mg per day for at least 21 days previously. In subsequent cycles, they failed to improve even with addition of above mentioned adjuvants. Participants/materials, setting, methods: After initial failed attempt, they were given tamoxifen citrate 20 mg for 5 days from day 2 of periods. They underwent ultrasound for measuring follicle size and endometrial thickness from day 7/8 of periods. Cycles without dominant follicle were changed to estrogen replacement cycles by adding 8 mg of estradiol valerate. Ovulation day endometrial thickness was measured in case the follicular grew, or else, estradiol was continued for total of 21 days and endometrial thickness measured at repeated intervals. Main results and the role of chance: 52 women were evaluated for 136 endometrial preparation cycles. Total 116 cycles using estradiol valerate, vaginal sildenafil citrate, oral pantoxiphylene, vitamin E and intrauterine instillation of G-CSF were cancelled as mean endometrial thickness (ET) of these cycles was less than 6.8 mm. With addition of tamoxifen in the subsequent cycle, the ET showed significant improvement compared to the previous cycles. Of these, 43 women had improvement in endometrial thickness to \( > 8 \) mm, while for the remaining 9 women, endometrial thickness remained less than 6.9 mm. Out of these 43 women 35 women attained a mean of 9.8 mm thickness in first tamoxifen cycle while other 8
women reached mean endometrial thickness of 7.3 mm. In second tamoxifen cycle these women attained mean ET more than 8 mm. Overall, the biochemical pregnancy rate was 48% and clinical pregnancy rate was 39%. Limitations, reasons for caution: It is a retrospective study with small sample size. The women acted as their own controls. Wider implications of the findings: This study adds a new and potentially safer option for women with persistently thin endometrium. Further robust data in terms of large multicentric randomised controlled trials are needed to substantiate the findings since it will be difficult to get an adequately powered study in single centric study.

**Database:** EMBASE

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### 33. Collagen for sustained release of growth factors for treating patients with poorly developed thin endometrium

**Author(s):** Kim C.; Lee J.H.; Moon J.W.; Kang B.M.; Ko J.H.; Park S.N.

**Source:** Human Reproduction; Jul 2016; vol. 31

**Publication Date:** Jul 2016

**Publication Type(s):** Conference Abstract

**Abstract:**

**Study question:** Does collagen enable sustained release of growth factors and improve their treatment effect on poorly developed thin endometrium of infertile women? **Summary answer:** Collagen enables sustained release of epidermal growth factor (EGF) and improves the treatment effect of EGF on poorly developed thin endometrium of infertile women. **What is known already:** Although several treatment modalities have been offered to patients with thin endometrium, treatment for them is still challenging. Several growth factors and cytokines are required for proper preparation of the endometrium. Granulocyte colony-stimulating factor (G-CSF) and EGF have been shown to cure patients with thin endometrium. However, study on sustained release of growth factors for treating patients with thin endometrium has not been reported. **Study design, size, duration:** In vitro release test of EGF and granulocyte-macrophage colony-stimulating factor (GM-CSF) was performed. In addition, we analyzed the results of a total of 66 consecutive infertile women with thin endometrium <6 mm despite estradiol treatment who underwent intrauterine treatment with either EGF-loaded collagen solution (study group, n = 37) or EGF alone solution (control group, n = 29) between March 2014 and November 2015 for this retrospective study. **Participants/materials, setting, methods:** For in vitro release test, 0.8% collagen gel was mixed with EGF or GM-CSF solution in phosphate buffered saline (PBS). The growth factor-loaded gels were incubated in PBS at 37 degreeC and supernatant was taken at 4, 8, 24, 48 and 72 h after mixture. In the study group, slow intrauterine infusion of 0.8% collagen in which 50 ng/ml EGF was loaded was performed every 2-3 days during the follicular phase of 3-4 menstrual cycles. **Main results and the role of chance:** Percentages of released EGF and GM-CSF from 0.8% collagen gel at 24 h after mixture were 58.5 +/- 3.7 and 51.9 +/- 2.3%. Percentages of released growth factors at 72 h was significantly higher in EGF of 83.5 4.8% compared with 58.3 +/- 3.0% in GM-CSF loading (p < 0.001). Endometrial thickness after EGF treatment compared with before treatment significantly increased in both study and control groups (p < 0.001, p < 0.01, respectively). When study and control groups were compared after treatment, endometrial thickness was significantly higher in the study group (p = 0.002) and resistance index (RI) of subendometrial artery (SEA) was significantly lower in the study group (p < 0.001). **Limitations, reasons for caution:** Compared with EGF, released amount of GM-CSF from collagen gel was much smaller. In addition, our study may have a limitation to evaluate the effect of EGF-loaded collagen solution on thin endometrium due to a small number of sample available and retrospective nature. **Wider implications of the findings:** This is the first study to evaluate the effect of collagen on sustained release of growth hormones for intrauterine treatment.
of thin endometrium. This new treatment regimen may have a new therapeutic potential for infertile women with poorly developed thin endometrium.

**Database:** EMBASE

34. Growth hormone intrauterine perfusion combined with replacement cycle in the treatment of non-response thin endometrium: Report of 5 cases

**Author(s):** Yu H.; Gao S.; Tang H.; Chen H.; Deng Z.; Yang L.; Liu Z.; Tang Q.; Tang T.

**Source:** International Journal of Clinical and Experimental Medicine; Jun 2016; vol. 9 (no. 6); p. 11982-11989

**Publication Date:** Jun 2016

**Publication Type(s):** Article

**Abstract:** To investigate the effects of the frozen embryo transplantation for patients with poor outcome of endometrial growth by using growth hormone intrauterine perfusion combined with replacement cycle in the treatment of non-response thin endometrium. This is a prospective study and study participants were consecutively recruited between Jun 2014 and December 2014. A total of 5 non-response thin endometrium patients were selected, with treatment by frozen thawed embryo transfer from the Reproductive Center of Hunan Provincial Maternal and Child Health Hospital. The mean endometrial thickness of 5 patients on progesterone day was 7.96 +/- 0.71 mm, more than the mean endometrial thickness of the first perfusion (5.78 +/- 0.65) mm, the difference was statistically significant (t=10.46, P<0.05). All endometrial thickness on transplantation day was more than 7 mm. The average concentration of E2 was 9387.8 + 2623.87 pmol/l on the progesterone day. Clinical pregnancy and implantation rate of all cases was 72.73% (8/11), including 2 patients with full-term delivery and 1 patient with continued pregnancy; Embryo development of 1 patient diapause due to incision pregnancy, abortion embryo genetic testing results indicated normality. GH uterine cavity perfusion was a useful method for treatment of non-reactivity thin endometrium, and was helpful for improvement of endometrial thickness and receptivity, improve embryo implantation environment by assistance for HRT under the high estrogen levels. Copyright © 2016, E-Century Publishing Corporation. All rights reserved.

**Database:** EMBASE

**Author(s):** Garcia-Velasco J.A.; Acevedo B.; Alvarez C.; Alvarez M.; Bellver J.; Fontes J.; Landers J.; Manau D.; Martinez F.; Munoz E.; Robles A.; Rodriguez-Tabenero L.

**Source:** Reproductive BioMedicine Online; May 2016; vol. 32 (no. 5); p. 474-489

**Publication Date:** May 2016

**Publication Type(s):** Review

**PubMedID:** 26947451

**Abstract:** The endometrium is one of a number of factors involved in achieving optimal outcomes after assisted reproductive treatment. Owing to its "passive" growth following adequate ovarian stimulation, it has received virtually no attention. Only when either endometrial thickness or ultrasonographic pattern seem inadequate have different strategies been assessed to try to improve it, especially in those cases where it seems difficult or impossible to make it grow. The objective of this review is to summarize the different strategies that have been investigated in patients with inadequate endometrium, to attempt to provide solid evidence of therapies that may be beneficial and to move away from empirism. A review of the existing literature was performed by searching MEDLINE, EMBASE, Cochrane library and Web of Science for publications in English related to refractory endometrium. Most current treatments are based on anecdotal cases and not on solid data, although worldwide many doctors and patients use them. In conclusion, this review found that it is not easy to provide a pragmatic, evidence-based approach to help physicians and patients confused by the available data on how to improve a poor endometrium. Honest balanced information provided to our patients is the best that we can do. Copyright © 2016 Reproductive Healthcare Ltd. Published by Elsevier Ltd. All rights reserved.

**Database:** EMBASE

36. G-CSF intrauterine and thin endo-metrium, and pregnancy outcome, non randomized clinical trial

**Author(s):** Davari-Tanha F.

**Source:** International Journal of Fertility and Sterility; 2015; vol. 9 ; p. 77

**Publication Date:** 2015

**Publication Type(s):** Conference Abstract

**Available at** International Journal of Fertility and Sterility - from Europe PubMed Central - Open Access

**Abstract:** Background: Is G-CSF has any effects on cancelled ART cycle due to thin endometrium. This study showed the beneficial effects of G-CSF on thin endometrium. In two previous studies, some beneficial effects were reported and in another no effects were seen. Materials and Methods: In a nonrandomized clinical trial, fifteen cases were evaluated from June 2011 till September 2012. All cases had history of cycle cancellation due to thin endometrium which are referred to our center. They had used estradiol, and sildenafil citrate unsuccessfully in their previous cycle. Intrauterine infusion of G-CSF was done on the day of oocyte pick-up or 5 days before embryo transfer in recipient cycles. Primary outcome was endometrial thickness at least till 6.5 mm and secondary outcome as clinical pregnancy rate and then take home baby. All previous cycle was considered as control for each patient, the mean of age, gravidity, parity, FSH, were 35.13 +/- 9.531, 3(20%), 1(6.6%), 32.78 +/- 31.10 mIU/ml, respectively. (46.6%) had diminished ovarian reserve according to the FSH levels and averagely they had 1.2 +/- 0.532 cycle cancellation due to thin endometrium. Results: The G-CSF infused at the day of oocyte puncture or 5 days before embryo transfer, the endometrial thickness reached from 3.593 mm +/- to 7.120 mm +/- 0.84, the difference was 3.53
mm +/- 0.88, and clinical pregnancy rate was 20%, one missed abortion, a mother death at 34 weeks, and a pre-term labor at 30 weeks due to PROM. Conclusion: Remarkable results for a small group of patients who had no choice except cycle cancellation or surrogacy, but respond to G-CSF and acceptable outcome.

