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ROLE OF INTRAUTERINE GRANULOCYTE COLONY-STIMULATING FACTOR IN IMPROVING ENDOMETRIAL RECEPTIVITY IN WOMEN UNDERGOING OVULATION INDUCTION: A PROSPECTIVE INTERVENTIONAL STUDY

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ABSTRACT

Introduction: Endometrial receptivity plays a crucial role in successful embryo implantation, and its insufficiency remains a major challenge in infertility management. Granulocyte Colony-Stimulating Factor (G-CSF) is a hematopoietic cytokine that has shown potential in improving endometrial thickness, vascularization, and decidualization, thereby enhancing implantation rates. This study evaluates the role of intrauterine G-CSF instillation in improving endometrial receptivity in women undergoing ovulation induction. **Objective:** To assess the effect of intrauterine G-CSF instillation on endometrial thickness and vascularity and to compare its efficacy with standard estrogen therapy. **Methods:** A total of 80 infertile women with thin endometrium undergoing ovulation induction were enrolled. Participants were randomized into two groups: the G-CSF group (Group A, n = 40), which received intrauterine G-CSF (300 mcg/ml) on the day of ovulatory trigger, and the standard estrogen therapy group (Group B, n = 40). Endometrial thickness was measured before and 36 hours after intervention using transvaginal ultrasonography. Changes in endometrial parameters were assessed using the USSR scoring system and analyzed statistically. **Results:** Both groups demonstrated progressive endometrial thickening from cycle days 5 to 11, with Group A showing a more favorable trend. By day 11, 52.5% of women in Group A achieved an endometrial thickness >7 mm compared to 45% in Group B; however, this difference was not statistically significant (p = 0.341). A favorable triple-line endometrial pattern was significantly more common in the G-CSF group (75%) than in the estrogen group (40%) (p = 0.01), indicating improved structural receptivity. Endometrial vascularity in zones I–II was comparable between the groups (87.5% in Group A vs. 85% in Group B; p = 0.312). Subendometrial blood flow showed a statistically significant improvement in Group A, with a lower mean resistance index (RI) of 0.63 compared to 0.66 in Group B (p = 0.038), suggesting enhanced endometrial perfusion with G-CSF. **Conclusion:** Intrauterine G-CSF instillation is an effective intervention for enhancing endometrial receptivity, particularly by improving endometrial pattern and subendometrial blood flow. Further studies are required to standardize its application in fertility treatments.

KEYWORDS : Endometrial Receptivity; Granulocyte Colony-Stimulating Factor; Ovulation Induction; Infertility; Endometrial Thickness; Endometrial Pattern; Subendometrial Blood Flow; USSR Scoring.

INTRODUCTION

Endometrial receptivity is a fundamental determinant of successful embryo implantation and refers to the state in which the endometrium undergoes coordinated biochemical, structural, and molecular changes that allow embryo attachment and invasion. This period, termed the window of implantation, is tightly regulated by ovarian hormones, primarily estrogen and progesterone. Impaired development of endometrial receptivity is a major cause of implantation failure, affecting both natural conception and assisted reproductive techniques [1].

The transition from the proliferative to the secretory phase is essential for achieving a receptive endometrium. Progesterone induces morphological and functional changes, including the development of pinopods on the luminal surface, increased glycodelin secretion promoting immune tolerance, and expression of adhesion molecules such as integrins that facilitate embryo attachment. Regulation of mucin-1 (MUC-1) and maintenance of an optimal estrogen-to-progesterone ratio further determine endometrial readiness for implantation [2].

At the molecular level, endometrial receptivity is influenced by specific genes and cytokines. Homeobox genes HOXA10 and HOXA11 are critical for endometrial differentiation, while leukemia inhibitory factor (LIF) and interleukin-11 (IL-11) play essential roles in stromal decidualization and embryo–endometrium crosstalk [3]. Immunological regulation is equally important; regulatory T cells (Tregs) prevent embryo rejection, and uterine natural killer (uNK) cells support vascular remodeling and secretion of growth factors necessary for implantation [4].

Endometrial thickness and vascularity are widely used clinical indicators of receptivity. Doppler ultrasonography allows assessment of endometrial and subendometrial blood flow and helps predict implantation potential. Therapeutic approaches aimed at improving receptivity include estrogen and progesterone supplementation, growth factors such as granulocyte colony-stimulating factor (G-CSF), and platelet-rich plasma (PRP), particularly in women with thin endometrium [5]. Lifestyle factors, including diet, physical activity, and stress reduction, may also influence endometrial health and receptivity [6].

Challenges Associated with Poor Endometrial Receptivity

Poor endometrial receptivity poses a significant challenge in infertility treatment. Inadequate endometrial thickness, commonly defined as <7–8 mm, is associated with reduced implantation rates. Factors such as uterine infections, intrauterine adhesions, and suboptimal response to estrogen therapy contribute to thin endometrium and poor receptivity [7].

Alterations in the endometrial microenvironment, including chronic inflammation and immune dysregulation, further impair implantation. Abnormalities in natural killer cells and macrophages, along with hormonal imbalances, adversely affect endometrial proliferation and differentiation. Conditions such as endometriosis are associated with progesterone resistance, leading to impaired decidualization and reduced receptivity [8].

