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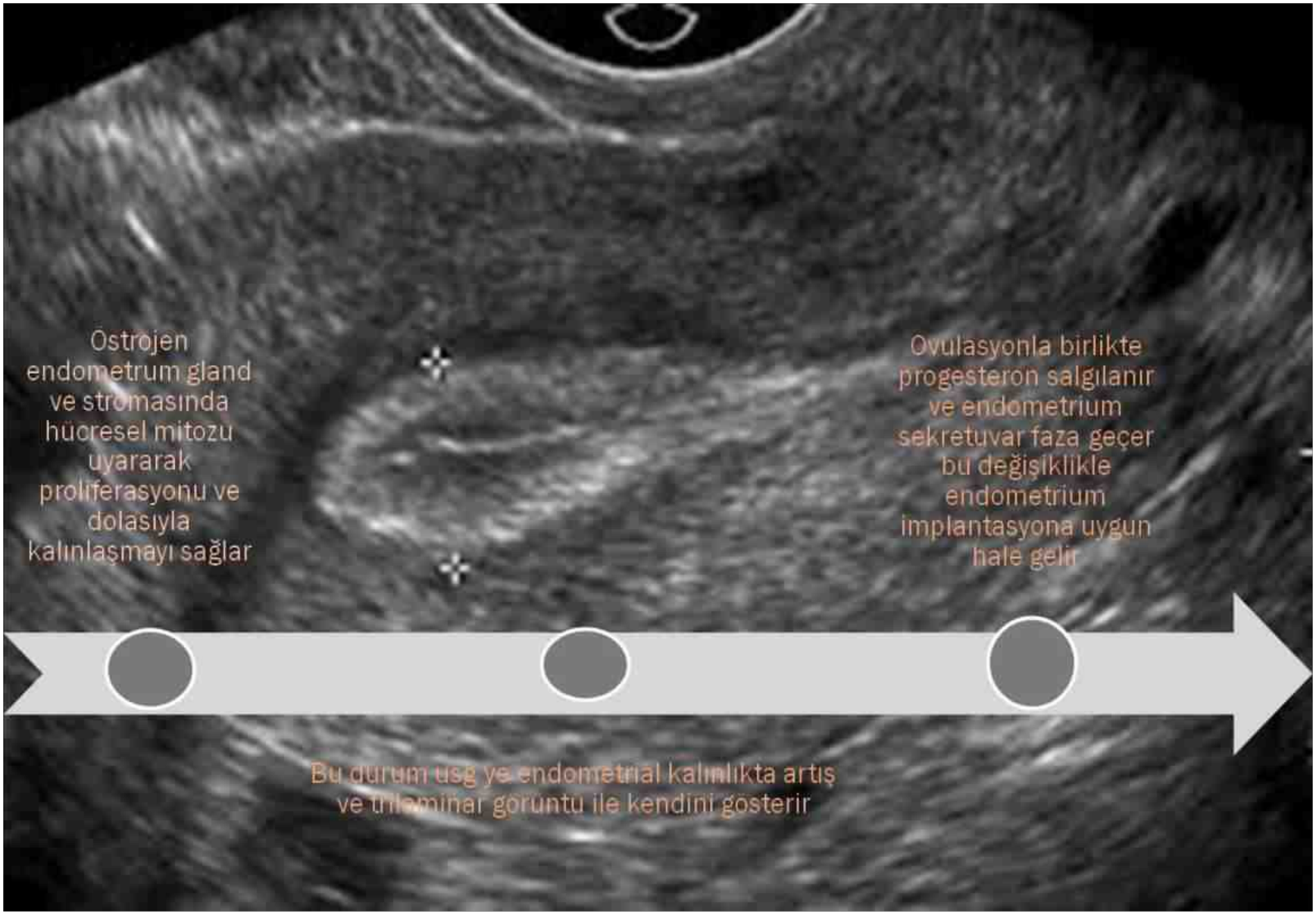
İnce Endometriumun Yönetimi

Prof.Dr. Mesut ÖKTEM


Östrojen endometrum gland ve stromasında hücresel mitozu uyararak proliferasyonu ve dolasıyla kalınlaşmayı sağlar
Ovulasyonla birlikte progesteron salgılanır ve endometrium sekretuvar faza geçer bu değişiklikle endometrium implantasyona uygun hale gelir
Bu durum usg ve endometrial kalınlıkta artış ve trilaminar görüntü ile kendini gösterir

İNCE ENDOMETRİUM

- Endometrial kalınlığının embriyo implantasyonu için eşik kalınlığa ulaşamadığı hallerde İNCE ENDOMETRİUM
- 3.7 mm altında canlı gebelik gösterilememiş
- Genelde 7mm>, tercihan 9 mm üzerinde endometrial kalınlıklarda gebelik oranları artmakta
- < 9 mm endometrial kalınlıkta klinik gebelik oranları % 53 iken > 16 mm endometrial kalınlıkta klinik gebelik oranları % 77 olmakta
- Yaş, embriyo kalitesi ve endometrial kalınlık klinik gebelik ve canlı doğum oranlarını ön görmede en etkili değişkenler

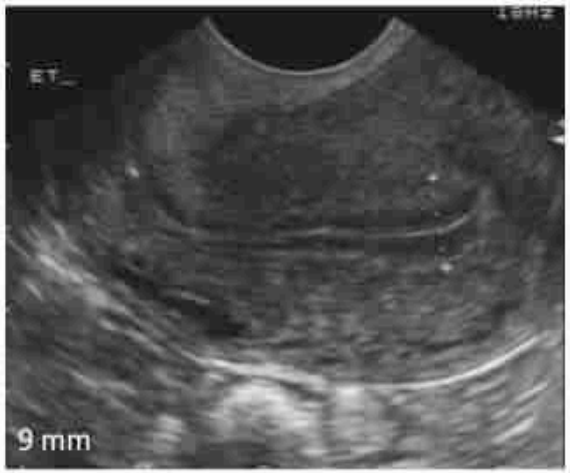
Richter KS, Fertil Steril 2007

El-Toukhy T, Fertil Steril 2008

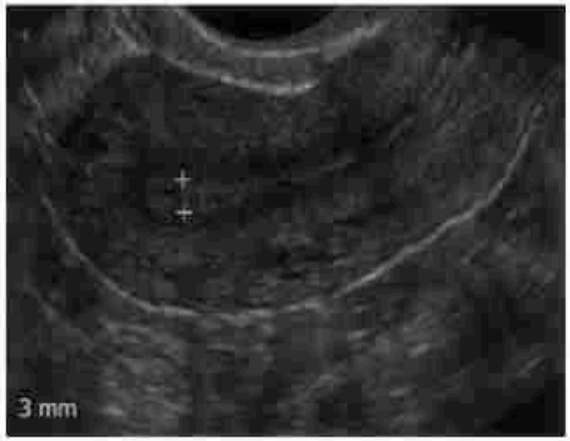
Check JH, Clin Exp Obstet Gynecol 2011

Ultrasound measurement of endometrial thickness

Three-layered normal endometrium



Thin endometrium



Pathophysiologic features of "thin" endometrium

Ichiro Miwa, M.D.,[a] Hiroshi Tamura, M.D., Ph.D.,[a] Akihisa Takasaki, M.D., Ph.D.,[b] Yoshiaki Yamagata, M.D., Ph.D.,[a] Katsunori Shimamura, M.D., Ph.D.,[b] and Norihiro Sugino, M.D., Ph.D.[a]

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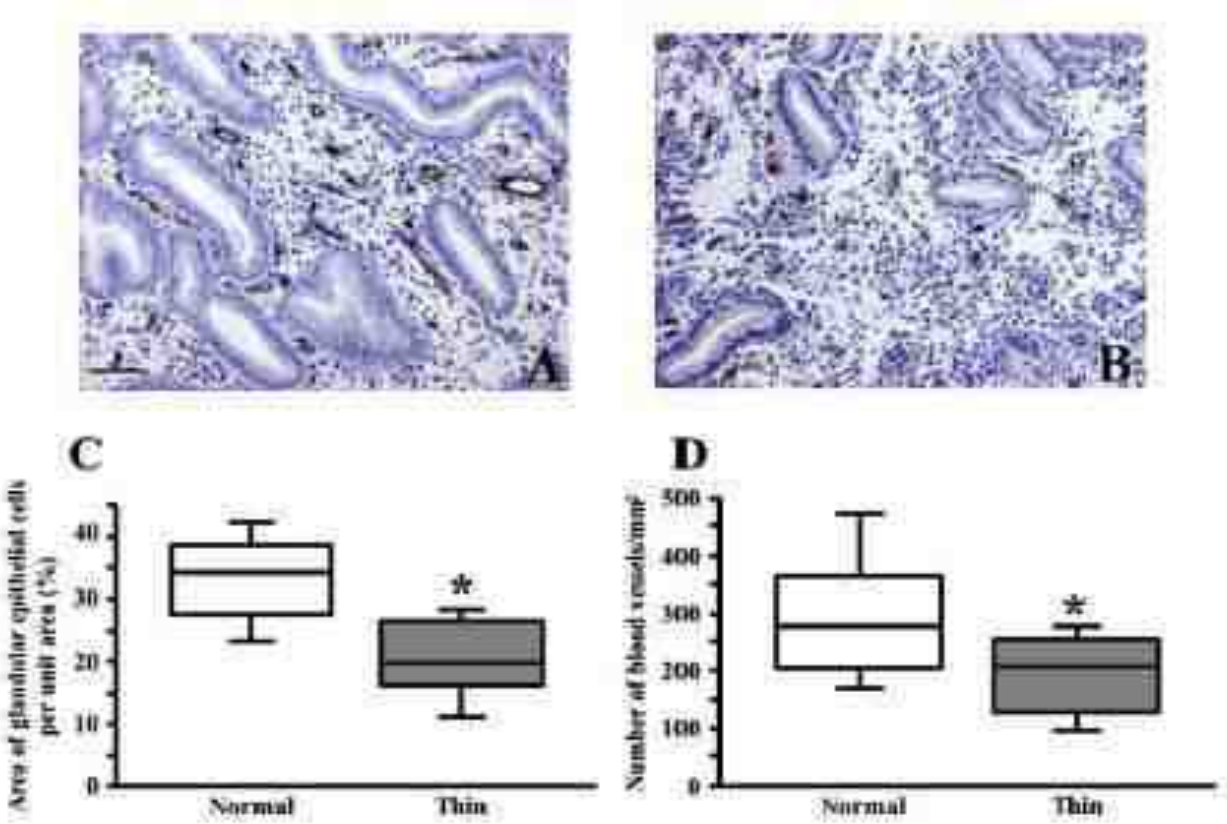
TABLE 1