**Database:** EMBASE

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**37. Granulocyte colony stimulating factor for treatment of thin endometrium in assisted reproduction technology cycles**

**Author(s):** Kamath M.S.; Lele P.

**Source:** International Journal of Infertility and Fetal Medicine; 2015; vol. 6 (no. 3); p. 97-102

**Publication Date:** 2015

**Publication Type(s):** Review

**Available at**: International Journal of Infertility & Fetal Medicine - from Unpaywall

**Abstract:** Granulocyte colony stimulating factor (G-CSF), a glycoprotein, belongs to colony stimulating factor family and mainly regulates the growth and differentiation of granulocytes. However, it also plays an important role in endometrial stromal cell decidualization, ovulation, implantation, placental metabolism, trophoblast development and endometrial regeneration. It is due to these effects, it has been used in difficult clinical scenarios, such as unresponsive thin endometrium during assisted reproductive technology treatment, repeated implantation failure and recurrent miscarriages. Most of the studies have investigat-ed its use in thin endometrium. In this review, we have summarized the current updated evidence with regards to use of G-CSF in women with thin endometrium. Copyright © 2015, Jaypee Brothers Medical Publishers (P) Ltd. All Rights Reserved.

**Database:** EMBASE

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**38. Effect of adding human chorionic gonadotropin to frozen thawed embryo transfer cycles with history of thin endometrium**

**Author(s):** Davar R.; Farid Mojtahedi M.; Miraj S.

**Source:** Iranian Journal of Reproductive Medicine; 2015; vol. 13 (no. 4); p. 63

**Publication Date:** 2015

**Publication Type(s):** Conference Abstract

**Available at**: Iranian Journal of Reproductive Medicine - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:** Introduction: Embryo implantation process is a complex phenomenon and depends on fetal and maternal factors interaction. Endometrial thickness is needed for successful implantation. Increasing endometrial thickness, raise the chance of clinical pregnancy. The triple line pattern, with thickening more than 7mm, is indicating the greater chance of successful implantation. We designed this study to assess adding HCG to the conventional protocol in endometrial preparation in women with thin endometrium and history of IVF-ET failure. Materials and Methods: This non-randomized clinical trial study (quasi experimental design) was performed in Yazd Research and Clinical Center for Infertility on 28 patients. Participants were women who candidate for frozen thawed embryo transfer and had 2 previous failed ET cycle because of thin endometrium. All patients received 8 mg estradiol valerate on second day of menstrual cycle and continued during the study. HCG was administrated (150 IU, IM) from 8th days of cycle. In 12th-13th day Trans-vaginal sonography was done, when endometrial thickness reached at least 7mm, HCG was discontinued and frozen thawed embryo transfer was done. Results: Totally 28 patients were included. The mean age of participants...
was 30.39+/−4.7 years. The mean of endometrial thickness before and after HCG were 5.07+/−0.43 and 7.85+/−0.52 mm which were significantly different (p=0.00). After HCG administration 100% patient’s endometrial thickness reached more than 7mm. The frequency of 20% improvement after HCG was 89.3% (25 patients). Also there were 5 (17.8%) clinical and chemical pregnant women after HCG. Conclusion: Our study findings suggest that adding HCG to the conventional preparation method is an effective protocol and significantly improved endometrial thickness and pregnancy outcomes in women with previous embryo transfer failure because of thin endometrium.

**Database:** EMBASE

### 39. Methods for thin endometrium treatment in infertile women

**Author(s):** Kuznetsova I.V.; Zemlina N.S.; Kovalenko M.A.; Rashidov T.N.; Musina R.A.; Guschin A.E.; Dolgova T.I.

**Source:** International Journal of Gynecology and Obstetrics; Oct 2015; vol. 131

**Publication Date:** Oct 2015

**Publication Type(s):** Conference Abstract

**Abstract:** Objectives: Evaluation of efficiency of non-hormonal therapy focused on improvement of thin endometrium growth. Method: 35 females from 21 to 44 years with in infertility, failed attempts of IVF, associated with thin endometrium (<7 mm). Study methods included transvaginal ultrasound diagnostics, office hysteroscopy, real-time PCR diagnostics of vaginal, cervical and uterine infections. The following therapy methods were applied: human placental hydrolysate 6 mL by drop intravenous infusion No.10 during preconception preparation (20 patients), granulocyte colonystimulating factor as intrauterine instillations during proliferative phase of the cycle of scheduled spontaneous conception or IVF (12 patients). Mesenchymal stem cells of menstrual blood were applied to treat 7 patients. Results: Persistence of pathogenic microorganisms in the endometrium was found in 65.7% of observations. Ultrasound monitoring showed growth of endometrial from 6.27+/−0.29 to 8.41+/−0.37 with placental drug. Effect was evaluated by pregnancy onset as a result of conducted controlled ovarian stimulation or IVF in 61% of patients. Patients receiving GCS-F, thickness of endometrium increased from 6.12+/−0.27 to 8.2+/−0.40, pregnancy was registered in 75% of patients. For conduct of MSC therapy, 4 patients who did not respond to the therapy with placental drug, GCS-F and 3 patients with extremely thin endometrium were selected. Mean thickness endometrium increased from 5.10+/−0.21 to 6.74+/−0.56 mm. Conclusions: High frequency of persistence of facultative microflora in the endometrium is the basis for microbiological examination by real-time PCR diagnostic of infection in all patients with thin endometrium. Administration of human placental hydrolysate at the preconception stage and GCS-F in the cycle of controlled ovarian stimulation and ART (assisted reproductive technologies) programs are promising methods for fertility restoration in patients with infertility and thin endometrium. Application of MSC of menstrual blood allows solving a problem of endometrial growth in case of absolute non-response to hormonal and non-hormonal treatment methods. Further studies in this field are required.

**Database:** EMBASE

**Author(s):** Tehraninejad, Ensieh; Davari Tanha, Fateme; Asadi, Ebrahim; Kamali, Koorosh; Aziminikoo, Elham; Rezayof, Elahe

**Source:** Journal of family & reproductive health; Sep 2015; vol. 9 (no. 3); p. 107-112

**Publication Date:** Sep 2015

**Publication Type(s):** Journal Article

**PubMedID:** 26622308

Abstract:

**OBJECTIVE**
To evaluate effects of G-CSF on a cancelled ART cycle due to thin endometrium.

**MATERIALS AND METHODS**
In a nonrandomized clinical trial from January 2011 to January 2013 in two tertiary university based hospitals fifteen patients undergoing embryo transfer and with the history of cycle cancellation due to thin endometrium were studied. Intrauterine infusion of G-CSF was done on the day of oocyte pick-up or 5 days before embryo transfer. The primary outcome to be measured was an endometrium thickened to at least 6 mm and the secondary outcome was clinical pregnancy rate and consequently take-home baby. All previous cycles were considered as control for each patient.

**RESULT**
The G-CSF was infused at the day of oocyte retrieval or 5 days before embryo transfer. The endometrial thickness reached from 3.593±0.251 mm to 7.120 ± 0.84 mm. The mean age, gravidity, parity, and FSH were 35.13± 9.531 years, 3, 1 and 32.78 ± 31.10 mIU/ml, respectively. The clinical pregnancy rate was 20%, and there was one missed abortion, a mother death at 34 weeks, and a preterm labor at 30 weeks due to PROM.

**CONCLUSION**
G-CSF may increase endometrial thickness in the small group of patients who had no choice except cycle cancellation or surrogacy.

Database: Medline

41. Effects of icariin on the expression of ER, VEGF, and KDR in the endometrial cells of thin endometrium.

**Author(s):** Le, A W; Shan, L; Wang, Z H; Dai, X Y; Xiao, T H; Zuo, R

**Source:** Genetics and molecular research : GMR; Sep 2015; vol. 14 (no. 3); p. 11250-11258

**Publication Date:** Sep 2015

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 26400356

Abstract:

We explored the effects of icariin on the expression of estrogen receptor (ER), vascular endothelial growth factor (VEGF), and kinase insert domain receptor (KDR) in the endometrial cells of the thin endometrium. Primary endometrial cells were obtained and divided into a blank control group, a high-, a middle-, and a low-dose icariin groups, as well as an estrogen treatment group to undergo cellular identification by immunocytochemistry. The expression levels of ER, VEGF, and its receptor were estimated by western blotting. The expression levels of ER, VEGF, and KDR gradually increased from the control group to the estrogen (E2) treatment and icariin treatment groups; the differences were statistically significant. However, the differences were not statistically significant among the different icariin dose groups. The endometrium may be thickened by icariin treatment by increasing the expression levels of ER, VEGF, and KDR in endometrial cells.

Database: Medline
42. Combined treatments of intrauterine perfusion with G-CSF and injection of hCG enhance the endometrial growth, implantation and pregnancy rates in thin endometrium patients


Source: Human Reproduction; Jun 2015; vol. 30

Publication Date: Jun 2015

Publication Type(s): Conference Abstract

Available at Human Reproduction - from Oxford Journals - Medicine

Abstract: Study question: Intrauterine perfusion with G-CSF (granulocyte colonystimulating factor) and intrauterine injection of hCG improved the endometrial growth and implantation rates, respectively. This study was examined the efficiency between endometrium perfusion of G-CSF and a combination of G-CSF and intrauterine injection of hCG in the patients. Summary answer: For patients who had a thin endometrium (<8 mm) on the hCG day, the combined treatments of endometrium perfusion of G-CSF on the day of hCG and intrauterine injection of hCG before embryo transfer significantly improved the endometrial thickness, implantation and pregnancy rates. What is known already: An adequate endometrial thickness is necessary for successful implantation. The treatment of Vitamin E, L-arginine, or sildenafil citrate was not sufficient to improve the endometrial growth in patients with a thin endometrium, but intrauterine perfusion with G-CSF was effective to patients showing a resistance to the treatment. More recently, intrauterine injection of hCG before the embryo transfer improved significantly both the implantation success and the pregnancy rates of the patients with recurrent implantation failure. Study design, size, duration: Prospective study was examined using 58 patients who had a thin endometrium (<8 mm) on the hCG day and failed to conceive with high-quality embryos in previous IVF cycles in a private fertility clinic from 2011 to 2014. Groups were established according to the treatments. Participants/materials, setting, methods: Group A (n = 34) was received G-CSF (filgrastim 300 m/mL) by slow intrauterine infusion using embryo transfer catheter on the day of hCG. Group B (n = 24) was received G-CSF on the day of hCG and 500 IU of hCG intrauterine administration approximately 7 min before embryo transfer. Main results and the role of chance: There were no significant differences in endometrial thickness on the day of hCG among both groups (Group A vs. Group B; 6.9 +/- 0.8 vs.6.8 +/- 7.2) whereas both groups showed significant increase of the endometrial thickness on the day of embryo transfer (8.6 +/- 1.0 vs. 8.5 +/- 0.8). The endometrial thickness was gradually increased from the hCG to the ET day, but it was not significantly differed on the day of ET in both groups. Interestingly, the rates of implantation (13.0 vs. 22.6%) and clinical pregnancy (29.4 vs. 41.7%) were significantly higher in Group B than those in Group A (P < 0.01). Thus, the combined treatments of G-CSF and hCG intrauterine infusion enhanced the endometrial thickness, implantation and pregnancy rates of the patients. Limitations, reason for caution: The clinical results are necessary to confirm its efficacy and safety via further studies. Thus, further large cohort studies are required. Wider implications of the findings: This study shows the most recent finding that the combined treatments of G-CSF and hCG intrauterine infusion enhance the increase of endometrial thickness as well as the implantation and pregnancy rates in patients with thin endometrium. The combined treatments will improve the efficacy for patients with recurrent implantation failure.

