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ROLE OF GRANULOCYTE COLONY STIMULATING FACTOR IN IMPROVING ENDOMETRIAL THICKNESS IN INFERTILITY

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ABSTRACT

Despite of effective artificial reproductive techniques there is a plateau in rates of positive outcomes. So, now infertility clinicians and researchers have moved their focus towards endometrium and its ability to promote implantation.[1] **Objective:** We planned this study to demonstrated the use of granulocyte colony stimulating factor in patients undergoing IUI with thin endometrium (<7mm) on day of HCG trigger. **Materials and Methods:** This is a prospective study. 21 patients with thin endometrium on the trigger with endometrial thickness ≤7 mm received intra uterine instillation of G CSF (Neukin 300 mcg pre filled syringe) using IUI catheter. Endometrial thickness was reassessed after 48 hours. Results: endometrial thickness was improved in all the patients. Mean endometrial thickness pre infusion was 6.44±0.60 and post infusion was 8.22±1.12 (p value 0.0001, S). Difference in endometrial thickness was 2.22±1.12. There was no cycle cancellation. UPT was positive in 38.1% of patients. **Conclusion:** G CSF has the potential to improve endometrial thickness.

KEYWORDS: Thin Endometrium, Granulocyte Colony Stimulating Factor, IUI.

INTRODUCTION

It was also demonstrated that endometrial thickness <7 mm negatively affected pregnancy rate.[2] In about 5% of patients seeking infertility treatment have problem due to uterine factors[3] A thin endometrium can result from intrauterine adhesions, after infections or curettage, use of oral contraceptives or clomiphene citrate, congenital anomalies such as Turner syndrome, or previous radiotherapy.[4] Sharkey showed that immunological mechanisms in the endometrium are very important and crucial in the implantation process.[5] Definition of thin endometrium is controversial but the most accepted one is the minimum required endometrial thickness for successful pregnancy. There are various schools of

thoughts which define a cut off for the thin endometrium. Some investigators say that pregnancy occurs when endometrium reaches ≥7mm, and others that ≥8 mm or ≥9 mm is required for successful conception.[6] In our study we have taken ≤7 mm as cut off for thin endometrium.[6] The suggested treatment strategies for unexplained thin endometrium include high-dose estrogen supplementation, vaginal sildenafil, low-dose aspirin, pentoxifylline, or tocopherol. Although such medical treatments are sometimes effective, some women still do not respond. Conclusive evidence is still lacking regarding their therapeutic effects on the endometrium.[7] Intrauterine instillation of granulocyte colony-stimulating factor (G-CSF) to promote endometrial development was first proposed by Gleicher et al. Preliminary studies demonstrated that G-CSF stimulated neutrophilic granulocyte proliferation and differentiation, acted on macrophages of decidual cells, and finally affected the implantation[8] G CSF is secreted by reproductive tract: human leutinised follicular granulosa cells, endometrial cells, cells from decidua, placenta and membranes. It is essential for blastocyst development and subsequently viability. It was proposed to be beneficial in treatment of recurrent miscarriages and implantation failures.[9] A growth spurt in endometrial thickness was be observed with intrauterine instillation of G CSF as it improves c amp mediated decidulisation of human endometrial stromal cells in both autocrine and paracrine fashion.[10]

MATERIALS AND METHODS

This was a prospective study done at AVBRG sawangi meghe wardha from august 2016 to July 2017 and was approved by institutional ethicial committee.A total of 21 women with persistent thin endometrium (≤7 mm) unresponsive to other treatment and had a previously cancelled cycle due to thin endometrium were included in the study.

Inclusion criteria were

1. Women aged 18 to 45 years
2. Previously cancelled cycle due to thin endometrium.
3. Inadequate endometrial thickness that is less than 7 mm on day 12 or on the day of HCG trigger.
4. Lack of contraindication for use of granulocyte colony stimulating factor (like hypersensitivity, any past medical condition eg. sickle cell disease, renal insufficiency)
5. Willing to participate in the study.

The exclusion criteria were

1. Patients not given consent.
2. Patients with good endometrial thickness.
3. Patient with intrauterine adhesions or polyps or sub mucous fibroids.

Written informed consent was taken. Subjects were evaluated on the basis of predesigned and pretested proforma with respect to history, clinical examination and investigations. Findings of general and systemic examination were noted. Pelvic examination was done with empty bladder in dorsal position. Per speculum and per vaginal examination was done and findings were noted. Serial trans-vaginal ultra-sonographic evaluation was done for endometrial thickness from day 7 of menstrual cycle. Trans-vaginal ultra-sonography was done with GE (logic S8 machine) and A 6.5 mhz trans-vaginal probe. Patients with endometrial thickness less than 7 mm till day 12 were given Granulocyte Colony Stimulating Factor 300 mcg/ml intrauterine instillation was done slowly by using IUI catheter. 48 hours after instillation, the endometrial thickness was reassessed by ultrasonography with the same machine, following the same technique and by the same operator.