Resistance index (RI) of the uterine artery (UA) and radial artery (RA).

	Normal thickness endometrium (n = 57)	Thin endometrium (n = 17)	*P* value
Age	31 (23–44)	34 (26–38)	<.05
UA-RI	0.888 (0.761–1.000)	0.923 (0.886–1.000)	<.05
RA-RI	0.751 (0.549–0.840)	0.852 (0.826–0.955)	<.05
Serum E_2 (pg/mL)	135.3 (49.7–293.2)	170.8 (84.8–244.9)	N.S.
Serum P (ng/mL)	16.0 (3.6–33.0)	13.0 (10.4–28.7)	N.S.

Note: UA-RI and RA-RI were measured for the patients with normal-thickness endometrium (endometrial thickness ≥8 mm) and thin endometrium (endometrial thickness <8 mm) in the midluteal phase (days 6–8 after ovulation). Values are median (range). Data were analyzed by Mann-Whitney *U* test. N.S. = not significant.

Miwa. Characterization of thin endometrium. Fertil Steril 2009.

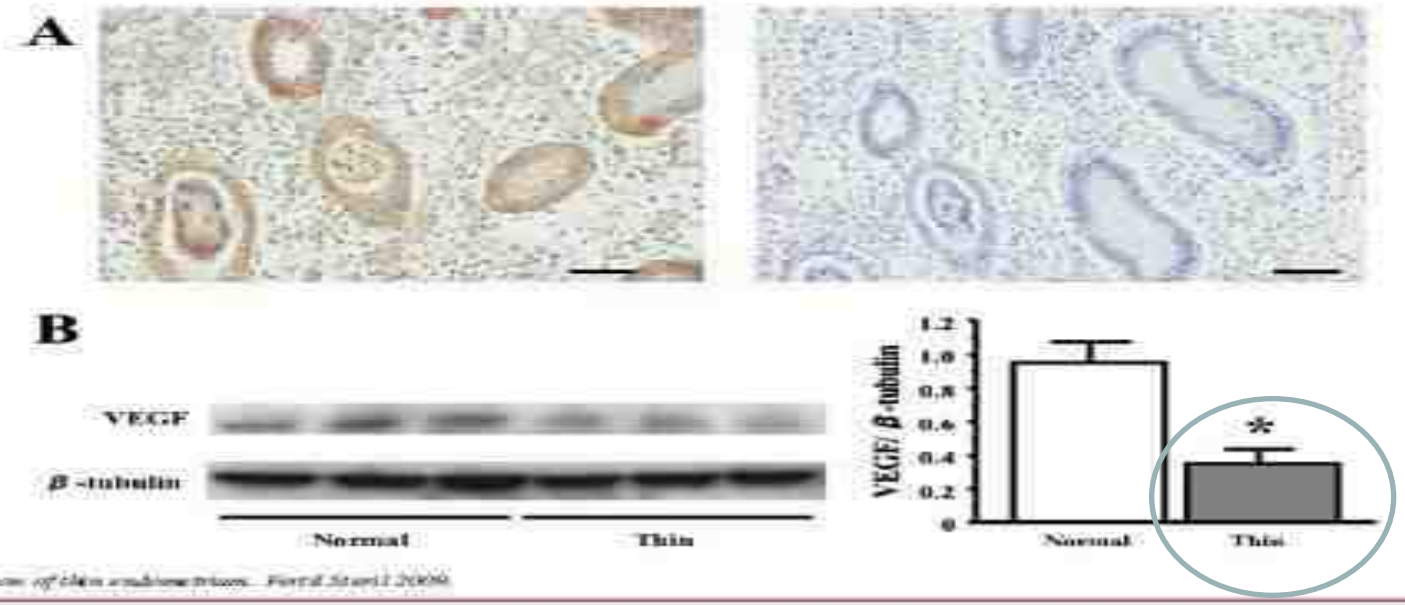


Mirea. Characterization of thin endometrium. Fertil Steril 2009.

- Glandüler epitel alanı oranı ince endometriumlu hastalarda düşük olarak izlenmiştir

FIGURE 4

Vascular endothelial growth factor (VEGF) expression in the endometrium. (**A**) Immunohistochemical staining for VEGF (*left panel*) and a negative control (*right panel*) in the midsecretory phase. Bar = 40 μm. (**B**, *left panel*) Representative immunoblots of VEGF protein expression in the midsecretory phase in the normal-thickness (n = 6) and thin (n = 3) endometrium groups. The tissue samples that showed out-of-phase by endometrial dating were not included in the analysis of VEGF expression. (**B**, *right panel*) Quantification of immunoblot signals (ratio of VEGF to β-tubulin), mean ± SEM. *$P < .05$ vs. normal-thickness endometrium (Mann-Whitney *U* test).



- İnce endometriumlu hastalarda VEGF ekspresyonu da anlamlı oranda azalmaktadır

İnce Endometrium Pathofizyolojisi

- Sonuç olarak ince endometrium;
  - Azalmış glandüler epitel gelişimi
  - Artmış uterin kan akımı rezistansı
  - Azalmış VEGF ekspresyonu
  - Azalmış vasküler gelişim ile karakterizedir

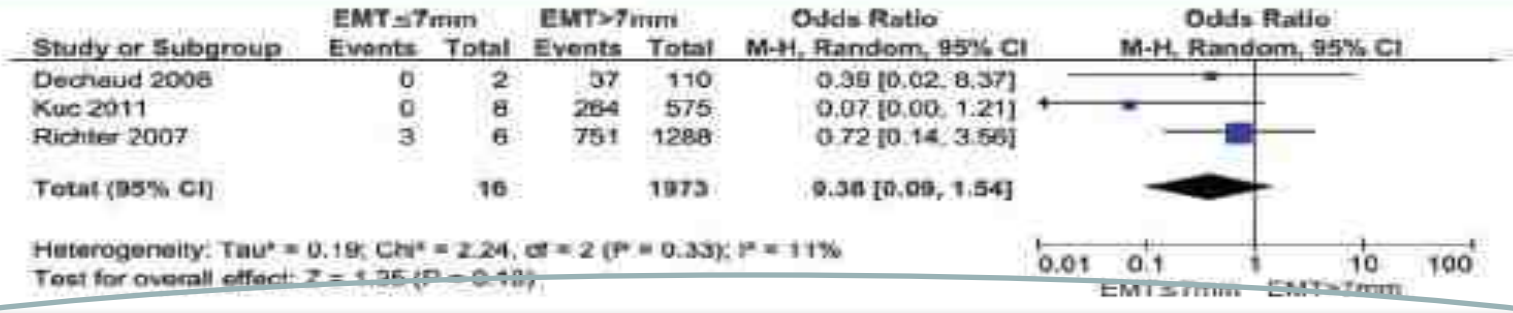


Figure 5 Forest plot of ongoing pregnancy and live birth for women with EMT ≤ 7 mm and EMT > 7 mm. Chances of live birth and ongoing pregnancy are lower for women with EMT ≤ 7 mm, but the results are not significant. The I^2 statistic of 11% indicates that study heterogeneity was low. CI, confidence interval.