Uterine vascular health, genetic and epigenetic influences, and structural abnormalities such as fibroids, adenomyosis, intrauterine adhesions, and congenital anomalies also play significant roles in implantation failure [9,10]. Advancing maternal age further compromises receptivity due to diminished hormonal responsiveness and reduced ovarian reserve. Although conventional treatments such as hormonal supplementation, aspirin, low-dose heparin, and sildenafil are commonly used, their effectiveness remains inconsistent [11]. Consequently, newer therapeutic modalities are being explored.

Granulocyte Colony-Stimulating Factor (G-CSF) and Endometrial Receptivity

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic cytokine primarily involved in granulopoiesis through its action on the G-CSF receptor (G-CSFR). Activation of intracellular signaling pathways, including JAK/STAT, PI3K/Akt, and MAPK, promotes cell survival, proliferation, and differentiation [13]. Beyond its hematopoietic role, G-CSF exhibits immunomodulatory and angiogenic properties, contributing to tissue repair and regeneration [15].

In reproductive medicine, G-CSF has gained attention for its potential role in improving endometrial receptivity. By enhancing endometrial thickness, vascularization, and immune modulation, G-CSF may create a favorable environment for embryo implantation [16]. Its clinical use in conditions such as neutropenia and stem cell mobilization is well established, and emerging evidence suggests broader therapeutic applications [17].

The role of G-CSF in ovulation induction cycles can be assessed through changes in endometrial thickness, vascularity, and ultrasonographic pattern. Doppler studies demonstrate that improved subendometrial blood flow following G-CSF administration may reflect enhanced receptivity [18]. The effect appears particularly beneficial in women with persistently thin endometrium or poor response to conventional hormonal therapy [19]. Further evaluation using robust statistical methods may clarify its role in ovulation induction protocols [20].

The present study aims to evaluate the effect of intrauterine instillation of granulocyte colony-stimulating factor in infertile women with poor endometrial receptivity by assessing changes in endometrial thickness and vascularity during ovulation induction cycles.

MATERIALS AND METHODS

Study Design and Setting

This study was a prospective interventional study conducted in the Department of Obstetrics and Gynecology, S.N. Medical College, Agra, over a period of 18 months, from February 2023 to July 2024. The study aimed to evaluate the role of granulocyte colony-stimulating factor (G-CSF) in improving endometrial receptivity in women undergoing ovulation induction.

Study Population

The study population comprised women diagnosed with primary or secondary infertility attending the outpatient department of the Department of Obstetrics and Gynecology, S.N. Medical College, Agra, during the study period. A total of 80 women fulfilling the inclusion criteria were enrolled.

Participants were allocated into two groups:

- **Intervention Group (G-CSF Group / Group A):** Forty women with thin endometrium undergoing ovulation induction who received intrauterine infusion of granulocyte colony-stimulating factor (G-CSF).
- **Control Group (Standard Estrogen Therapy Group / Group B):** Forty age- and BMI-matched women with thin endometrium undergoing ovulation induction who received standard estrogen supplementation (oral estradiol) for endometrial support.

Inclusion Criteria

Women undergoing ovulation induction were included if they met the following criteria:

- Primary or secondary infertility for more than one year
- Age between 18 and 37 years
- Diagnosis of unexplained infertility (<36 months)
- Regular menstrual cycles (25–35 days)
- Evidence of ovulation (positive ovulation test and/or mid-luteal serum progesterone >25 mmol/L in an unstimulated cycle)
- Normal semen analysis of the male partner
- Normal uterine cavity and patent fallopian tubes
- Negative genitourinary screening for Chlamydia and Gonorrhea within the preceding year
- Presence of thin endometrium with poor vascularity on transvaginal ultrasonography
- History of recurrent pregnancy loss

Exclusion Criteria

Women were excluded if they had any of the following:

- Congenital uterine anomalies
- Endometrial polyp or uterine fibroid
- History of previous uterine surgery
- Current pregnancy
- Body mass index (BMI) >35 kg/m^2
- Use of anticoagulant therapy
- Ongoing chemotherapy or radiotherap

Intervention

All participants underwent ovulation induction as per the institutional protocol and were monitored with serial transvaginal ultrasonography (TVS) for follicular development and endometrial assessment. Ovulatory trigger was administered when at least one dominant follicle reached appropriate maturity.

Participants were allocated into two groups:

- **Intervention Group (G-CSF Group / Group A):** Women in this group received intrauterine instillation of granulocyte colony-stimulating factor (G-CSF) at a dose of 300 μg, administered on the day of ovulatory trigger. The procedure was performed under aseptic conditions using an intrauterine insemination (IUI) catheter, with the patient placed in the dorsal lithotomy position. After instillation, patients were advised to remain in the supine position for approximately 15–20 minutes.
- **Control Group (Standard Estrogen Therapy Group / Group B):** Women in this group received standard estrogen supplementation in the form of oral estradiol, initiated during the follicular phase and continued as per institutional protocol to support endometrial growth and receptivity.