Database: EMBASE
A prospective randomized controlled study (RCT) of Intra-uterine administration of Granulocyte Colony-Stimulating Factor (G-CSF) before embryo-transfer on resistant thin endometrium in IVF cycles

Author(s): Singh R.; Singh M.; Jindal A.; Jindal P.C.

Source: Human Reproduction; Jun 2015; vol. 30

Publication Date: Jun 2015

Publication Type(s): Conference Abstract

Abstract: Study question: Does intrauterine administration of G-CSF (granulocyte colony-stimulating factor) prior to Embryo Transfer in patients with resistant thin endometrium improve endometrial thickness and pregnancy rate in IVF cycles? Summary answer: Yes, intrauterine administration of G-CSF (granulocyte colony-stimulating factor) before embryo transfer in patients with resistant thin endometrium increases endometrial thickness and improves the pregnancy rate in IVF cycles. What is known already: Optimal endometrial thickness reflects an adequate maturation, which is a key factor for embryo implantation. Proliferative and secretory changes in the endometrial lining are the result of a complex intrauterine environment where sex steroid hormones and different local factors play an important role for endometrial thickening. Lucena and Moreno-Ortiz found that the uterine infusion of G-CSF quickly increased endometrial thickness resulting in a successful pregnancy and healthy born baby. Li et al. aimed to evaluate the effectiveness of G-CSF administration for infertile women with a thin endometrium in a frozen ET program. These results suggested that G-CSF is a factor that participates during endometrial remodeling enhancing the synchronization between uterine environment and embryo development. Study design, size, duration: 48 Infertile patients with thin endometrium younger than 42 years from Jan.2014 to Dec.2014 were included in this study. All using traditional treatments with estradiol and sildenafil citrate (Viagra) had been unsuccessful. Patients were randomly divided into two groups using a computer generated list. The study group received intrauterine administration of G-CSF (300 mg/ml) and control group received placebo-saline before Embryo Transfer. G-CSF was administered per int 72 hour on the day of hCG administration. If the endometrium had not reached at least a 7-mm within 48 h, a second infusion was given following oocyte retrieval. Main results and the role of chance: The endometrial growth was significantly different within the two groups. An improvement was shown between the control and G-CSF infused groups. Endometrial expansion to minimal thickness occurred within approximately 48 - 72 hour from G-CSF infusion. In all the subjects at the time of infusion of G-CSF, endometrial thickness was 6.49 +/- 1.65 mm, and, after infusion, it increased significantly to 8.79 +/- 1.57 mm. The IR and PR were statistically significantly higher in the group that received intrauterine infusion of G-CSF (23 and 33%, respectively) as compared with the control group (12 and 16%, respectively). Limitations, reason for caution: A relatively new concept in thin endometrium, requiring more multicentric trials worldwide. Our study is not without limitations. Firstly, we did not have a large number of patients. Secondly, we applied Aspirin and/or Sildenafil citrate which also could have a positive effect on endometrial thickness. We can only speculate that the other factors could have impact on endometrial thickness. But we do not believe that this could have essential impact on our results. Wider implications of the findings: Uterine perfusion with G-CSF represents a promising new tool for the currently mostly intractable problem of inadequate, thin endometrium. A thin endometrium is one of the most difficult problems encountered in assisted reproduction every day practice. Several methods were proposed, to increase thin endometrium in women undergoing IVF. These therapies included tocopherol, pentoxifylline, low-dose aspirin, sildenafil citrate, estradiol administration and hCG priming. Endometrial perfusion with G-CSF may
be effective in expanding chronically unresponsive thin endometrium, which was resistant to
traditional remedies. This treatment also deserves further investigation for its potential to improve
implantation chances in association with IVF and, therefore, pregnancy rates.

Database: EMBASE

44. Granulocyte colony stimulating factor (G-CSF): Does it really improve the endometrial
thickness in women with persistent thin endometrial thickness undergoing frozen endometrial
transfer?

Author(s): Swati S.; Sankalp S.; Ashraf C.M.

Source: Human Reproduction; Jun 2015; vol. 30

Publication Date: Jun 2015

Publication Type(s): Conference Abstract

Available at Human Reproduction - from Oxford Journals - Medicine

Abstract: Study question: Does a persistently unresponsive endometrium improves in thickness with
administration of granulocyte colony-stimulating factor (G-CSF) in frozen embryo transfer cycle?
Summary answer: The study failed to show a significant improvement in the endometrial thickness
after administration of G-CSF. What is known already: Endometrial thickness less than 7 mm has
been shown in studies to hamper pregnancy rates. Many women continue to have unresponsive thin
endometrium despite using all available modalities of treatment. Few small studies have reported
the use of G-CSF to be efficacious in increasing the endometrial thickness in women with thin
endometrium. None of the reported studies are randomized controlled trials (RCT) though. Study
design, size, duration: Prospective observational cohort study of 250 women with persistent
unresponsive endometrium < 7 mm was conducted in craft hospital from 2012-2014. These women
have tried and failed high dose estradiol therapy, long duration estradiol therapy, different routes of
estradiol, natural cycle endometrial preparation, sildenafil citrate and vitamin E before they were
offered off label use of G-CSF. Participants/materials, setting, methods: Endometrial preparation was
done with estradiol valerate 2 mg three times a day and escalated in phased manner. On day 20th of
estradiol, if the endometrium was less than 7 mm, they were recruited for the study. Intrauterine G-
CSF infusion was done and endometrial thickness was assessed 2 days later. Main results and the
role of chance: Overall, there was no significant increase in the endometrial thickness at 48 h post
infusion. (p = 0.09). 73/220 women (33.18%) had their endometrium improved to above 7 mm. They
underwent embryo transfer and resulted in clinical pregnancy rate of 34.2% (25/73) per embryo
transfer and implantation rate of 18%. Limitations, reason for caution: Despite the fact that it is one
of the largest reported study till now, it was not a randomized controlled trial. Also, since
pregnancies have been reported with endometrium as thin as 3.7 mm, 7 mm cut off for thin
endometrium is at best arbitrary. Wider implications of the findings: The persistently thin
endometrium can be improved by G-CSF in only approximately 1/3rd of the women. This raises
questions over the previous studies showing significant benefit of the intervention. The solution for
the ongoing controversy can be achieved only by a large preferably multicentric RCT.

Database: EMBASE
45. Effect of long term combined pentoxifylline and tocopherol administration on the endometrial proliferation: A prospective cohort study of 368 cases of thin endometrium

Author(s): Turki F.; Methni A.; Balet R.; El Irani E.; Ledee N.; Rahmati M.

Source: Human Reproduction; Jun 2015; vol. 30

Publication Date: Jun 2015

Publication Type(s): Conference Abstract

Abstract: Study question: Does long term administration of combined Pentoxifylline and Tocopherol improve endometrial proliferation (thickness and volume) in infertile patients with a documented thin unresponsive endometrium? Summary answer: Long term combined Pentoxifylline and Tocopherol administration significantly promotes endometrial proliferation and increases endometrial thickness and endometrial volume. What is known already: Previous Meta-analysis reported that the probability of clinical pregnancy in patients with thin endometrium (<7 mm) is significantly lower compared with cases presenting an appropriate endometrial proliferation. Its Treatment remains a real challenge since repeated failure to achieve adequate endometrial development may request gestational surrogacy. Long term combined Pentoxifylline and Tocopherol treatment has been previously reported to improve the endometrial growth, but no study has evaluated their long term endometrial effects on a large prospective cohort of infertile patients during the implantation window. Study design, size, duration: We are presenting a prospective cohort study including 368 women with thin endometrium. Thin endometrium was defined as an endometrial volume below 2ml or an endometrial thickness below 7 mm during the mid luteal phase of a non conceptional cycle. Patients were included between 2012 and 2014. Participants/materials, setting, methods: Patients were evaluated during mid luteal phase twice three months apart: once before, then after the introduction of the combined treatment including 800 mg of Pentoxifylline and 1000 UI of Tocopherol administered daily. An endometrial ultrasonic evaluation in two and three dimension defined the endometrial thickness and volume. Main results and the role of chance: 15% of the included patients did not improve their endometrial volume, 67% normalised their volume while 18% improve their endometrial volume but without a complete normalisation after 3 months of treatment. The mean endometrial volume and thickness increased significantly from 1.6 ml (+/-0.4) and 4.7 mm (+/-1.6) before, to 2.1 ml (+/-0.3 ml) and 7.1 mm (+/- 1.8) respectively after 3 months of treatment (p < 0.001, p = 0.001).No change was observed regarding Doppler of the uterine artery or the endometrial vascularization under treatment. Limitations, reason for caution: Only a randomized trial using a placebo may definitely prove the effectiveness of a long term combined treatment with Pentoxifylline and Tocopherol to improve thin unresponsive endometrium. Wider implications of the findings: Approximately 80% of the replaced human embryos fail to implant. Multiple factors may contribute to this failure, but the majority of these failures are linked to a poor endometrium conjugated with a poor embryo quality. Even if an ideal thickness has never been able to predict pregnancy, deficiency of the endometrial proliferation is clearly associated with a poor prognosis for implantation and placentation. Preventive treatment optimizing the endometrial proliferation may be useful to increase implantation rates.