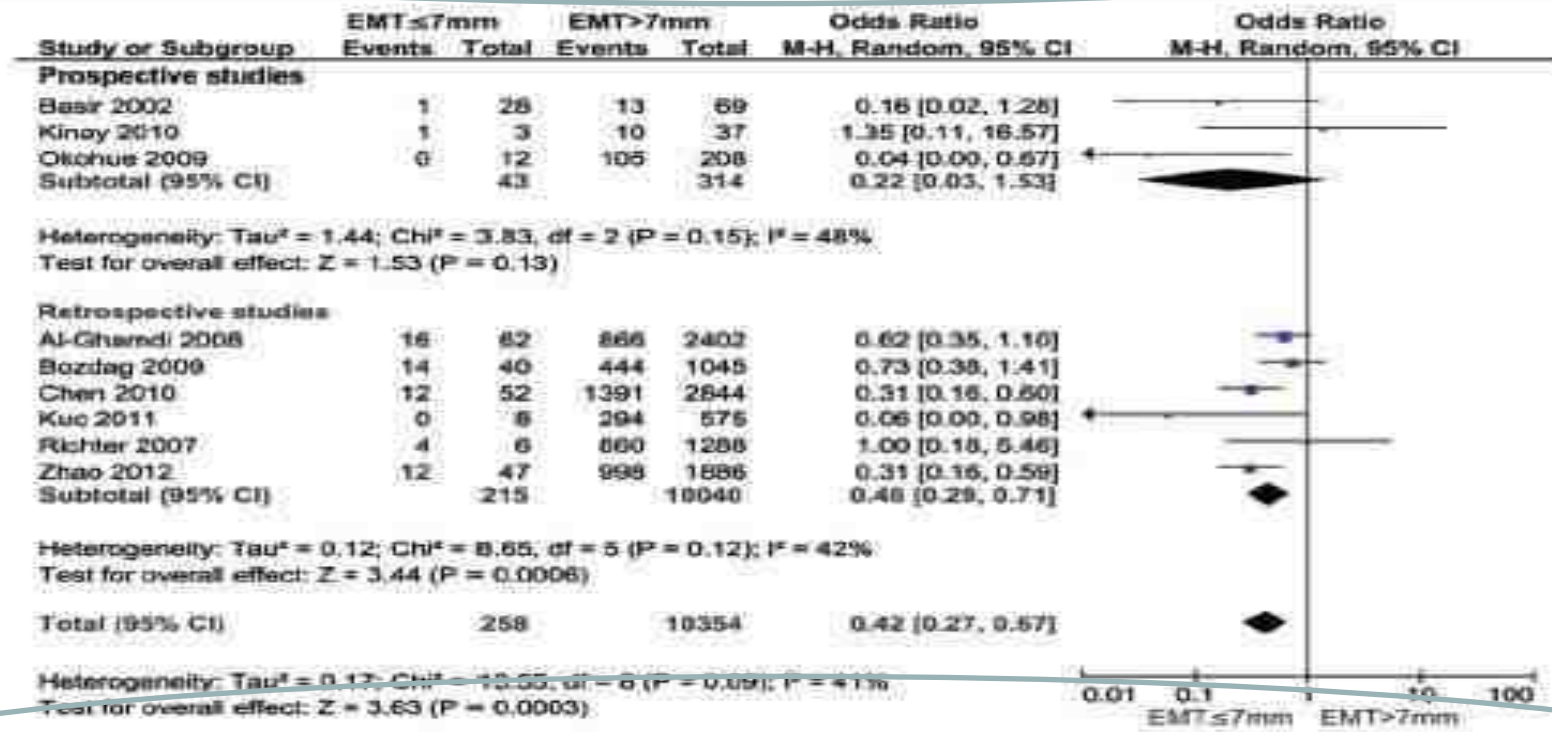


Figure 6 Forest plot of clinical pregnancy for women with EMT ≤ 7 mm and women with EMT > 7 mm. The probability of clinical pregnancy is significantly lower for women with EMT ≤ 7 mm. The I^2 statistic was 41%, indicating that study heterogeneity was low.

İNCE ENDOMETRİUM TEDAVİ

Table 1. Treatment of thin endometrium.

Hysteroscopic adhesiolysis
Hormonal manipulation
Estrogen: PO, transdermal, IM and vaginal.
Modified long GnRH-agonist protocol with exogenous estrogen therapy.
Midluteal GnRH-agonist.
Improving endometrial perfusion
Low dose aspirin
Pentoxifylline and vitamin E.
Sildenafil.
New modalities
Granulocyte colony-stimulating factor (G-CSF)
Regenerative medicine: endometrial SP cells, bone marrow mesenchymal stem cells

Histeroskopik Adezyolizis

- Myer ve Hurst (2012) tranvajinal ultrasonografi, HSG veya salin sono-histerografi ince endometrium izledikleri hastaları preoperatif 2-8 hafta oral estrojen tedavisi vermişler
- Histereskopik adezyolizis sonrası intra- uterin balon kateter (1 hafta) ve oral estrojen 4-6 hafta devam etmişler. Balon kateteri çıkardıktan sonra IUD uygulamışlar.
- IUD 4-6 hafta sonra çıkarılmış ve hastalar HSG, salin sono-histerografi ve histeroskopik tekrar değerlendirilmişler.

Hormonal tedavi- estrojen

- Oral,transdermal,intra musculer veya vaginal yol
- Transdermal yol ile daha sabit serum düzeyleri elde ediliyor
- Vajinal yol ile daha yüksek serum ve endometrial düzeyleri sağlanıyor
- Tourgeman ve arkadaşları donor sikluslarında progesteron tedavisinden 4-6 hafta önce oral estradiol tedavisiyle 7mm üzerinde endometrial kalınlık elde etmişler ve devam eden gebelik oranlarını % 70 lere çıkarmışlar

Hormonal tedavi- estrojen

- Coughlan ve arkadaşları GnRHa long luteal sikluslarda adetin 2. günü estradiol tedavisine başlamışlar ve 5 mm üzerine çıkan endometrial kalınlık durumlarında bu tedaviyi Hcg gününe kadar devam etmişler ve başarılı gebelik sonuçları bildirmişler

Hormonal tedavi -GnRH - agonisti

- Qublah ve ark yaptığı prospektif kontrollü randomize çalışmada ince endometriumlu IVF hastalarında (7mm) OPU günü, ET ve 3 gün sonrası 0,1 mg Triptorelin uygulamışlar
- Plasebo grubu ile karşılaştırıldığında anlamlı olarak yüksek endometrial kalınlık,implantasyon ve gebelik oranları elde edilmiştir.
- GnRHa direk endometriuma ve corpus luteuma etkisi (growth factors, cytokines, angiogenetic and adhesion molecules)

Qublah H, Amarin Z, Al-Quda M, et al. Luteal phase support with GnRH-a improves implantation and pregnancy rates in IVF cycles with endometrium of 7mm on day of egg retrieval. Hum Fertil (Camb) 2008;11:43–7.

Endometrial Perfüzyonu arttırıcı tedaviler

- İnce endometrium patofizyolojisinde kan akımı rolü mevcuttur

- Bu nedenle vaso-aktif ajanlar endometrial perfüzyonu arttırarak endometrial kalınlığı arttırabilir, implantasyonda olumlu etki oluşturabilirler

Endometrial Perfüzyonu arttırıcı tedaviler- düşük doz aspirin

- Weckstein ve ark 28 ince endometriumlu (8mm altı) IVF hastasında yaptığı randomize kontrollü çalışmada düşük doz aspirin implantasyon ve klinik gebelik oranını anlamlı olarak arttırmaktadır

Weckstein LN, Jacobson A, Galen D, et al. Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective,randomized study. Fertil Steril 1997;68:927–30.

- Ancak yapılan diğer çalışmalarda ve Cochrane review'da anlamlı bir etki gösterilememiştir

Glujovsky D, Pesce R, Fiszbajn G, et al. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. Cochrane Database Syst Rev 2010;1: CD006359.

Endometrial Perfüzyonu arttırıcı tedaviler- Pentoksifilin ve Vitamin E

Pentoksifilin- metilksantin derivesi….. vazodilatatör

Vitamin E…… antioksidan

- Acharya ve ark yaptığı çalışmada konvansiyonel tedavinin başarısız olduğu hastalarda kombine tedavi ile %40 hastada endometrial kalınlıkta gelişme sağlamıştır

Acharya S, Yasmin E, Balen AH. The use of a combination of pentoxifylline and tocopherol in women with a thin endometrium undergoing assisted conception therapies:a report of 20 cases.Human Fertility 2009;12:198–203.

- 18 IVF hastasında vaginal başarısız E2 uygulamasını takiben kombine tedavinin verildiği hastaların %72 sinde endometrial kalınlıkta ve gebelik oranlarında artış izlenmiştir

,

Ledee-Bataille N, Olivennes F, Lefaix JL, et al. Combined treatment by pentoxifylline and tocopherol for recipient women with a thin endometrium enrolled in an oocyte donation programme. Hum Reprod 2002;17:1249–53

Endometrial Perfüzyonu arttırıcı tedaviler- Sildenafil

- Sildenafil, fosfodiesteraz-5 inhibitörü, nitrik oksitin vasodilatör etkisini arttırır

- Sher ve Fisch vajinal sildenafil uygulamasının ince endometriumlu IVF hastalarında kan akımını, gebelik oranlarını, implantasyonu arttırdığını göstermişlerdir

Sher G, Fisch JD. Effect of vaginal sildenafil on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. Fertil Steril 2002;78:1073–6.