The primary aim was to see the increase in endometrial thickness and second was to see result of urine pregnancy test. We divided the patients in two groups depending on the whether urine pregnancy test was positive or negative. Statistical analysis was done by using descriptive and inferential statistics using student's paired t test and software used in the analysis were SPSS 22.0 version and Graph-Pad Prism 6.0 version and $p<0.05$ is considered as level of significance.

RESULTS

Out of 21 patients who participated endometrial thickness was increased in all. 8 out of 21 patients showed positive urine pregnancy test that is 38.06%.

Table. 1: shows the comparison of endometrial thickness in pregnant and nom-pregnant.

Characteristics	All Women(n=21)	Women who conceived(n=8)	Women who did not conceived(n=13)	p-value
ET Before GCSF infusion	6.44±0.60	6.32±0.43	6.52±0.68	0.47,NS
ET after GCSF infusion	8.22±1.12	8.41±1.10	8.11±1.16	0.57,NS
Difference in ET	2.22±1.12	2.08±0.98	1.59±1.03	
t-value	7.97	5.52	5.99	
p-value	0.0001,S	0.0001,S	0.001,S	

The average endometrial thickness pre infusion was 6.44±0.06 which increased to 8.22±1.12 post infusion. The difference was 2.22±1.12. By using student's paired t test statistically significant difference was found in mean endometrial thickness before and after infusion (t=7.97 and p-value 0.0001S).

Mean endometrial thickness in patients who conceived with IUI was 6.32±0.43 before infusion and 8.41±1.10 after infusion. By using student's paired t test statistically significant difference was found in mean endometrial thickness before and after infusion (t=5.52 and p-value 0.0001S).

Mean endometrial thickness in patients who did not conceived with IUI was 6.52±0.68 before infusion and 8.11±1.16after infusion. By using student's paired t test statistically significant difference was found in mean endometrial thickness before and after infusion (t=5.99 and p-value 0.001S). However in this study the endometrial thickness in both the groups increased but there was not statistically significant difference of increase in endometrial thickness in two groups.(p value 0.47NS p value 0.57NS).

Table. 2: showing the outcome of pregnancy in relation to endometrial thickness post infusion.

	4.6-5.5 mm		5.6-6.5 mm		6.6-7.5 mm		7.6-8.5 mm		8.6-9.5 mm		≥9.6 mm	
	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve
IUI	0	0	0	0	2	2	2	4	3	5	1	2
%	0	0	0	0	9.52	9.52	9.52	19.05	14.29	23.81	4.76	9.52

In our study it was observed that out of 5 patients 3 patients conceived when the endometrial thickness was 8.6-9.5 mm which accounts for 37.5% of patients conceived in this range of endometrial thickness and 37.5% of total patients who conceived and 14.29% of total patients who participated in the study. When the endometrial thickness was in the range of 7.6-8.5mm 2 patients (33.33% for the range and 25% of total patients conceived and 9.52% of total patients participated) conceived.

Table. 3: showing general characteristics of patients.

Parameter	All patients
Mean age	28.76±6.12
Primary infertility	58%
Secondary infertility	42%
Average duration of infertility	3.6years

DISCUSSION

In the present study, intrauterine instillation of G CSF resulted in acceptable increase in endometrial thickness in women with thin endometrium. Unlike other studies we instilled G CSF in IUI cycles on the day of trigger.

Like the study conducted by Gliescher et al[11] endometrial thickness increased in all women after G CSF instillation which is similar to our observation. Studies by Lee et al[6] and Michal[12] et al also showed similar findings.

However, in the study by Check JH et al[13] and Maryam E et al[14] there was no increase in endometrial thickness pre and post infusion of G CSF.

The mean increase of thickness was 1.59 mm in our study. This finding was consistent with the study done by Tehraninejad ES et al[15] and Gliescher et al.[11]

In our study a growth spurt in endometrial thickness was observed within 48 hours. This was similar to study by Gliescher et al.[11] In studies by Sarvi et al (16) G CSF instillation was done twice in 3 patients out of 15 patients in their investigation group as they did not show sufficient increase in endometrial thickness after 48 hours. In the study by Vineet M et al[17] also they measured endometrial thickness 48 hours after intrauterine instillation and found increase in endometrial thickness.

Maximum percentage of patients with endometrial thickness in range of 8.6-9.5 mm showed positive pregnancy test. This finding was similar to meta-analysis by Kasius A et al done on endometrial thickness and IVF outcome. In our study 8 out of 21 patients in present IUI cycle conceived. Considering the general profile of patients and condition of their endometrium this number is significant.

In our study the mean age of patients was 28.76 years which was similar to studies by Mangal et al[19] and Paul CA et al.[20] In this study 58% patients had primary and 42% had secondary infertility. this was consistent with the fiindings by Zhong et al[21] and Ali F et al.[22]

CONCLUSION

From our study we conclude that intrauterine granulocyte colony stimulating factor improves the endometrial thickness. It improves the rate of conception.