Database: EMBASE
46. Two protocols to treat thin endometrium with granulocyte colony-stimulating factor during frozen embryo transfer cycles.

**Author(s):** Xu, Bin; Zhang, Qiong; Hao, Jie; Xu, Dabao; Li, Yanping

**Source:** Reproductive biomedicine online; Apr 2015; vol. 30 (no. 4); p. 349-358

**Publication Date:** Apr 2015

**Publication Type(s):** Journal Article

**PubMedID:** 25682303

**Abstract:** The efficacy of two granulocyte colony-stimulating factor (G-CSF) protocols for thin endometrium were investigated. Eighty-two patients were diagnosed with thin endometrium (<7 mm). Thirty patients with previously cancelled embryo transfers received intrauterine G-CSF in subsequent frozen embryo transfer (FET) cycles. Patients were divided into the G-CSF only and G-CSF with endometrial scratch subgroups. Compared with previous cycles, endometrial thickness increased from 5.7 ± 0.7 mm to 8.1 ± 2.1 mm after G-CSF treatment (P < 0.001). Endometrial thickness increases were not significantly different between the two subgroups. The G-CSF with endometrial scratch subgroup established nominally higher though non-significant clinical pregnancy and live birth rates than the G-CSF only subgroup (53.8 % versus 42.9% and 38.5% versus 28.6%, respectively). Fifty-two patients underwent FET despite edometrial thickness less than 7 mm, and were included as controls. Significantly higher embryo implantation and clinical pregnancy rates were observed in the G-CSF group compared with the control group (31.5% versus 13.9%; P < 0.01; 48.1% versus 25.0%; P = 0.038, respectively). Endometrial scracth did not impair G-CSF treatment for thin endometrium and favoured pregnancy and live birth rates. For patients with thin endometrium, embryo transfer cancellation and G-CSF treatment in subsequent FET cycles is beneficial.

**Database:** Medline

47. Evaluation of granulocyte colony-stimulating factor effects on treatment-resistant thin endometrium in women undergoing in vitro fertilization.

**Author(s):** Kunicki, Michał; Łukaszuk, Krzysztof; Woclawek-Potocka, Izabela; Liss, Joanna; Kulwikowska, Patrycja; Szczyptańska, Joanna

**Source:** BioMed research international; 2014; vol. 2014 ; p. 913235

**Publication Date:** 2014

**Publication Type(s):** Clinical Trial Journal Article

**PubMedID:** 24693540

**Available at BioMed Research International - from Europe PubMed Central - Open Access**

**Abstract:** The aim of the study was to assess the granulocyte colony-stimulating factor (G-CSF) effects on unresponsive thin (<7 mm) endometrium in women undergoing in vitro fertilization (IVF). We included thirty-seven subjects who had thin unresponsive endometrium on the day of triggering ovulation. These patients also failed to achieve an adequate endometrial thickness in at least one of their previous IVF cycles. In all the subjects at the time of infusion of G-CSF, endometrial thickness was 6.74 ± 1.75 mm, and, after infusion, it increased significantly to 8.42 ± 1.73 mm. When we divided the group into two subgroups according to whether the examined women conceived, we showed that the endometrium expanded significantly from 6.86 ± 1.65 to 8.80 ± 1.14 mm in the first group (who conceived) and from 6.71 ± 1.80 to 8.33 ± 1.85 mm in the second, respectively. There were no significant differences between the two subgroups in respect to the endometrial thickness both before and after G-CSF infusion. The clinical pregnancy rate was 18.9%. We concluded that the infusion of G-CSF leads to the improvement of endometrium thickness after 72 hours.

**Database:** Medline
Effect of intrauterine instillation of granulocyte colonystimulating factor on endometrial thickness and clinical pregnancy rate in women undergoing in vitro fertilization cycles: An observational cohort study

Author(s): Shah J.; Gangadharan A.; Shah V.

Source: International Journal of Infertility and Fetal Medicine; 2014; vol. 5 (no. 3); p. 100-106

Publication Date: 2014

Publication Type(s): Article

Abstract: Introduction: In spite of significant advances in the field of reproductive medicine, repeated implantation failure (RIF) is a challenging and extremely disappointing problem. The success of in vitro fertilization and embryo transfer (IVF-ET) cycles depends mainly on uterine receptivity and embryo quality. Successful evaluation of endometrial receptivity conducive to embryo implantation continues to be a challenge in assisted reproductive technology (ART). Several researcher groups have reported the successful use of granulocyte-colony stimulating factor (G-CSF) during IVF cycles in terms of achieving higher clinical pregnancy rates on account of increased endometrial thickness. Women who fail to achieve adequate endometrial thickness despite conventional treatment with high dose estrogen or those with a history of repeated implantation failures in spite of normal endometrial thickness often do not achieve pregnancy and resort to gestational surrogacy. A new therapeutic approach to achieve successful pregnancy in such patients would be very desirable.

Study objectives: To assess the efficacy of a single dose of intrauterine G-CSF on endometrial thickness, implantation and clinical pregnancy rates in women who either had a thin endometrium (< 8 mm) or a history of repeated implantation failures (RIF) at IVF-ET cycles despite adequate endometrium (>= 8 mm). All were infused with a single dose of G-CSF (300 mcg) in the uterine cavity after 10 days of priming with oral estradiol valerate and vaginal sildenafil. Materials and methods: Two hundred and thirty-one women (between 24 and 46 years of age) undergoing IVF-ET were recruited for the study. All cases were prospectively studied at the Mumbai Fertility Clinic and IVF Center (a subdivision of Kamala Polyclinic and Nursing Home) over a period of 6 months from January to June 2014, after their written informed consent. Subgroup I consisted of 117 patients who had a persistently thin endometrium (< 8 mm) in spite of high dose oral estradiol valerate and vaginal sildenafil priming. Subgroup II consisted of 114 patients who had a history of repeated (two or more) implantation failures (RIF) at IVF-ET cycles despite adequate endometrium (>= 8 mm). All were infused with a single dose of G-CSF (300 mcg) in the uterine cavity after 10 days of priming with oral estradiol valerate and vaginal sildenafil citrate. Endometrial thickness was reassessed 4 days after G-CSF instillation. This was followed by administration of intramuscular progesterone in oil (100 mg) daily with embryo transfer on day 5 of progesterone for all patients. All embryo transfers for patients undergoing oocyte donation or embryo donation were done at the 4-cell stage on day 2. All Frozen embryo transfers (FET) of vitrified embryos were at 8 cell stage. Estimation of serum beta hCG was at 14 days post-embryo transfer for all patients. Successful implantation and net clinical pregnancy rate was confirmed based on appearance of gestational sac on sonogram after 10 days and observation of fetal cardiac activity after 20 days of positive beta-hCG results. Results: Out of total 231 patients recruited in the study, 95% patients from subgroup I (n = 111) and 94% patients from subgroup II (n = 107) showed mean increase in endometrial thickness by at least 2.5 mm within 4 days of G-CSF single dose instillation. A total of 218 patients from both subgroups underwent S. beta-hCG estimation 14 days post IVF-ET. Out of 103 beta-hCG positive patients, 83 showed net clinical pregnancy (fetal cardiac activity present) giving a net pregnancy rate of 38.07% for the whole study group with 37% in the subgroup with thin endometrium (< 8 mm) and 39.25% in the subgroup with adequate (>= 8 mm) endometrium with history of two or more failed implantation at previous IVF-ET cycles. There were no adverse events for the whole study population. Conclusion: There can be a strong possibility with a single dose of 300 mcg intrauterine infusion of G-CSF to achieve...
significant increase in the endometrial thickness with higher successful pregnancy rate among infertile women undergoing IVF-ET cycles with a history of a persistently thin endometrium or repeated implantation failures (rather difficult to treat patients). G-CSF could be a valuable tool to consider before advising the option of surrogacy. In the absence of a control group, our conclusions warrant conduct of further studies.

Database: EMBASE


Author(s): Eftekhar, Maryam; Sayadi, Mozhgan; Arabjahvani, Farideh

Source: Iranian journal of reproductive medicine; Oct 2014; vol. 12 (no. 10); p. 661-666

Publication Date: Oct 2014

Publication Type(s): Journal Article

PubMedID: 25469123

Available at Iranian Journal of Reproductive Medicine - from ProQuest (Hospital Premium Collection) - NHS Version

Available at Iranian Journal of Reproductive Medicine - from PubMed Central

Abstract: BACKGROUND We often see patients with a thin endometrium in ART cycles, in spite of standard and adjuvant treatments. Improving endometrial growth in patients with a thin endometrium is very difficult. Without adequate endometrial thickness these patients, likely, would not have reached embryo transfer. OBJECTIVE We planned this study to investigate the efficacy of intrauterine granulocyte colony-stimulating factor (G-CSF) perfusion in improving endometrium, and possibly pregnancy rates in frozen-thawed embryo transfer cycles. MATERIALS AND METHODSThis is a non-randomized intervention clinical trial. Among 68 infertile patients with thin endometrium (<7 mm) at the 12(th)-13(th) cycle day, 34 patients received G-CSF. G-CSF (300 microgram/1mL) to improve endometrial thickness was directly administered by slow intrauterine infusion using IUI catheter. If the endometrium had not reached at least a 7-mm within 48-72 h, a second infusion was given. Endometrial thickness was assessed by serial vaginal ultrasound at the most expanded area of the endometrial stripe. RESULTS The cycle was cancelled in the patients with thin endometrium (endometrial thickness below 7mm) until 19(th) cycle day ultimately. The cycle cancelation rate owing to thin endometrium was similar in G-CSF group (15.20%), followed by (15.20%) in the control group (p=1.00). The endometrial growth was not different within 2 groups, an improvement was shown between controlled and G-CSF cotreated groups, with chemical (39.30% vs. 14.30%) and clinical pregnancy rates (32.10% vs. 12.00%) although were not significant. CONCLUSION Our study fails to demonstrate that G-CSF has the potential to improve endometrial thickness but has the potential to improve chemical and clinical pregnancy rate of the infertile women with thin endometrium in frozen-thawed embryo transfer cycle.