Endometrial Perfüzyonu arttırıcı tedaviler- Sildenafil

- Takasaki ve ark 61 ince endometriumlu hastada yaptığı çalışmada hastalara sırasıyla vitamin E, L-arjinin, sildenafil sitrat tedavileri verilmiştir
- Endometrial kalınlıktaki artış sildenafil grubunda en yüksek olarak izlenmiştir(%52,%67,**%92**)
- RA-RI; ((%72,%89,**%92**) bulunmuş
- Vitamin E grubunda; endometrial glandlarda büyüme, damar artışı ve VEGF ekspresyonunda artış izlenmiş

Takasaki A, Tamura H, Miwa I, et al. Endometrial growth and uterine blood flow: a pilot study for improving endometrial thickness in the patients with a thin endometrium. Fertil Steril 2010;93:1851–8.

Rejeneratif tedaviler

- Jing ve ark; ethanol uygulaması ile ince endometrium oluşturdukları ratlara iv kemik iliği mezenkimal kök hücre enjeksiyonu uygulamışlardır

- Randomize kör değerlendirme sonrası kök hücre enjeksiyonu yapılan grupta endometrial kalınlıkta anlamlı artış izlenmiştir

Jing Z,Qiong Z, Yonggang W, Yanping L. Rat bone marrow mesenchymal stem cells improve regeneration of thin endometrium in rat. Fertil Steril 2014;101:587–94.

Rejeneratif tedaviler

- Nagori ve ark; ashermanı olan bir vakada uyguladıkları kök hücrenin intrauterin kaviteye uygulanması endometriumun 8 mm olması ve gebelik oluşmasını sağlamıştır

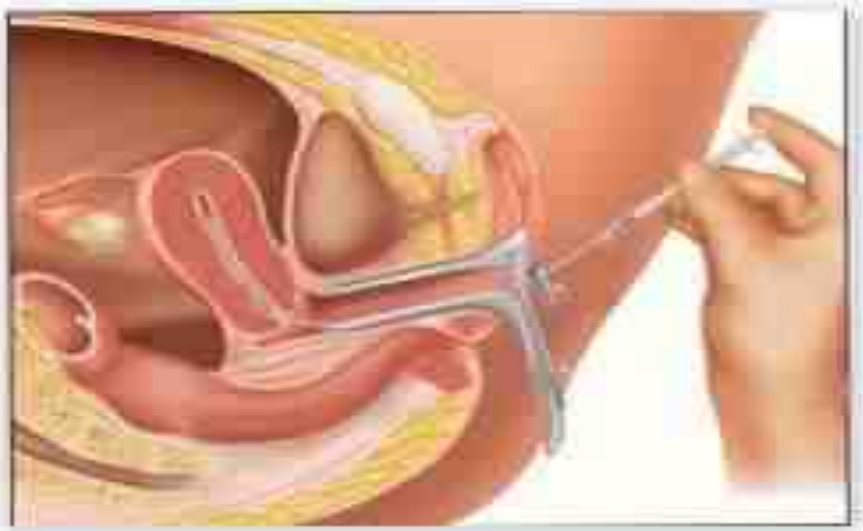
Nagori CB, Panchal SY, Patel H. Endometrial regeneration using autologous adult stem cells followed by conception by in vitro fertilization in a patient of severe Asherman's syndrome. J Hum Reprod Sci 2011;4:43–8.

İNCE ENDOMETRİUM
TEDAVİ

YENİ YAKLAŞIMLAR

Mid-luteal endometrial interlökin-11, LIF seviyeleri gibi çeşitli büyüme faktörleri ve pro-inflamatuar sitokinlerin ekspresyonunu, modülasyonunu ve sekresyonunu arttırma

GRANÜLOSİT KOLONİ STİMÜLE EDİCİ FAKTÖR (G-CSF)



G-CSF

- Glycoprotein, growth factor ve cytokine
- Endometrium, macrophages ve diğer immunocytes
- Terapotik kullanım alanları:
  - Akyuvarların üretimini stimüle eder → **neutropenia tedavisi** (Kemoterapi veya KİT durumlarında)
  - Donörden toplanmadan önce hematopoietic kök hücrelerinin sayısını artırır → **hematopoietic stem cell transplantasyonu**
  - CNS: Nörogenesisi ve anti-apoptosisi indükler ----> **nörojeneratif hastalıklar**
  - Endometrial receptivity artırır ?
- *Filgrastim*®: recombinant human G-CSF (synthesised in *E. coli* expression system)

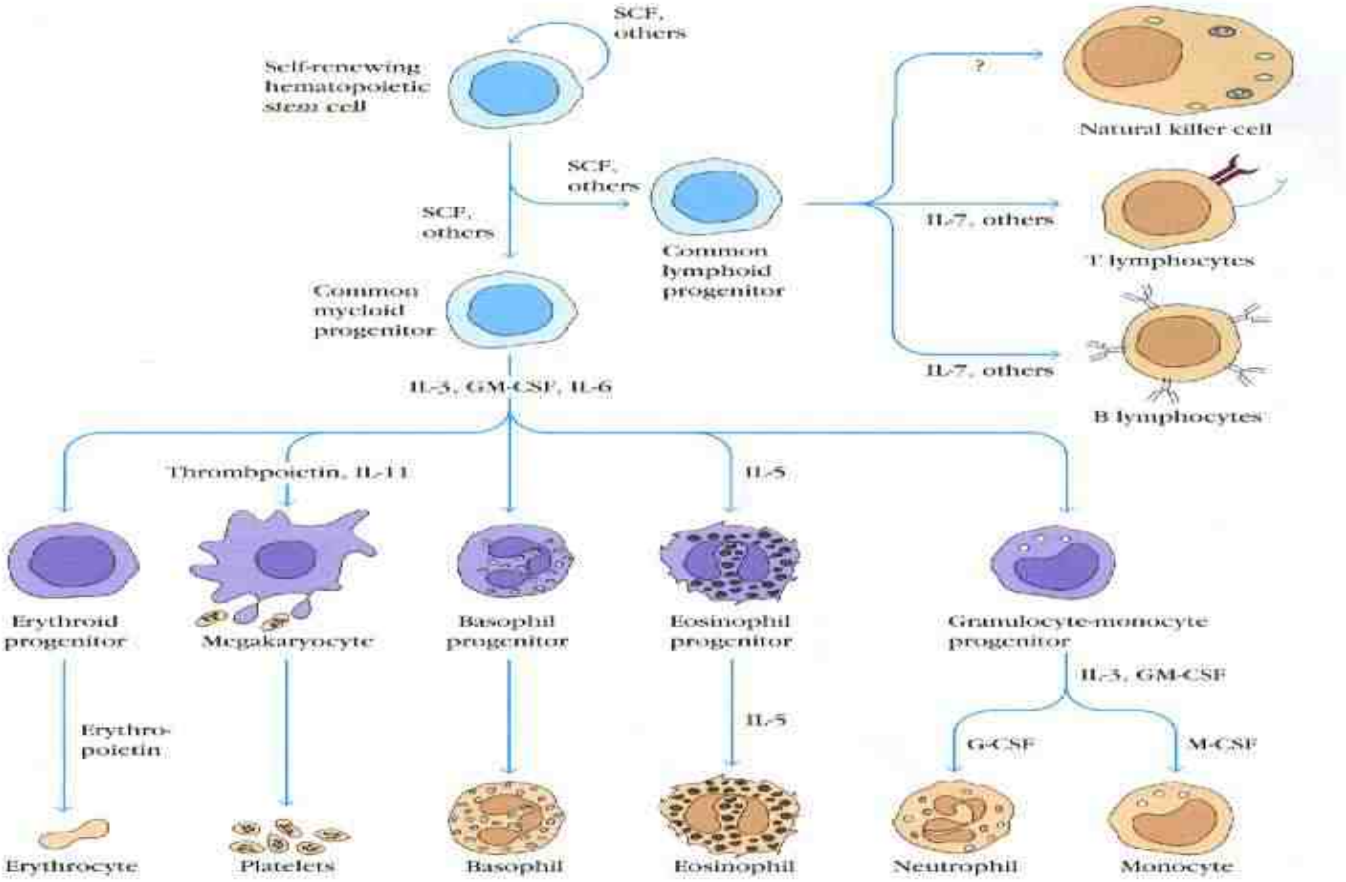
G-CSF

- Embriyo implantasyonunu artırmakta
- İnsan desidual makrofajları etkilemekte
- Ovülasyonu ve over fonksiyonunu etkilemekte
- Granulosa hücrelerini etkilemekte
- Kötü over yanıtlı hastalarda gonadotropinlere olan cevabı artırmakta
- Açıklanamayan rekürren gebelik kayıplarını azaltmakta
- Oto-immüniteyi süprese etmekte
- IVF sikluslarında folliküler sıvıda oosit/embriyonun implantasyon gücünü belirlemek için bir biomarker olarak kullanılabilmekte
- Yeni doğan ratlarda follikül gelişimi stimüle etmekte
- Endometrial co-culture (> 130pg/ml G-CSF) ,IVF gebelik oranları artmakta
- Embriyonik kromozomal gelişimi etkilememekte

G-CSF

- G-CSF, cAMP- aracılığı ile insan endometrial stromal hücrelerinde otokrin ve parakrin etkiyle desidualizasyonu artırmakta
- GM-CSF içeren **embryo growth mediumu** insan embriyo gelişimi blastosist evresine kadar desteklemektedir
  - GM-CSF içeren Embryo growth medium 2011'den itibaren ticari olarak Avrupa ülkelerinde mevcuttur (Embriyogen)
  - 2012'nin sonlarından itibaren de ABD'de kullanılmaktadır ***(implantasyon oranlarında %44' lere varan artış)***

Endometriumda hızlı proliferasyon nasıl olmakta?