REFERANCES

1. Maryam Eftekhar, M.D., Mozhgan Sayadi, M.D., and Farideh Arabjahvani, M.D, Transvaginal perfusion of G-CSF for infertile women with thin endometrium in frozen ET program: A non-randomized clinical trial.
2. Al-Ghamdi A, Coskun S, Al-Hassan S, Al-Rejjal R, Awartani K. The correlation between endometrial thickness and outcome of in vitro fertilization and embryo transfer (IVF-ET) outcome. Reproductive Biology and Endocrinology, 2008; 6: 37.
3. G-CSF Intrauterine for Thin Endometrium, and Pregnancy Outcome Ensieh Tehraninejad, M.D.,1 Fateme Davari Tanha, M.D.,2 Ebrahim Asadi, M.Sc.,3 Koorosh Kamali, M.D.- MPH- Ph.D.,4 Elham Aziminikoo, M.D.,1 and Elahe Rezayof, B.Sc.1
4. Senturk LM, Erel CT. Thin endometrium in assisted reproductive technology. Curr Opin Obstet Gynecol, 2008; 20: 221-228.
5. The endometrium as a cause of implantation failure Author links open overlay panelAndrew MSharkeyPhD(Senior Research Associate)Stephen KSmithfrcog(Professor)
6. Dayong lee et al the efficacy of intrauterine instillation of granulocyte colony stimulating factor I infertile women with thin endometrium: a pilot study.
7. Senturk LM, Erel CT. Thin endometrium in assisted reproductive technology. Curr Opin Obstet Gynecol, 2008; 20: 221-228.
8. Loke YW, King A, Burrows TD. Decidua in human implantation. Human Reproduction, 1995; 10(supplement 2): 14–21.
9. Dominguez F, Remohi J, Pellicer A and Simon C Human endometrial receptivity: a genomic approach. Reprod Biomed Online, 2003; 6: 332–338.
10. Journal of Therapeutic advances January 2014 Issue.
11. A pilot cohort study of granulocyte colony stimulating factor in treatment of unresponsive thin endometrium resistant to standard therapies N Gliecher, A Kim, T. Michaeli.
12. Evaluation of Granulocyte Colony-Stimulating Factor Effects on Treatment-Resistant Thin Endometrium in Women Undergoing In Vitro Fertilization Kunicki M et al.
13. Failure to increase the thickness of thin endometria with intrauterine infusion of granulocyte colony stimulating factor (G-CSF). Check JH, Choe JK, Summers-Chase D.
14. Efficacy of Intrauterine infusion of granulocyte colony stimulating factor on patients with history of implantation failure: A randomized control trial Maryam Eftekhar, M.D., 1 Sepideh Miraj, M.D.,1,2 Maryam Farid Mojtahedi, M.D., 3 and Nosrat Neghab, M.D.

15. G-CSF Intrauterine for Thin Endometrium, and Pregnancy Outcome Ensieh Tehraninejad, M.D.,1 Fateme Davari Tanha, M.D.,2 Ebrahim Asadi, M.Sc.,3 Koorosh Kamali, M.D.- MPH- Ph.D.,4 Elham Aziminikoo, M.D.,1 and Elahe Rezayof, B.Sc.1.
16. Effect of increased endometrial thickness and implantation rate by granulocyte colony stimulating factor on unresponsive thin endometrium in fresh endometrial cycle: a randomized clinical trial Fatemah Sarvi et al.
17. Effects of Granulocyte Colony-Stimulating Factor (GCSF) on Persistent Thin Endometrium in Frozen Embryo Transfer (FET) Cycles Mishra et al.
18. Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. Kasius A, Smit JG, Torrance HL, Eijkemans MJ3, Mol BW4, Opmeer BC5, Broekmans FJ1.
19. Mangal S, Mehirishi S. To study and compare the effect of vaginal sildenafil and estradiol valerate on endometrial thickness, blood flow and pregnancy rates in infertile women undergoing intrauterine insemination. Int J Reprod Contracept Obstet Gynecol, 2016; 5: 2274-7.
20. Prevalence & correlates of primary infertility among young women in Mysore, India Paul C. Adamson, 1,4 Karl Krupp,3 Alexandra H. Freeman,2 Jeffrey D. Klausner,1,2 Arthur L. Reingold,4 and Purnima Madhivanan 3,5.
21. The efficacy of conversion from IUI to IVF-ET in infertility patients with hyper-response to ovulation induction: A retrospective studyYiping Zhong, Jin Lib#, Ying Yinga, Haitao Wua Canquan Zhou Yanwen Xua, Qiong Wanga Jie Lia Xiaoting Shena.
22. Ali F. Al- Assadi Tikrit Medical Journal, 2012; 18(2): 330-338. Bhattacharya S. Infertility. In: Edmonds DK. Dewhurst's Textbook of Obstetrics and Gynaecology. 17th ed. Blackwell Publishin.