Database: Medline
50. Tamoxifene is better than low dose clomiphene or gonadotropins in women with thin endometrium (<6mm) after clomiphene in IUI cycles: A prospective study

Author(s): Sharma S.; Geetha B.R.; Ghosh S.; Saha I.; Sarkar A.; Chakravarty B.

Source: Fertility and Sterility; Sep 2014; vol. 102 (no. 3)

Publication Date: Sep 2014

Publication Type(s): Conference Abstract

Abstract: OBJECTIVE: Second line of treatment in patients with thin endometrium following clomiphene (CC) is gonadotropin stimulation, which is associated with higher cost, multiple births and ovarian hyperstimulation syndrome. Tamoxifen, a selective estrogen receptor modulator acts as an estrogen agonist on endometrium. The objective of the present study was to compare the efficacy of low dose CC, tamoxifene, and gonadotropins in women with thin endometrium (<6mm) following CC in IUI cycle. DESIGN: Prospective study between 12/2011 and 6/2013. MATERIALS AND METHODS: Women (n=502) undergoing IUI with endometrium <6mm after CC 100mg were divided into 3 treatment groups. Women in Gr A (n=182, cycles=364) received CC (50mg/day from day 3-7), Gr B (n=179, cycles=221) received Tamoxifene (40mg/day from day 3-7) & Gr C (n=141, cycles=226) received continuous u-FSH 75IU-150IU from day 3 onwards until hCG injection. The number of follicles, size of follicle on day of hCG, day of hCG, endometrial thickness (ET), pregnancy rate, cancellation rates, multiple pregnancy, miscarriage and live birth were compared. RESULTS: Pregnancy and live birth rate were statistically significant in tamoxifene and gonadotropin group compared to CC. Tamoxifene results in monofollicular development. In PCOS patients tamoxifene results in higher cancellation rates due to non response while cancellations in CC were due to luteinised unruptured follicle and thin endometrium. PCOS women with tamoxifene had longer follicular phase than CC and gonadotropin. In gonadotropin group cancellations were mainly due to multi follicular development (>4 follicles). There were no multiple pregnancies in tamoxifene group. CONCLUSION: Tamoxifene can improve endometrial thickness and live birth rate in patients with thin endometrium after CC. Though its outcome is comparable with gonadotropin, it is devoid of complications. (Table Presented).

Database: EMBASE
51. Treating patients with "thin" endometrium - an ongoing challenge.

Author(s): Lebovitz, Oshrit; Orvieto, Raoul

Source: Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology; Jun 2014; vol. 30 (no. 6); p. 409-414

Publication Date: Jun 2014

Publication Type(s): Journal Article Review

PubMedID: 24693854

Abstract: OBJECTIVE To review the literature regarding inadequate growth ("thin") of the endometrium and to present the hitherto published methods aimed to improve endometrial thickness and the consequent endometrial receptivity. MATERIALS AND METHODS A literature review was conducted for all relevant articles assessing the effect of various treatment modalities on "thin" endometrium and the consequent reproductive outcome. RESULTS Several treatment modalities have been offered to patients with "thin" endometrium, including hysteroscopic adhesiolysis, hormonal manipulation by estrogen and GnRH-agonist, vasoactive measures such as aspirin, vitamin E, pentoxifylline, l-arginine or sildenafil, intra-uterine infusion of growth factor such as G-CSF and the recent application of regenerative medicine. In spite of the vast diversity of treatment, most of the options accomplish only minor change in the endometrium thickness and subsequent pregnancy rate, and when they fail, patients are usually referred to surrogacy. CONCLUSIONS "Thin" endometrium is known to adversely affect reproductive performance. Treatment of "thin endometrium" remains a challenge and future large researches are required to further elucidate and optimal management of patients with "thin" endometrium.

Database: Medline

52. Vagifem is superior to vaginal premarin in induction of endometrial thickness in the frozen-thawed cycle patients with refractory endometria: A randomized clinical trial

Author(s): Zolghadri J.; Haghbin H.; Dadras N.; Behdin S.

Source: Iranian Journal of Reproductive Medicine; Jun 2014; vol. 12 (no. 6); p. 415-420

Publication Date: Jun 2014

Publication Type(s): Article

Available at Iranian journal of reproductive medicine - from ProQuest (Hospital Premium Collection) - NHS Version

Available at Iranian journal of reproductive medicine - from PubMed Central

Abstract: Background: Embryo transfer to a developed endometrium is an important prognostic factor in frozen-thawed embryo transfer cycle outcome. Vaginal estrogen, such as Vagifem vaginal tablets and Premarin vaginal cream, is a regimen used for the patients with refractive endometria. Objective: Our objective was to compare the effects of Vagifem and Premarin on the endometrial thickness of the patients with refractive endometria. Materials and Methods: In this randomized clinical trial, 30 patients with refractive endometria in frozen-thawed embryo transfer cycles received Vagifem vaginal tablets and 30 women received Premarin vaginal cream. Endometrial thickness was measured on the 14th day of drug administration. Results: Comparing the endometrial thicknesses of the two groups showed that the endometria of the Vagifem group was significantly thicker than that of the Premarin group (5.93+/-.038 vs. 6.74+/-.032; p<0.001). Conclusion: Vagifem is superior to Premarin in induction of endometrial thickness in frozen-thawed embryo transfer cycles in the patients with refractive endometria. Copyright © 2014, Research and Clinical Center for Infertility. All Rights reserved.

Database: EMBASE
53. Granulocyte colony-stimulating factor administration for infertile women with thin endometrium in frozen embryo transfer program

Author(s): Li Y.; Pan P.; Chen X.; Li L.; Yang D.

Source: Reproductive Sciences; Mar 2014; vol. 21 (no. 3); p. 381-385

Publication Date: Mar 2014

Publication Type(s): Article

PubMedID: 23885097

Abstract: We aimed to evaluate the effectiveness of granulocyte colony-stimulating factor (G-CSF) administration for infertile women with thin endometrium in frozen embryo transfer program. Among 59 infertile patients with thin endometrium (<=7 mm), 34 patients received uterine infusion of recombinant human G-CSF (100 mug/0.6 mL) on the day of ovulation or administration of progesterone or human chorionic gonadotropin, with 40 cycles defined as G-CSF group and 49 previous cycles as self-controlled group, and 25 patients refused, with 80 cycles defined as the control group. Higher proportion of induced cycles and lower proportion of natural cycles were observed in the G-CSF group, when compared to the self-controlled group or control group (P <.05). The cycle cancellation rate was, in descending order, 69.39% in self-controlled group, 48.75% in control group, and 17.50% in G-CSF group, with significant difference (P <.05). The implantation rate and clinical pregnancy rate per embryo transfer were similar in all the groups (P >.05). Our study fails to demonstrate that G-CSF has the potential to improve embryo implantation and clinical pregnancy rate of the infertile women with thin endometrium. © 2013 The Author(s).

Database: EMBASE

54. "Follicular HCG endometrium priming for IVF patients experiencing resisting thin endometrium. A proof of concept study".

Author(s): Papanikolaou, E G; Kyrou, D; Zervakakou, G; Paggou, Efstathia; Humaidan, P

Source: Journal of assisted reproduction and genetics; Oct 2013; vol. 30 (no. 10); p. 1341-1345

Publication Date: Oct 2013

Publication Type(s): Clinical Trial Journal Article

PubMedID: 23949214

Available at Journal of Assisted Reproduction and Genetics - from ProQuest (Hospital Premium Collection) - NHS Version

Available at Journal of Assisted Reproduction and Genetics - from Europe PubMed Central - Open Access

Abstract: PURPOSEA thin endometrium is one of the most difficult problems encountered in assisted reproduction every day practice. Whether a daily dose of 150 IU HCG for 7 days concomitant with estrogen administration in estrogen replacement cycles can increase the endometrial thickness and improve pregnancy outcome, was the objective of the current study.

METHODS Seventeen infertile patients with successive implantation failures and resisting thin endometrium, being recipients of fresh donor or frozen embryos were recruited. This was a prospective cohort, proof of concept study, NCT01768247. On day-8 or 9 of the estrogen administration, and continuing 8 mg estrogen per day, subcutaneous injections of 150 IU HCG were initiated daily for 7 days. After a week on HCG priming, (day-14 or 15) endometrial thickness was controlled with ultrasound, and progesterone was initiated.

RESULTS Mean endometrial thickness was increased from 5.2 mm to 6 mm (p = 0.008). 35.3 % of the patients had more than 20 % improvement of their endometrial thickness after HCG priming. 17 % achieved an endometrial thickness more than 7 mm, and 29.4 % did not improve their thickness at all. Interestingly, from the later two became pregnant. Overall, 41 % of them (7/17)
finally delivered.

**CONCLUSIONS**

One hundred fifty IU HCG endometrial priming for 7 days in the proliferative phase of estrogen substituted cycles for frozen embryos is highly promising, as not only the thickness of the endometrium improves but also eventually the receptivity appears normalized.

**Database:** Medline

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**55. Prospective randomized study of endometrial perfusion with granulocyte colony-stimulating factor (G-CSF) in unselected IVF cycles: Impact on endometrial thickness and clinical pregnancy rates**

**Author(s):** Barad D.H.; Kushnir V.A.; Shohat-Tal A.; Lazzaroni E.; Lee H.-J.; Gleicher N.

**Source:** Fertility and Sterility; Sep 2013; vol. 100 (no. 3)

**Publication Date:** Sep 2013

**Publication Type(s):** Conference Abstract

**Abstract:**

**OBJECTIVE:** Since G-CSF has been reported to expand chronically thin endometrium, resistant to traditional treatments, to investigate whether G-CSF also affects endometrial thickness and clinical pregnancy rates in routine, unselected IVF cycles. **DESIGN:** Registered, prospectively randomized, blinded placebo-controlled clinical trial (RCT, ClinicalTrials.gov. ID# NCT01202656).