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PLOS ONE

Use of Granulocyte Colony-Stimulating Factor for the Treatment of Thin Endometrium in Experimental Rats

Jing Zhao[9], Tian Tian[9], Qiong Zhang, Yonggang Wang, Yanping Li*

Reproductive Medicine Center, Xiangya Hospital, Central South University, Changsha, Hunan, China

Table 1. Comparison of the endometrial thickness betwee groups ($\bar{x}\pm s$).

groups	Uteri (n)	Endometrial thickness(μm)
experimental group I	20	569.37±37.01*☆
control group I	20	234.96±37.82*○
experimental group II	20	487.78±19.48※☆
control group II	20	231.21±17.81※○

Note: *P※P☆P<0.01, ○P>0.05. There is significant difference between the groups when P<0.05.

doi:10.1371/journal.pone.0082375.t001

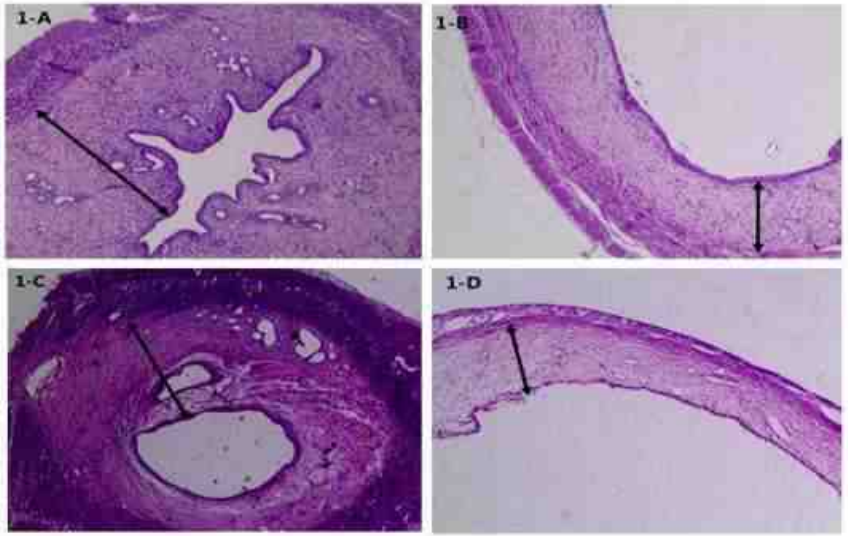


Figure 1. The morphology observation of the endometrium with HE staining of the four groups. 1 -A: experimental group I, 1-B: control group I, 1-C: experimental group II, 1-D: control group II. Significantly thicker endometrial lining was observed in experimental groups compared with the corresponding control groups. The endometrial lining was significantly thicker in experimental group I than that of experimental group II, and there was no significant difference between control group I and control group II (HE, ×80).

doi:10.1371/journal.pone.0082375.g001

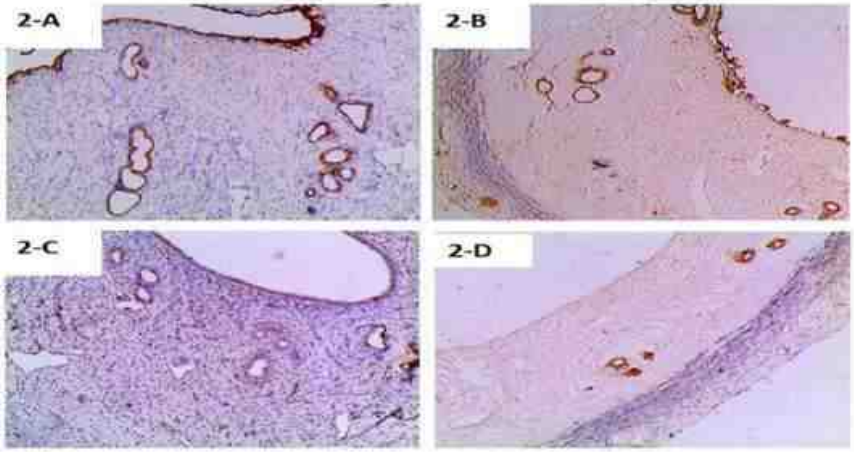


Figure 2. Regeneration of epithelial cells in the endometrium immunohistochemical staining with cytokeratin. 2-A: experimental group I, 2-B: control group I, 2-C: experimental group II, 2-D: control group II. The expression of cytokeratin in experimental group I and experimental group II were significantly stronger than that of corresponding control groups. The expression of cytokeratin in the experimental group I was significantly stronger than that of the experimental group II, but there was no difference between control group I and control group II (PV, ×200).
doi:10.1371/journal.pone.0082375.g002

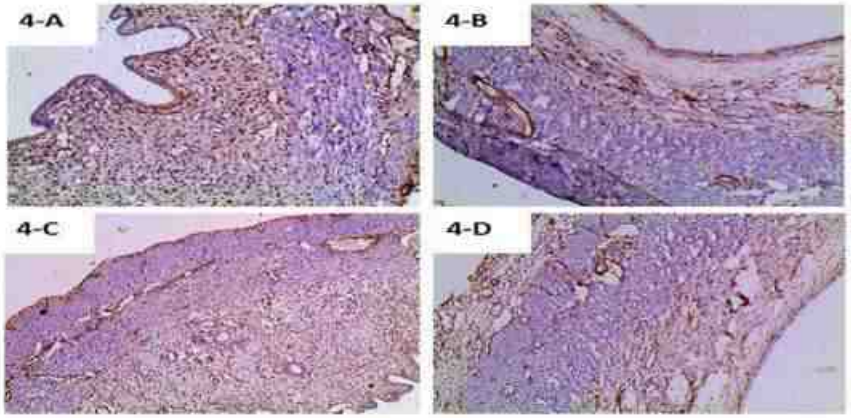


Figure 4. Regeneration of stroma cells in the endometrium immunohistochemical staining with vimentin. 4-A: experimental group I, 4-B: control group I, 4-C: experimental group II, 4-D: control group II. The expression of vimentin in experimental group I and experimental group II were significantly stronger than that of corresponding control groups. The expression of vimentin in the experimental group I was significantly stronger than that of the experimental group II, but there was no difference between control group I and control group II (PV, ×200).
doi:10.1371/journal.pone.0082375.g004

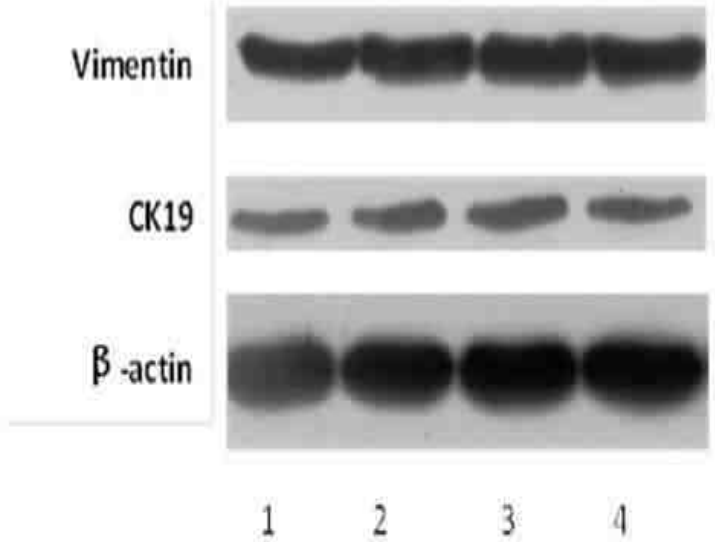


Figure 3. Expression of vimentin and cytokeratin with western blot. Group1–4: experimental group I, experimental group II, control group I, control group II. The results showed that the expression of cytokeratin, vimentin in experimental groups were significantly stronger compared with the corresponding control groups, and there was no significant difference between group I and group II when the G-CSF was given or not given.
doi:10.1371/journal.pone.0082375.g003

G-CSF

- ✓ Histolojik olarak endometrial kalınlıkta artış, endometrial glandlarda ve kapillerde sayısal artma
- ✓ Vimetin ve cytokeratin ekspresyonlarında artış ve yeni kapiller sayında artma
- ✓ Epitel hücrelerinin, stromal hücrelerin ve endotelyal hücrelerin rejenerasyonunda artış
- ✓ Erişkin stem cell proliferasyonu ve differansiasyonu ?

Successful treatment of unresponsive thin endometrium

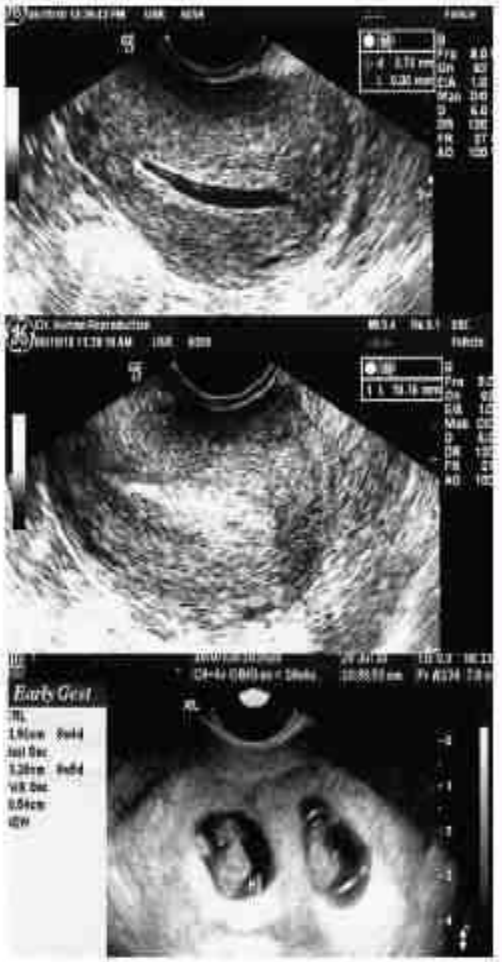
Norbert Gleicher, M.D.,[a,b] *Andrea Vidali, M.D.,*[c] *and David H. Barad, M.D., M.S.*[a,d]

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. (Fertil Steril® 2011;95: 2123.e13–e17. ©2011 by American Society for Reproductive Medicine.)

Key Words: Granulocyte colony-stimulating factor, in vitro fertilization (IVF), endometrial thickness, inadequate endometrium, implantation, pregnancy chance

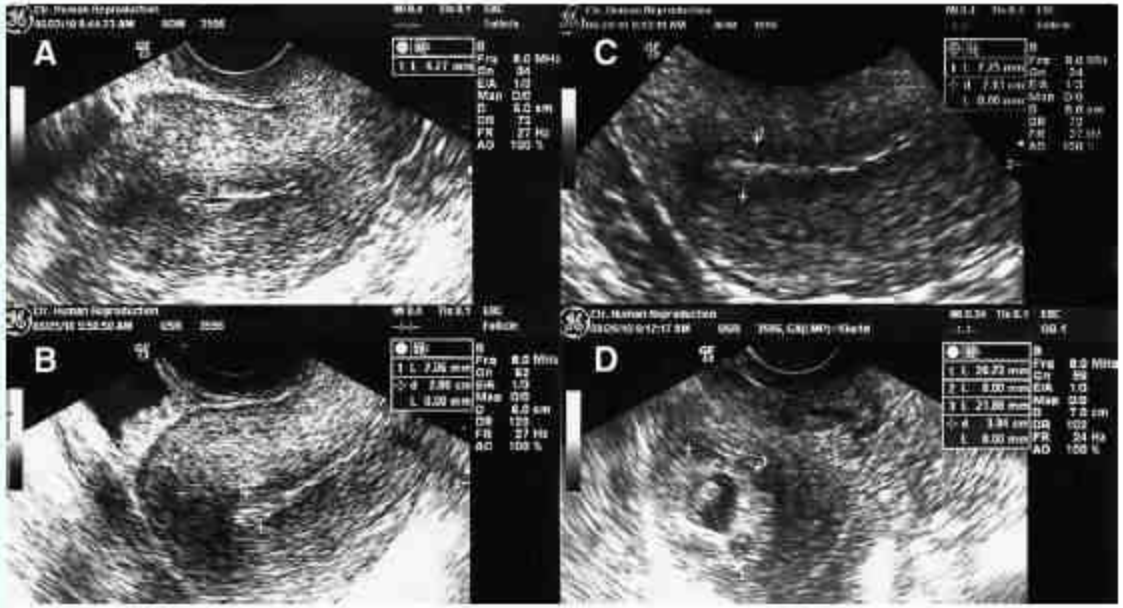
FIGURE 1

Ultrasound studies in patient 1. (**A**) Very thin endometrium (depending on area of measurement, 3.0–4.0 mm), surrounding an entirely fluid-filled endometrial cavity on day −5 before ET. (**B**) Same endometrium 4 days later, 1 day before ET (day −1). (**C**) Twin pregnancy at approximately 8 weeks, 3 days gestational age.



Gleicher. Thin endometrium. Fertil Steril 2011.

Ultrasound studies in patient 2. (**A**) Thin endometrium (4.8 mm) and minor fluid accumulation within fundal area of endometrial cavity only on day −10 before ET. Also seen are small calcifications, primarily below endometrial basement membrane. Patient received G-CSF the next day (day −9). (**B**) Remarkable improvement within 48 hours from infusion (day −7), with endometrium reaching thickness of 7.1 mm in fundal area and absence of endometrial fluid. (**C**) Endometrium at 7.3 mm on day −4. (**D**) Right intramural corneal pregnancy after methotrexate failure and before surgical removal.



Gleicher. Thin endometrium. Fertil Steril 2011.

TABLE 1

Patient characteristics.

Patient	Age (y)	Diagnosis	Day of diagnosis	Day of perfusion	Endometrium before/after (mm)	Other procedures	Embryo transfer	Pregnancy	Outcome
1[a]	34	POI	−5	−5	3–4/10.2	Fluid aspiration	Yes	Yes (twin)	Ongoing
2[b]	45	Partial Asherman	−10	−9	4.8/7.3		Yes	Yes	Intramural ectopic
3[c]	33	Repeated IVF failures	−7	−7	6.5/9.1		Yes	Yes	Ongoing
4[d]	41	POI	−6	−2	Right: 4.3/8.1 Left: 6.2/8.3	Both horns perfused	Yes	Yes	Ongoing

- Estrojen ve diğer vazodilatatörlere dirençli 4 vaka
- 30 MU(300mcg/1 mL, Neupogen, Filgastrim; Amgen Manufacturing, Thousand Oaks, CA),
- <7 mm olan vakalarda 48 saat içinde endometrial kalınlık artışı sağlamakta
- 3 vakada devam eden gebelik, 1 vaka ektopik gebelik

Human Reproduction, Vol.28, No.1 pp. 172–177, 2013
Advanced Access publication on October 18, 2012 doi:10.1093/humrep/des370

human reproduction ORIGINAL ARTICLE *Infertility*

A pilot cohort study of granulocyte colony-stimulating factor in the treatment of unresponsive thin endometrium resistant to standard therapies

N. Gleicher*, A. Kim, T. Michaeli, H-J. Lee, A. Shohat-Tal, E. Lazzaroni, and D.H. Barad

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 48 h, 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.

Table I Characteristics of patients in a study of the effect of G-CSF on endometrial thickness in IVF cycles.

Number of patients	21
Age (years)	40.5 ± 6.5
Parity (range)	0.4 ± 1.1 (0–4)
Gravidity (range)	1.8 ± 2.1 (0–7)
Failed prior IVF cycles (range)[a]	2.0 ± 2.1 (0–9)
BMI (kg/m^2)	23.6 ± 4.0
FSH (mIU/ml)	15.2 ± 19.3
Anti-Mullerian hormone (ng/ml)	1.5 ± 2.6
Gonadotrophin dosage (IU)	4491.7 ± 2241.4
Race (*n*/%)	
Caucasian	12/57.1
African	4/19.0
Asian	5/23.8
Primary infertility diagnosis (*n*/%)	
Diminished ovarian reserve	16/76.2
Male factor	2/9.5
Uterine factors	4/19.0
Polycystic ovary syndrome	1/4.8

Data are mean ± SD.
FSH and Anti-Mullerian hormone levels were tested before cycle start.
[a]0.1 ± 0.4 (range 0–1) prior IVF cycles were cancelled because of thin endometrium.

Table II Endometrial thickness in women before and after intrauterine treatment with G-CSF.

	All patients ($n = 21$)	Patients who conceived ($n = 4$)	Patients who did not conceive ($n = 17$)
First G-CSF infusion to embryos transfer (days)	5.2 ± 1.9	5.5 ± 2.9[1]	5.2 ± 1.7[1]
Endometrial lining (mm) at first G-CSF infusion	6.4 ± 1.4[2]	5.6 ± 1.5[3]	6.6 ± 1.4[4]
Endometrial lining (mm) at embryo transfer (mm)	9.3 ± 2.1[2]	8.8 ± 1.7[3]	9.5 ± 2.2[4]
Δ endometrial thickness (mm)	2.9 ± 1.9	3.2 ± 1.7[5]	2.9 ± 2.1[5]

Values are mean ± SD; Based on *t*-tests, $P < 0.05$ denotes significance.
[1]$P = 0.767$.
[2]$P < 0.001$.
[3]$P = 0.034$.
[4]$P < 0.001$.
[5]$P = 0.793$.

İleri yaş (ortalam 40,5), önceden başarısız IVF denemeleri olan ve
% 76,2 si kötü over rezervi olan hastada % 19,1 klinik gebelik oranı edilmiş
3 hastada 2. infüzyona gerek duyulmuş
(bu çalışmanın yapıldığı klinikte 41 yaş için klinik gebelik oranı % 25
olarak verilmekte, yine 18 ayda spontan gebelik oranı % 3,6 olarak belirtilmekte)

Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 913235, 5 pages
http://dx.doi.org/10.1155/2014/913235

Hindawi

Clinical Study

Evaluation of Granulocyte Colony-Stimulating Factor Effects on Treatment-Resistant Thin Endometrium in Women Undergoing *In Vitro* Fertilization

Michał Kunicki,[1] Krzysztof Łukaszuk,[2,3,4] Izabela Woclawek-Potocka,[5] Joanna Liss,[4] Patrycja Kulwikowska,[4] and Joanna Szczyptańska[4]

TABLE 1: Baseline patient characteristics and IVF cycle characteristics in women with thin endometrium.