**MATERIALS AND METHODS:** The RCT involved 126 consecutive, unselected IVF patients in their first IVF cycles. A randomization table assigned 66 to G-CSF and 60 to placebo. G-CSF utilized was Nupogen (Filgrastim, Amgen, Thousand Oaks, CA; 300mcg/1.0ml). G-CSF or placebo was administered on the morning of hCG administration by slow transcervical intrauterine infusion. Endometrial thickness was assessed by routine vaginal ultrasound prior to infusion and again 5 days later at time of embryo transfer. **RESULTS:** Mean age for the whole study group was 39.7 +/- 5.4 years (G-CSF 40.1 +/- 4.98 and placebo 39.2 +/- 5.8; NS). Endometrial thickness significantly increased over the 5-day observation period for the whole group by approximately 1.34 mm (95% CI -1.736, -0.947; P < 0.0001). The increase was, however similar in treatment and placebo groups. Subdividing initial endometrial thickness into 4 strata (endometrium <8.23 mm, 8.24-10.35, 10.36-12.47 and >12.48mm) also revealed no differences. A logistic regression model, looking at treatment effects on clinical pregnancy rates demonstrated no effect of G-CSF treatment, a finding confirmed by adjustment for age and dividing into above noted 4 strata by initial endometrial thickness. **CONCLUSION:** G-CSF neither affects endometrial thickness nor pregnancy rates in randomly selected IVF patients. Since these results were obtained in an older patient population, they may not necessarily apply to younger women.

**Database:** EMBASE

Author(s): Gleicher, N; Kim, A; Michaeli, T; Lee, H-J; Shohat-Tal, A; Lazzaroni, E; Barad, D H

Source: Human reproduction (Oxford, England); Jan 2013; vol. 28 (no. 1); p. 172-177

Publication Date: Jan 2013

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

PubMedID: 23081869

Available at Human Reproduction - from Oxford Journals - Medicine

Abstract: STUDY QUESTIONIs thin endometrium unresponsive to standard treatments expandable by intrauterine perfusion with granulocyte colony-stimulating factor (G-CSF)?

SUMMARY ANSWERThis cohort study is supportive of the effectiveness of G-CSF in expanding chronically unresponsive endometria.

WHAT IS KNOWN ALREADY In a previous small case series, we reported the successful off-label use of G-CSF in four consecutive patients, who had previously failed to expand their endometria beyond 6.9 mm with the use of standard treatments.

STUDY DESIGN, SIZE AND DURATION In a prospective observational cohort pilot study over 18 months, we described 21 consecutive infertile women with endometria <7 mm on the day of hCG administration in their first IVF cycles at our center. All previous cycles using traditional treatments with estradiol, sildenafil citrate (Viagra™) and/or beta-blockers had been unsuccessful. G-CSF (Nupogen™) was administered per intrauterine catheter by slow infusion before noon on the day of hCG administration. If the endometrium had not reached at least a 7-mm within 48h, a second infusion was given following oocyte retrieval. Primary and secondary main outcomes were an increase in endometrial thickness and clinical pregnancy, respectively. Endometrial thickness was assessed by vaginal ultrasound at the most expanded area of the endometrial stripe.

PARTICIPANTS/MATERIALS, SETTINGS AND METHOD This study was uncontrolled, each patient serving as her own control in a prospective evaluation of endometrial thickness. The mean ± SD age of the cohort was 40.5 ± 6.6 years, gravidity was 1.8 ± 2.1 (range 0-7) and parity was 0.4 ± 1.1 (range 0-4); 76.2% of women had, based on age-specific FSH and anti-Müllerian hormone, an objective diagnosis of diminished ovarian reserve and had failed 2.0 ± 2.1 prior IVF cycles elsewhere.

MAIN RESULTS AND THE ROLE OF CHANCE With 5.2 ± 1.9 days between G-CSF perfusions and embryo transfers, endometrial thickness increased from 6.4 ± 1.4 to 9.3 ± 2.1 mm (P < 0.001). The Δ in change was 2.9 ± 2.0 mm, and did not vary between conception and non-conception cycles. A 19.1% ongoing clinical pregnancy rate was observed, excluding one ectopic pregnancy.

LIMITATIONS AND REASONS FOR CAUTION Small sample size (but a highly selected patient population) in an uncontrolled cohort study and in unselected first IVF cycles at our center.

WIDER IMPLICATIONS OF THE FINDINGS This pilot study supports the utility of G-CSF in the treatment of chronically thin endometrium and suggests that such treatment will, in very adversely affected patients, result in low but very reasonable clinical pregnancy rates.

STUDY FUNDING/COMPETING INTEREST(S) This work was supported by the Foundation for Reproductive Medicine, New York, New York, USA, a not-for-profit research foundation and intramural grants from the Center for Human Reproduction (CHR)-New York. N.G. and D.H.B. are members of the board of the Foundation for Reproductive Medicine. N.G. is owner of CHR-New York, where the study was conducted. N.G. and D.H.B. have been recipients of research awards, travel grants and speaker honoraria from various pharmaceutical and medical device companies. None of these companies was, however, in any way associated with the materials and the manuscript presented here. N.G. and D.H.B. are listed as co-inventors on a number of awarded and still pending U.S. patents, none related to the materials presented here. N.G. is on the board of a medically related company, not in any way associated with the data presented here.

Database: Medline
OBJECTIVE

Clomiphene citrate (CC) has some negative effects on the endometrium. We aimed to determine the effect of vaginally administered local estrogen (LE) on endometrial thickness (ET) and pregnancy rates in CC stimulated cycles.

MATERIAL AND METHOD

This was a prospective randomized crossover study that took place in a university hospital. The patients had received CC due to unexplained infertility (UI). Two different treatment protocols were given sequentially as, either CC+LE or CC alone. Each protocol was planned for two cycles and there was a one-month wash-out period between protocols. The effects of LE on the 3(rd) and 9(th) day, the ovulation day (OD) and 7(th) postovulation day (POD7) were investigated.

RESULT

A total of 6 pregnancies were achieved with 3 patients from each protocol. The ET was 7.6±1.4 mm and 8.3±2.1 mm respectively and significantly different in the CC group and the CC+E2 groups on the OD (p=.039), while these values were 9.7±2.3 mm and 10.9±3.0 mm respectively and significantly different on the POD7 (p=.007). There was no significant difference between the groups for arterial PI values on the OD and POD7. The frequency of thin endometrium (<6 mm) was 15.2% and 12.2% respectively in the CC group and the CC+E2 group on the OD (p=.628) and 5.1% and 1.2% respectively on the POD7 (p=.182).

CONCLUSION

Adding vaginal LE to CC stimulated cycles led to a significant increase in ET on the OD and POD7. However, this difference in thickness was not reflected in the pregnancy rates in this study.
58. Successful treatment with intrauterine perfusion of granulocyte colony stimulating factor (G-CSF) of chronically intractable thin endometrium

Author(s): Vidali A.; Barad D.H.; Gleicher N.

Source: Human Reproduction; 2011; vol. 26

Publication Date: 2011

Publication Type(s): Conference Abstract

Abstract: Introduction: Chronically intractable thin endometrium, resistant to standard treatments, is an unresolved problem, especially in association with in vitro fertilization (IVF). We here report a new treatment approach. Material and Methods: We are describing a prospectively collected cohort of 4 women who presented with inadequate endometrium after failing standard therapies at 2 independent fertility centers. Prior treatment failure was defined as failing to reach minimal endometrial thickness of 7 mm with estrace supplementation (2mg BID, per os, and 1mg TID per vagina) and sildenafil citrate (Viagra, 25mg QID per vagina). Patients were treated with slow perfusion of the endometrial cavity with 1 ampule (300U/1ml) granulocyte colony stimulating factor (G-CSF, Neupogen, Filgastrim, Amgen Manufacturing Limited, Thousand Oaks, CA) via a vaginally placed catheter. Results: All 4 patients successfully expanded their endometrium to at least 7 mm within 48 hours from infusion, allowing for embryo transfer. All 4 patients also conceived and, except for one, have normally progressing pregnancies. One pregnancy had to be terminated due to intramural ectopic location. One ongoing pregnancy is a twin gestation. Conclusions: Treatment with G-CSF has previously been proposed for implantation failure and repeated unexplained pregnancy loss. This study suggests that the intrauterine application of G-CSF can also overcome chronically intractable thin endometrium, an unresolved problem in infertility care. Unexpectedly high implantation rates warrants evaluation of G-CSF in routine IVF. A blinded, prospectively randomized study to test this hypothesis is underway.

Database: EMBASE
59. A gradual increase of endometrial thickness from the day of HCG to the day of ET is predictive of pregnancy outcome in patients with a thin endometrium (<8mm)

Author(s): Jung Y.H.; Kim Y.Y.; Kim M.H.; Cho J.D.

Source: Fertility and Sterility; Sep 2011; vol. 96 (no. 3)

Publication Date: Sep 2011

Publication Type(s): Conference Abstract

Abstract: OBJECTIVE: An adequate endometrial thickness is necessary for successful implantation. Numerous studies have demonstrated that thin endometrium on the day of hCG is associated with low pregnancy rates. This study was carried out to evaluate the relationship between a gradual increase of endometrial thickness from the day of hCG to the day of ET and pregnancy success and applied to the patients who have less than 8 mm of endometrial thickness on the day of hCG.

DESIGN: A prospective study. MATERIALS AND METHODS: One hundred two patients who have an endometrial thickness < 8 mm on the hCG day were examined and divided into two different groups by the changes of endometrial thickness. Group I belonged a gradual increase of endometrial thickness from the hCG day to the ET day and Group II with a slow decrease. Luteal phase was supported by 8% progesterone gel daily and 6-8 mg/day oral E2. RESULTS: Among 102 patients, 46 patients showed a gradual increase of endometrial thickness (Group I) whereas 56 patients showed a slow decrease (Group II). Both groups were similar age, E2 levels on the hCG day, no. of retrieved oocytes and transferred embryos. Clinical PR and ongoing PR were significantly higher in Group I than Group II (P<0.01). (Table presented) CONCLUSION: If endometrial thickness of patients having a thin endometrium (<8 mm) on the day of hCG has gradually increased from the hCG day to the ET day, we would expect high pregnancy rate and ongoing pregnancy rate. Therefore, endometrial thickness on the ET day is important parameter than that on the hCG day in patients with a thin endometrium.

Database: EMBASE

60. Neuromuscular electrical stimulation and biofeedback therapy may improve endometrial growth for patients with thin endometrium during frozen-thawed embryo transfer: a preliminary report.