Characteristic	All women $n = 37$	Women who conceived $n = 7$	Women who did not conceive $n = 30$
Age (years)	34.68 ± 4.13 (35)	32.14 ± 2.79 (33)	35.32 ± 4.20 (36)
Primary infertility diagnosis	24/37 (64.86%)	4/7 (57.14%)	20/30 (66.67%)
Secondary infertility diagnosis	13/37 (35.14%)	3/7 (42.86%)	10/30 (30.33%)
BMI (kg/m^2)	23.09 ± 2.78 (23.31)	21.89 ± 1.37 (22.15)	23.36 ± 2.97 (23.85)
FSH (mIU/mL)	7.18 ± 1.91 (7.3)	6.87 ± 1.40 (7)	7.31 ± 2.19 (7.60)
AMH (ng/mL)	4.28 ± 3.29 (3.8) 0.1–12.8	6.37 ± 4.17 (4.60) 1–12.8	3.78 ± 2.91 (3.4) 0.1–10.8
Cycles	3.46 ± 2.23 (3.00) 1–11	3.29 ± 1.80 (3.00) 2–7	3.5 ± 2.35 (3.00) 1–11

Continuous variables are shown as mean ± standard deviation.
Categorical variables are shown as ratio.

TABLE 2: Endometrial thickness in women before and after infusion of G-CSF who had IVF-ET.

Characteristic	All women $n = 37$	Women who conceived $n = 7$	Women who did not conceive $n = 30$
Endometrial thickness before G-CSF-infusion	6.74 ± 1.75[1]	6.86 ± 1.65[2]	6.71 ± 1.80[3]
Endometrial thickness after G-CSF infusion	8.42 ± 1.73[1]	8.80 ± 1.14[2]	8.33 ± 1.85[3]
Endometrial thickness (Δ)	1.68 ± 1.05	1.94 ± 0.99[4]	1.62 ± 1.07[4]

Data are shown as mean ± standard deviation.
P value for two dependent samples (before versus after).
[1] $P < 0.001$.
[2] $P = 0.0020$.
[3] $P < 0.0001$.
P value for two independent samples (women who conceived versus women who did not conceive).
[4] $P = 0.8481$.
[5] $P = 0.2444$.
[6] $P = 0.4650$.

%18,9 gebelik oranı mevcut
34,6 yaş ortalaması
72 saat sonra endometrium ölçümü
2. İnfüzyon yapılmamış

A randomized clinical trial of endometrial perfusion with granulocyte colony-stimulating factor in in vitro fertilization cycles: impact on endometrial thickness and clinical pregnancy rates

David H. Barad, M.D.,[a,b] Yao Yu, Ph.D.,[a,b] Vitaly A. Kushnir, M.D.,[a,b] Aya Shohat-Tal, Ph.D.,[a,b] Emanuela Lazzaroni, M.S.,[a,b] Ho-Joon Lee, Ph.D.,[a,b] and Norbert Gleicher, M.D.[a,b]

Objective: To investigate whether granulocyte colony-stimulating factor (G-CSG) affects endometrial thickness, implantation rates, and clinical pregnancy rates in routine, unselected IVF cycles.

Design: Registered, individually randomized, two-group, parallel double-blinded placebo-controlled clinical trial.

Setting: Academically affiliated private clinical and research center.

Patient(s): 141 consecutive, unselected, consenting women with no history of renal disease, sickle cell disease, or malignancy who were undergoing IVF.

Intervention(s): Sealed, numbered, opaque envelopes assigned 73 patients to receive G-CSF (Filgrastim, Amgen, 300 μg/1.0 mL) and 68 to receive placebo (saline).

Main Outcome Measure(s): Endometrial thickness, clinical pregnancy, and embryo implantation rates.

Result(s): The mean age for the whole study group was 39.59 ± 5.56 years (G-CSF: 39.79 ± 5.13 years; placebo: 39.38 ± 6.03 years). Endometrial thickness statistically significantly increased over the 5-day observation period for the whole group by approximately 1.36 mm. The increase in the G-CSF group was not statistically significantly different from the control group. Statistical models looking at treatment effects on clinical pregnancy and implantation rates demonstrated no effect of G-CSF treatment. There were no adverse events for either treatment group.

Conclusion(s): In normal IVF patients, G-CSF does not affect endometrial thickness, implantation rates, or clinical pregnancy rates. Because these results were obtained in an older patient population, they may not necessarily apply to younger women.

Clinical Trial Registration Number: NCT01202656. (Fertil Steril® 2014;101:710–5. ©2014 by

TABLE 1

Characteristics (baseline and outcome) of study patients.

Variable	G-CSF	Placebo
First cycle (N = 141)	n = 73	n = 68
Endometrium (day of hCG trigger)	10.23 (± 2.01)	10.37 (± 2.22)
Endometrium (day of embryo transfer)	11.69 (± 2.50)	11.63 (± 2.14)
Change in endometrial thickness	1.45 (± 2.22)	1.25 (± 2.28)
Age (y)	39.79 (± 5.13)	39.38 (± 6.03)
Baseline FSH	8.64 (± 3.92)	8.27 (± 4.01)
Baseline AMH	2.07 (± 2.17)	1.99 (± 2.38)
Oocytes retrieval (patient)	8.88 (± 7.22)	8.56 (± 5.83)
Pregnancy (hCG+) cycle 1	18/73 (24.65%)	19/68 (27.94%)
SAB	1/18 (5.6%)	3/19 (15.8%)
Implantation rate	22/176 (12.5%)	28/168 (16.7%)
Clinical pregnancy (per hCG+)	17/18 (94.4%)	16/19 (84.2%)
Good quality embryos	72/158 (45.57%)	55/140 (39.29%)
Second cycle (N = 35)[a]	n = 19	n = 16
Endometrium (day of hCG trigger)	9.96 (± 2.27)	11.10 (± 1.93)
Endometrium (day of embryo transfer)	10.32 (± 2.15)	11.40 (± 1.17)
Change in endometrial thickness	0.36 (± 2.13)	0.16 (± 2.01)
Age (y)	40.09 (± 5.20)	39.68 (± 3.81)
Baseline FSH	9.26 (± 3.73)	8.87 (± 4.14)
Baseline AMH	1.16 (± 0.93)	1.50 (± 2.69)
Oocytes retrieval (patient)	7.08 (± 6.38)	10.18 (± 6.46)
Pregnancy (hCG+) cycle 2	7/19 (36.84%)	10/16 (62.5%)
SAB	2/7 (28.57%)	2/10 (20%)
Implantation rate	7/51 (13.7%)	11/48 (22.9%)
Clinical pregnancy (per hCG+)	5/7 (70.43%)	6/10 (60%)
Good quality embryos	14/45 (31.11%)	21/48 (43.75%)
Overall implantation rate	33/224 (14.73%)	35/219 (15.98%)

Note: AMH = antimüllerian hormone; FSH = follicle-stimulating hormone; G-CSF = granulocyte colony-stimulating factor; hCG = human chorionic gonadotropin; SAB = spontaneous abortion.
[a] The second cycle was a cross-over cycle. The 16 patients originally allocated to placebo received GCSF in the second cycle and the 19 received placebo.

Barad. Endometrial perfusion with G-CSF in IVF. Fertil Steril 2014.

İnce endometrial kalınlığı olmayan hastalarda etkisi yok

Reproductive Sciences
2014, Vol. 21(3) 381-385

DOI: 10.1177/1933719113497286
rs.sagepub.com
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Granulocyte Colony-Stimulating Factor Administration for Infertile Women With Thin Endometrium in Frozen Embryo Transfer Program

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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 μg/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.

Table 1. Characteristics of Patients Who Received G-CSF Administration and Those Who Did Not.

	With G-CSF (n = 34)	Without G-CSF (n = 25)	*P* Value
Age, years	30.91 ± 3.51	31.96 ± 3.65	NS
Gravidity	1.21 ± 1.23	1.16 ± 1.07	NS
Infertility type, n (%)			
Primary	11 (32.35)	8 (32.00)	NS
Secondary	23 (67.65)	17 (68.00)	
Infertility duration, years	4.26 ± 2.91	5.72 ± 4.02	NS
BMI, kg/m^2	20.83 ± 2.88	20.95 ± 2.91	NS
Basal FSH, IU/L	7.83 ± 2.25	7.10 ± 1.44	NS
Basal LH, IU/L	5.96 ± 4.72	6.43 ± 4.12	NS
Basal E_2, pmol/L	196.79 ± 174.03	162.03 ± 71.97	NS
No. of prior fresh IVF cycles	1.44 ± 0.82	1.40 ± 0.71	NS
Endometrial thickness in fresh IVF cycles, mm	7.77 ± 1.61	7.78 ± 1.46	NS
Thin endometrium in fresh IVF cycles, n (%)	21 (42.86)	18 (51.43)	NS
Cause of infertility, n (%)			
Pelvic/tubal factor	27 (79.41)	17 (68.00)	NS
Male factor	19 (55.88)	18 (72.00)	NS
Uterine factors	8 (23.53)	10 (40.00)	NS
Polycystic ovary syndrome	7 (20.59)	6 (24.00)	NS
Unexplained infertility	1 (2.94)	1 (4.00)	NS
Endometriosis	1 (2.94)	1 (4.00)	NS

Abbreviations: BMI, body mass index; NS, not significant; G-CSF, granulocyte colony-stimulating factor; IVF, in vitro fertilization; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E_2, estradiol.