Author(s): Bodomboossou-Djobo, Madafeiton M A; Zheng, Chengyu; Chen, Shaoqing; Yang, Dongzi

Source: Reproductive biology and endocrinology : RB&E; Aug 2011; vol. 9 ; p. 122

Publication Date: Aug 2011

Publication Type(s): Research Support, Non-u.s. Gov't Controlled Clinical Trial Journal Article

PubMedID: 21867532

Available at Reproductive Biology and Endocrinology - from ProQuest (Hospital Premium Collection) - NHS Version

Available at Reproductive Biology and Endocrinology - from BioMed Central

Abstract: BACKGROUNDTo investigate the effect of pelvic floor Neuromuscular Electrical Stimulation (NMES) Therapy in improving endometrial thickness in women with thin endometrium. METHODS 41 patients undergoing assisted reproduction with a thin endometrium (less than or equal to 7 mm) were recruited and advised to go for a pelvic floor NMES in frozen-thawed embryo transfer cycle. PHENIX Neuromuscular Electrical Stimulation Therapy System was used according to the manufacturer’s recommended protocol for 20 to 30 minutes of intermittent vaginal electrical stimulation on the treatment days. RESULTS A total of 20 and 21 were included in the NMES and non-NMES groups respectively. 12 out of 20 (60%) patients developed endometrial thickness equal to or more than 8 mm after the NMES therapy, which was the primary outcome. The mean thickness of
endometrium before and after was respectively 5.60 mm (0.82 mm) and 7.93 mm (1.42 mm) in the therapy group versus 5.50 mm (1.00) and 6.78 mm (0.47) in the control group; the difference was statistically significant (P = 0.002). There was higher pregnancy rate in the NMES group (42% versus 35%) but the difference was not statistically significant.

CONCLUSION Neuromuscular Electrical stimulation therapy may be effective for the patients with a thin endometrium. Further studies are needed to investigate its effectiveness.

Database: Medline

61. Successful treatment of unresponsive thin endometrium.

Author(s): Gleicher, Norbert; Vidali, Andrea; Barad, David H
Source: Fertility and sterility; May 2011; vol. 95 (no. 6); p. 2123
Publication Date: May 2011
Publication Type(s): Case Reports Multicenter Study Journal Article Evaluation Studies
PubMedID: 21324451
Abstract: OBJECTIVE To assess whether inadequate, thin endometrium (<7 mm), after failure to expand with standard treatment options, will be responsive to cytokine treatment. DESIGN Prospective cohort study of four patients. SETTING Two independent IVF centers in New York City. PATIENT(S) Four consecutive women undergoing IVF who, after standard endometrial preparation, still demonstrated highly inadequate endometrium. INTERVENTION(S) Transvaginal endometrial perfusion with granulocyte colony-stimulating factor (G-CSF). MAIN OUTCOME MEASURE(S) Endometrial thickness on day of ET, with pregnancy as secondary endpoint. RESULT(S) We report successful endometrial expansion to at least minimal thickness of 7 mm after uterine perfusion with G-CSF in four patients previously resistant to treatment with estrogen and vasodilators. All four patients therefore reached ET, and all four also conceived, although one pregnancy required termination because of intramural, corneal ectopic location. Endometrial expansion to minimal thickness occurred within approximately 48 hours from infusion. CONCLUSION(S) Uterine perfusion with G-CSF represents a promising new tool for the currently mostly intractable problem of inadequate, thin endometrium. This treatment also deserves further investigation for its potential to improve implantation chances in association with IVF and, therefore, pregnancy rates.
Database: Medline
62. Comparison of the effect of tamoxifen on endometrial thickness in women with thin endometrium (<7mm) undergoing ovulation induction with clomiphene citrate.

**Author(s):** Reynolds, Kasey; Khoury, Jane; Sosnowski, James; Thie, Jennifer; Hofmann, Glen

**Source:** Fertility and sterility; Apr 2010; vol. 93 (no. 6); p. 2091-2093

**Publication Date:** Apr 2010

**PubMedID:** 19775686

**Abstract:** Infertile women undergoing ovulation induction (OI) with clomiphene citrate (CC) who have adequate follicular recruitment and an endometrial thickness of <7 mm as determined by transvaginal sonography in the late follicular phase were switched to tamoxifen for OI in a subsequent cycle. A comparison between the endometrial thickness on CC and tamoxifen was made with by paired analysis. For women undergoing OI with CC who have adequate follicular recruitment and thin endometrium (<7 mm), switching to tamoxifen in subsequent cycles improves endometrial thickness.

**Database:** Medline

63. Endometrial growth and uterine blood flow: a pilot study for improving endometrial thickness in the patients with a thin endometrium

**Author(s):** Takasaki A.; Shimamura K.; Tamura H.; Miwa I.; Taketani T.; Sugino N.

**Source:** Fertility and Sterility; Apr 2010; vol. 93 (no. 6); p. 1851-1858

**Publication Date:** Apr 2010

**PubMedID:** 19200982

**Abstract:** Objective: To examine whether thin endometria can be improved by increasing uterine radial artery (uRA) blood flow. Design: A prospective observational study. Setting: University hospital and city general hospital. Patient(s): Sixty-one patients with a thin endometrium (endometrial thickness [EM] <8 mm) and high radial artery-resistance index of uRA (RA-RI >=0.81). Intervention(s): Vitamin E (600 mg/day, n = 25), l-arginine (6 g/day, n = 9), or sildenafil citrate (100 mg/day, intravaginally, n = 12) was given. Main Outcome Measure(s): EM and RA-RI were assessed by transvaginal color-pulsed Doppler ultrasound. Result(s): Vitamin E improved RA-RI in 18 (72%) out of 25 patients and EM in 13 (52%) out of 25 patients. L-arginine improved RA-RI in eight (89%) out of nine patients and EM in six (67%) patients. Sildenafil citrate improved RA-RI and EM in 11 (92%) out of 12 patients. In the control group (n = 10), who received no medication to increase uRA-blood flow, only one (10%) patient improved in RA-RI and EM. The effect of vitamin E was histologically examined in the endometrium (n = 5). Vitamin E improved the glandular epithelial growth, development of blood vessels, and vascular endothelial growth factor protein expression in the endometrium. Conclusion(s): Vitamin E, l-arginine, or sildenafil citrate treatment improves RA-RI and EM and may be useful for the patients with a thin endometrium. © 2010 American Society for Reproductive Medicine.

**Database:** EMBASE
64. Use of combined pentoxifylline and tocopherol (Vitamin E) treatment in women with thin endometrium in assisted conception - A report of twenty cases

Author(s): Acharya S.; Yasmin E.; Balen A.

Source: Human Fertility; Dec 2009; vol. 12 (no. 4); p. 232

Publication Date: Dec 2009

Publication Type(s): Conference Abstract

Abstract: Introduction: Optimal endometrial thickness is necessary for embryo implantation. Inadequate endometrial thickness is an uncommon but difficult problem encountered in women undergoing assisted reproduction. Pentoxifylline (PTX) causes vasodilatation, inhibits inflammatory reactions and reduces viscosity of blood by inhibiting red cell aggregation. Vitamin E is thought to act through its antioxidant properties. A combination of PTX and Vitamin E has been used to treat radiation-induced fibrosis with good response. In a recent series of 18 women with thin endometrium unresponsive to estrogen, enrolled for an oocyte donation programme, treatment with PTX and Vitamin E demonstrated significant improvement in endometrial thickness. Material & Methods: We performed an observational study in 20 women with thin endometrium (<6 mm), undergoing either ovulation induction in assisted conception or frozen embryo transfer cycles, who were prescribed 800 mg of PTX and 1000 mg of Vitamin E daily. Results: The mean age of the patients was 32 years. The group of patients we studied had mixed aetiologies that accounted for thin endometrium. In 11 cases the cause for thin endometrium was unknown. In our series, known causes included Turner's syndrome (3), Kallman's syndrome (1), idiopathic hypogonadotrophic hypogonadism (2), premature ovarian failure (1) and Asherman's syndrome (2). The mean duration of treatment was 8.1 months (+/-4.5, range 1-18 months). The mean thickness of endometrium before and after treatment with PTX and Vitamin E was 4.37 mm (+/-1.5 mm) and 6.05 mm (+/-1.83 mm), respectively (p = 0.001, 95% CI 0.84 to 2.5). Overall 14 (73.7%) women showed improvement in endometrial thickness. Pregnancy occurred in eight women (40%) of which three were natural, one had ovulation induction and another five had frozen embryo transfer. Conclusion: Inadequate endometrial thickness in patients undergoing assisted conception is a challenge. This small retrospective study confirms a combination of PTX and Vitamin E improves endometrial growth in resistant cases. However, larger prospective studies and more research regarding the precise mechanism of action are needed to confirm these results.

Database: EMBASE
**65. The use of a combination of pentoxifylline and tocopherol in women with a thin endometrium undergoing assisted conception therapies—a report of 20 cases.**

**Author(s):** Acharya, Santanu; Yasmin, Ephia; Balen, Adam H

**Source:** Human fertility (Cambridge, England); Dec 2009; vol. 12 (no. 4); p. 198-203

**Publication Date:** Dec 2009

**Publication Type(s):** Journal Article

**PubMedID:** 19938908

**Abstract:** An optimal thickness of the endometrium is considered to be one of the prerequisites for successful implantation of the embryo. A retrospective analysis was carried out to investigate the use of Pentoxifylline and tocopherol in improving the endometrial thickness in cases that are unresponsive to conventional therapy. Twenty women with thin endometrium (<6 mm) undergoing either ovulation induction or frozen embryo transfer cycles were prescribed 800 mg of PTX and 1000 IU of Vit E daily. In 11 cases, the etiology for thin endometrium was unknown. The known causes included Turner's syndrome (3), Kallman's syndrome (1), idiopathic hypogonadotrophic hypogonadism (2), premature ovarian failure (1) and Asherman's syndrome (2), none of which had responded to conventional hormonal stimulation. The mean duration of treatment was 8.1 months (+/-4.5, range 1-18 months). The mean thickness of endometrium before and after treatment was 4.37 mm (+/-1.5 mm) and 6.05 mm (+/-1.83 mm), respectively (p = 0.001, 95% CI 0.84-2.5). Overall, 14 (73.7%) women showed improvement in endometrial thickness which was the primary outcome. Pregnancy occurred in eight women (40%) of which three were natural, one had ovulation induction and another five had frozen embryo transfers. We conclude that a combination of pentoxifylline and tocopherol may improve endometrial growth in resistant cases that are unresponsive to conventional therapy.