Table 2. Treatment Protocol and Outcomes of FET Cycles in All 3 Groups.

	G-CSF Group (n = 40)	Self-Controlled Group (n = 49)	Control Group (n = 80)	*P* Value		
				1 vs 2[a]	1 vs 3[b]	2 vs 3[c]
Treatment protocol, n (%)						
Natural cycle	5 (12.50)	14 (28.57)	27 (33.75)	.013	.027	NS
Extended estrogen cycle	23 (57.50)	31 (63.27)	40 (50.00)			
Induced cycle	12 (30.00)	4 (8.16)	13 (16.25)			
Endometrial thickness at D0, mm	6.51 ± 0.69	6.26 ± 1.41	6.42 ± 0.91	NS	NS	NS
Cycle cancellation, %	17.50	69.39	48.75	.000	.001	.022
No. of completed cycles	33	15	41			
No. of transferred embryos	2.48 ± 0.57	2.53 ± 0.52	2.56 ± 0.55	NS	NS	NS
Transferred embryos feature, n (%)						
D3	62 (75.61)	33 (86.84)	91 (86.67)	NS	NS	NS
D5	20 (24.39)	5 (13.16)	14 (13.33)			
Frozen embryo recovery, %	93.94 ± 15.55	95.56 ± 11.73	92.93 ± 13.04	NS	NS	NS
Implantation, n (%)	13 (15.85)	3 (7.89)	14 (13.33)	NS	NS	NS
Clinical pregnancy/ET, n (%)	10 (30.30)	3 (20.00)	12 (29.27)	NS	NS	NS
Miscarriage, n	1	2	2	–	–	–
Ectopic pregnancy, n	0	1	0	–	–	–

Abbreviations: D0, the day of ovulation or administration of progesterone or hCG; D3, 72 hours after ovulation or the beginning of progesterone supplementation; D5, 120 hours after ovulation or the beginning of progesterone supplementation; NS, not significant; FET, frozen embryo transfer; hCG, human chorionic gonadotropin; G-CSF, granulocyte colony-stimulating factor; ET, embryo transfer.

[a] G-CSF group versus self-controlled group.

[b] G-CSF group versus control group.

[c] Self-controlled group versus control group.

Düşük doz G-CSF, Thaw siklusu, retrospektif
Non-randomize çalışma, klinik gebelikler arasında fark yok

Iran J Reprod Med Vol. 12. No. 10. pp: 661-666, October 2014

Original article

Transvaginal perfusion of G-CSF for infertile women with thin endometrium in frozen ET program: A non-randomized clinical trial

Maryam Eftekhar M.D., Mozhgan Sayadi M.D., Farideh Arabjahvani M.D.

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 Methods: This 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 direct 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.

Table I. Baseline characteristics in G-CSF cotreated and control groups

Variables	G-CSF cotreated group (n= 34)	Control group (n=34)	p-value
Age (years)	30.81 ± 4.60	28.57 ±5.16	0.06
BMI (kg/m^2)	25.27 ± 1.48	24.93 ± 1.59	0.38
Type of infertility			
Primary	27 (81.80%)	31 (93.90%)	0.12
Secondary	6 (18.20%)	2. (6.10%)	
Etiology of infertility			
Ovulatory	8 (24.20%)	5 (16.10%)	0.32
Tubal	1 (3%)	1 (3.2%)	
Male	11 (33.30%)	14 (45.20%)	
Mixed	9 (27.30%)	11 (35.5%)	
unexplained	4 (12.10%)	0 (0%)	

G-CSF: granulocyte colony-stimulating factor BMI: body mass index
OHSS: ovarian hyperstimulation syndrome IVF: in vitro fertilization
Continuous data presented as mean±SD with p-values obtained from Independent- Samples T test; Enumeration data presented as N (%) with p-value obtained from Chi-Square or fisher exact tests. A p-value of<0.05 was considered statistically significant

Table II. Cycle characteristics and outcomes of FET cycles in G-CSF cotreated treated and control groups

Variables	G-CSF cotreated group (n=34)	Control group (n= 34)	p-value
No. of Transferred embryos	2.46 ± 0.63	2.39 ± 0.49	0.64
Embryo quality			
A	20 (71.40%	17 (60.70%)	0.57
B	8 (28.60%)	11 (39.30%)	
Cycle cancellation	5 (15.20%)	5 (15.20%)	1.00
Endometrial thickness, (mm) at			
D1	5.63 ± 0.78	5.76 ± 0.86	0.88
D2	7.91 ± 0.55	8.23 ± 0.82	0.10
Chemical pregnancy	11 (39.30%)	4 (14.30%)	0.68
Clinical pregnancy	9 (32.10%)	3(12%)	0.10

G-CSF: granulocyte colony-stimulating factor FET: frozen embryo transfer
D1: endometrial thickness at the 12th-13th day of frozen- thawed embryo transfer cycle
D2: endometrial thickness at the first day of progesterone injection
Transfer day^{x}: The frozen- thawed cycle day which the embryos were transferred
Continuous data presented as mean±SD with p-values obtained from Independent-Samples T test; Enumerationl data presented as N (%) with p-value obtained from Chi-Square or fisher exact test. A p-value of<0.05 was considered statistically significant.

Non-randomize çalışma, Klinik gebelik oranı G-CSF grubunda
Daha yüksek olmakla beraber istatistiksel fark yok

ART de Tekrarlayan İmplantasyon Başarısızlıklarında G-CSF

Results of our first study (2000): patients with more than four IVF/ICSI treatments not resulting in pregnancy or more than four unsuccessful ETs received molgramostim, and, in a second series, filgrastim as a single shot. The age of all groups was between 37 and 38; all ETs were performed on day 2 (D+2).

	H-GM-CSF (molgramostim 300 μg)	No medication	Rh-G-CSF (filgrastim 34 mIU)	No medication
Number of patients	107	107	69	69
Number of embryo transfers (day 2)	107	106	69	69
Clinical pregnancies	46	21	35	13
Pregnancy rate/embryo transfer	42.9%	19.8%	50.7%	19.8%
Abortion rate (clinical pregnancies)	9 (19.5%)	2 (19.0%)	7 (29%)	2 (15.4%)

- 1149 ET sonrası GM-CSF kullanılan grupta implantasyon oranları %20 den % 23,5' e ve canlı doğum oranları % 24,1'den %28.9'a yükselmiş **Ziebe, S., Fertil.Steril. 2013**
- 109 hasta, en az 3 IVF siklus, en az 7 iyi kalitede embriyo transferi, en fazla 39 yaş, ET 2. gün ve 60 mg G-CSF başlanıyor, gebelik testi pozitif geldikten sonra 40. güne kadar devam ediliyor. Tedavi grubunda (58 hasta) gebelik oranı % 43,1 iken plasebo grubunda (51 hasta) %21,6 bulunuyor ($p<0.001$).

Scarpellini, F., Sbracia, M., J. Reprod. Immunol. 2012

GAZİ VERİLERİMİZ

	G-CSF (+) (91)	Kontrol (123)	p
Yaş	32,8±5,1	32,6±6	0.8
D3 FSH (IU/L)	7,6±3,5	7,1±3,1	0.4
HCG günü endometrial Kalınlık (mm)	10,3±2,1	10,1±1,8	0.7
Toplanan oosit sayısı	8,2±4	7,8±4,4	0.8
Matür oosit sayısı	5,5±3,3	5,3±4,4	0.6
Transfer edilen embriyo sayısı	1,1±0,4	1±0,5	0,7
Beta HCG (+) %	37,3	18,7	0.003
Klinik Gebelik %	32,9	15,4	0.008

SONUÇLAR

- Başarılı bir gebelik için blastosistin reseptif endometriuma implante olması gereklidir
- Yıllardır H/S adezyolizis, estrojen tedavisi, vazodilatatör ve antioksidan ajanlar uygulanagelmektedir
- Son dönemlerde rejeneratif tıbbi tedaviler ince endometriumun tedavisinde kullanulmaktadır.
- Tüm embriyoların dondurulması, siklus iptali, taşıyıcı annelik gibi seçeneklerden önce denenebilecek bir tedavi seçeneği olabilir

SONUÇLAR

- İnce endometriumun tedavi modalitelerinden biri de G-CSF olabilir
- Özellikle endometrial kalınlığın < 7mm olan hallerde kullanılabilir
- HCG günü intrauterin infüzyon veya ET sonrası sc olarak kullanılabilir (doz aralığı?)
- İnce endometrium ölçülmeyen hastalarda etkinliği tartışmalı
- Thaw sikluslarında çalışma gruplarında daha yüksek gebelikler olmasına rağmen istatistiksel anlama ulaşılmamış
- RIF olan hastalarda da etkili olabilmektedir