**Database:** Medline

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**66. Comparison of low-dose human menopausal gonadotropin and micronized 17beta-estradiol supplementation in in vitro maturation cycles with thin endometrial lining.**

**Author(s):** Elizur, Shai E; Son, Weon-Young; Yap, Raymond; Gidoni, Yariv; Levin, Dan; Demirtas, Ezgi; Tan, Seang-Lin

**Source:** Fertility and sterility; Sep 2009; vol. 92 (no. 3); p. 907-912

**Publication Date:** Sep 2009

**Publication Type(s):** Comparative Study Journal Article

**PubMedID:** 18976750

**Abstract:** OBJECTIVE A challenge of in vitro maturation (IVM) treatment in some women is insufficient development of the endometrium prior to embryo transfer. DESIGN Retrospective study. SETTING McGill Reproductive Center, Montreal, Canada. PATIENT(S) Women with endometrial thickness or =8 mm or a dominant follicle (>10 mm) was identified. MAIN OUTCOME MEASURE(S) Endometrial lining before oocyte retrieval. RESULT(S) In both groups endometrial lining significantly thickened following treatment. However, hMG treatment resulted in a higher number of follicles > or =7 mm compared to estradiol (7.4 +/- 4.8 vs. 3.4 +/- 2.5, respectively) and a significantly higher percentage of mature oocytes that were identified on the day of oocyte retrieval (in vivo matured oocytes) (15.1% vs. 10.5%). CONCLUSION(S) In IVM designated cycles with a thin endometrium both low-dose hMG and micronized 17beta-estradiol supplementation significantly improve endometrial thickness. However, low-dose hMG results in larger follicles and a greater number of in vivo matured oocytes.

**Database:** Medline
67. Thin endometrium in assisted reproductive technology.

**Author(s):** Senturk, Levent M; Erel, C Tamer

**Source:** Current opinion in obstetrics & gynecology; Jun 2008; vol. 20 (no. 3); p. 221-228

**Publication Date:** Jun 2008

**Publication Type(s):** Journal Article Review

**PubMedID:** 18460935

**Abstract:**

**Purpose of Review:** To review the etiology, diagnosis and clinical importance of thin endometrium during assisted reproductive technology cycles and to find out better ways to deal with it.

**Recent Findings:** Precise and specific endometrial maturational development is crucial in allowing implantation following assisted reproduction. As endometrial biopsy is invasive and hormonal milieu assessment inaccurate, the need to evaluate endometrial development encouraged the use of high-resolution ultrasonography as an alternative non-invasive method of assessment for uterine receptivity. Ultrasonographic endometrial thickness measurement, endometrial pattern investigation, endometrial volume computation, uterine and subendometrial blood flow analysis by Doppler sonography are just some of the methods that we can utilize to have an idea of uterine receptivity. There is a lot of debate on the administration of low-dose aspirin, estrogen, vaginal sildenafil citrate, pentoxifylline, vitamin E, and gonadotropin-releasing hormone agonist for the management of thin endometrium with an aim to increase the pregnancy and implantation rates in assisted reproductive technology cycles.

**Summary:** Various recent modalities proposed for the treatment of thin endometrium seem to be useless and inefficient from an evidence-based medicine point of view. At the moment, evaluation of endometrium using different ultrasonographic markers seems to be superior to all those therapies.

**Database:** Medline

68. Extended estrogen administration for women with thin endometrium in frozen-thawed in-vitro fertilization programs.

**Author(s):** Chen, Mei-Jou; Yang, Jehn-Hsiahn; Peng, Fu-Hsiang; Chen, Shee-Uan; Ho, Hong-Nerng; Yang, Yu-Shih

**Source:** Journal of assisted reproduction and genetics; 2006; vol. 23 (no. 7-8); p. 337-342

**Publication Date:** 2006

**Publication Type(s):** Journal Article

**PubMedID:** 16983519

**Abstract:**

**Purpose:** To evaluate the effect of extended estrogen administration for women with thin endometrium in frozen-thawed in-vitro fertilization (IVF) programs.

**Methods:** Thirty-six women undergoing IVF program had thin endometrium (<8 mm). Among them, 23 received fresh embryo transfer (control group), but 13 canceled embryo transfer and underwent frozen-thawed embryo transfer in the subsequent cycle after extended administration of exogenous estrogen (study group).

**Results:** In the study group, the mean endometrial thickness increased significantly from 6.7 mm in controlled ovarian hyperstimulation cycles to 8.6 mm after an extended estrogen therapy for
14 to 82 days (P=0.031). Their pregnancy rate was significantly higher than that in the control group (38.5% vs. 4.3%, P=0.016). Among 5 women achieving pregnancies in the study group, one was complicated with placenta accreta, and the other 4 had uneventful pregnancies.

CONCLUSIONS Extended estrogen administration followed by frozen-thawed IVF programs is beneficial for women with thin endometrium. However, the risk of abnormal placentation and peripartal complication should be kept in mind.

Database: Medline

69. Combined treatment by pentoxifylline and tocopherol for recipient women with a thin endometrium enrolled in an oocyte donation programme.

Author(s): Lédée-Bataille, N; Olivennes, F; Lefaix, J-L; Chaouat, G; Frydman, R; Delanian, S

Source: Human reproduction (Oxford, England); May 2002; vol. 17 (no. 5); p. 1249-1253

Publication Date: May 2002

Publication Type(s): Research Support, Non-u.s. Gov't Clinical Trial Journal Article

PubMedID: 11980747

Available at Human Reproduction - from Oxford Journals - Medicine

Abstract: BACKGROUND To evaluate the effect of an antifibrotic treatment by a combination of pentoxifylline (PTX) and tocopherol (vitamin E) in patients with a thin endometrium who were enrolled in an oocyte donation programme.

METHODS Eighteen oocyte recipients who failed to develop a pre-ovulatory endometrial thickness of at least 6 mm after receiving vaginal micronized estradiol were enrolled in the study. The patients received a combination of PTX (800 mg/day) and vitamin E (1000 IU/day) for 6 months. The main outcome measurements were the change in endometrial thickness and the pregnancy and delivery rates after treatment.

RESULTS Endometrial thickness increased significantly (P <0.001), with a mean of (+/-SD) 4.9 +/- 0.6 mm before and 6.2 +/- 1.4 mm after treatment, with 72% (13/18) of patients being good responders. Five patients either did not respond to the treatment or responded only slightly. Three patients, of which two had received previous radiotherapy, became spontaneously pregnant, and two became pregnant after embryo transfer. Three patients did not have embryo transfer. A total of four babies were delivered. The pregnancy rate was thus 33% and the delivery rate 27%.

CONCLUSION Treatment by combination of PTX and vitamin E appears to improve the pregnancy rate in patients with a thin endometrium by increasing the endometrial thickness and improving ovarian function. This was especially noticeable in patients who had previously received total body irradiation.

Database: Medline
70. Low-dose aspirin for infertile women with thin endometrium receiving intrauterine insemination: a prospective, randomized study.

**Author(s):** Hsieh, Y Y; Tsai, H D; Chang, C C; Lo, H Y; Chen, C L

**Source:** Journal of assisted reproduction and genetics; Mar 2000; vol. 17 (no. 3); p. 174-177

**Publication Date:** Mar 2000

**PubMedID:** 10911579

**Available at:** Journal of Assisted Reproduction and Genetics - from ProQuest (Hospital Premium Collection) - NHS Version

**Available at:** Journal of Assisted Reproduction and Genetics - from Europe PubMed Central - Open Access

**Abstract:**
**PURPOSE**
The objective was to evaluate the effect of aspirin on infertile women with thin endometrium.

**METHODS**
Patients who had thin endometrium (< or = 8 mm) and intrauterine insemination were divided into the aspirin and nonaspirin groups. Endometrial pattern (trilaminar and nontrilaminar) and thickness, the pulsatility index (PI) and resistance index (RI) of the uterine artery, spiral artery, and ovarian dominant follicles, and pregnancy rates of both groups were measured.

**RESULTS**
A total of 114 and 122 women were included in the aspirin and nonaspirin groups, respectively. There were significantly higher percentages of trilaminar endometrium (46.5% vs. 26.2%) and pregnancy rate (18.4% vs. 9.0%) after aspirin therapy. There was nonsignificant difference in the endometrial thickness, and PI/RI values of the uterine artery, spiral artery, and ovarian dominant follicle between both groups.

**CONCLUSION**
Higher pregnancy rate and better endometrial pattern were achieved in patients with thin endometrium after aspirin administration. Aspirin therapy could not significantly increase the endometrial thickness and the resistance of uterine and ovarian flow.

**Database:** Medline

71. Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective, randomized study.

**Author(s):** Weckstein, L N; Jacobson, A; Galen, D; Hampton, K; Hammel, J

**Source:** Fertility and sterility; Nov 1997; vol. 68 (no. 5); p. 927-930

**Publication Date:** Nov 1997

**PubMedID:** 9389827

**Abstract:**
**OBJECTIVE**
To evaluate the effect of low-dose aspirin use in oocyte donation recipients with an endometrial thickness of < 8 mm.

**DESIGN**
A prospective, randomized study.

**SETTING**
An oocyte donation program in a private infertility practice.

**PATIENT(S)**
Twenty-eight recipients undergoing oocyte donation who failed to develop an endometrial thickness of at least 8 mm in a previous evaluation cycle.

**INTERVENTION(S)**
Fifteen recipients received low-dose aspirin (81 mg/d) in addition to standard hormone replacement for an oocyte donation cycle. The remaining 13 recipients did not receive aspirin.

**MAIN OUTCOME MEASURE(S)**
Clinical pregnancy rates, delivery rates, implantation rates, and change in endometrial thickness were compared in the aspirin and nonaspirin groups.

**RESULT(S)**
There was no demonstrable increase in endometrial thickness in the aspirin-treated group. However, there was a statistically significant increase in implantation rates in the aspirin-treated group (24% versus 9%) and in implantation rates and clinical pregnancy rates in the aspirin-treated group when the final endometrial thickness was < 8 mm.

**CONCLUSION(S)**
Low-dose aspirin therapy improves implantation rates in oocyte donation recipients with a thin endometrium.
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