Endometrial thickness, pattern, and vascularity were assessed before intervention and 36 hours after the intervention using transvaginal ultrasonography and color Doppler studies. No additional experimental interventions were performed during the study period.

Outcome Measures

The outcomes of the study were assessed using transvaginal ultrasonography and color Doppler imaging. The primary outcome measures included changes in endometrial

thickness and endometrial vascularity following the intervention. Endometrial thickness was measured in the mid-sagittal plane as the maximum distance between the two endometrial–myometrial interfaces.

Secondary outcome measures included assessment of endometrial pattern, subendometrial blood flow, and overall endometrial receptivity. Endometrial pattern was classified based on ultrasonographic appearance, with particular attention to the presence of a triple-line (trilaminar) pattern. Endometrial and subendometrial vascularity were evaluated using color Doppler imaging, and blood flow was quantified by calculating the resistance index (RI) of subendometrial vessels.

Overall endometrial receptivity was assessed using the USSR scoring system, which incorporates endometrial thickness, pattern, and vascularity parameters. All outcome parameters were recorded before intervention and 36 hours after intervention in both study groups.

Ethical Considerations

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants prior to enrollment.

Statistical Analysis

Data were analyzed using the SPSS software. Continuous variables were assessed for normality using the Shapiro–Wilk test. Data were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Categorical variables were presented as frequencies and percentages. Baseline characteristics between the two groups were compared using the independent sample t-test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. Within-group comparisons before and after intervention were performed using the paired t-test or Wilcoxon signed-rank test, while between-group comparisons were analyzed using the independent t-test, Mann–Whitney U test, or Chi-square test, as applicable.

A p-value < 0.05 was considered statistically significant, and all tests were two-tailed.

RESULTS

A total of 80 infertile women with thin endometrium undergoing ovulation induction were enrolled and analyzed. Participants were equally distributed into two groups: the G-CSF group (Group A, n = 40) and the standard estrogen therapy group (Group B, n = 40). Baseline demographic characteristics, including age and body mass index, were comparable between the two groups.

Endometrial Thickness

Both groups demonstrated a progressive increase in endometrial thickness from cycle day 5 to day 11. On day 11, 52.5% of women in the G-CSF group achieved an endometrial thickness of >7 mm, compared to 45% in the estrogen group. Although the G-CSF group showed a more favorable trend, the difference was not statistically significant (p = 0.341).

Table- 40 Distribution of Patients According to Baseline Endometrial Thickness in Group A&B

Cycle Day	Group A Mean (mm)	Group B Mean (mm)	Group A Median (mm)	Group B Median (mm)	p-value
Day7	4.5	4.4	4	4	0.564
Day9	6.3	6.3	6	6	0.462
Day 11	7	6.9	8	6	0.341

Comparison of baseline endometrial thickness between Group A and Group B across different cycle days showed no statistically significant difference. On Day 7, mean endometrial thickness was 4.5 mm in Group A and 4.4 mm in Group B (p = 0.564), with a median of 4 mm in both groups. By Day 9, mean thickness increased to 6.3 mm in both groups, with median values of 6 mm (p = 0.462). On Day 11, mean endometrial thickness was 7.0 mm in Group A and 6.9 mm in Group B, with no significant difference (p = 0.341).

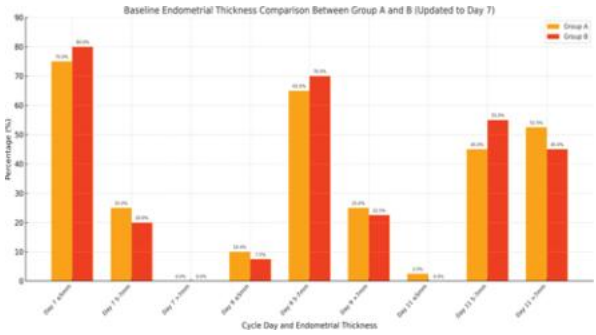


Figure 13: Comparison of Endometrial Thickness Over the Menstrual Cycle Days (Day5, Day9 andDay11) in Group A (Patients) and Group B (controls)

Endometrial Pattern

Table-41 Distribution of Patients According to Endometrial Pattern Before Treatment in Group A and Group B (n=40)

EndometrialPattern	Number of Patients (n=40)	Percentage (%)
Group A		
Triple-line	14	35.00%
Homogenous,Hyperechoic	26	65.00%
Group B		
Triple-line	12	30.00%
Homogenous,Hyperechoic	28	70.00%

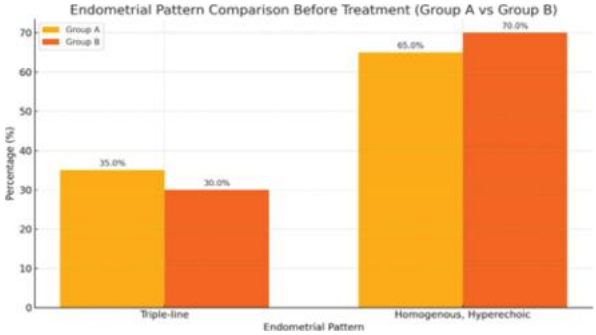
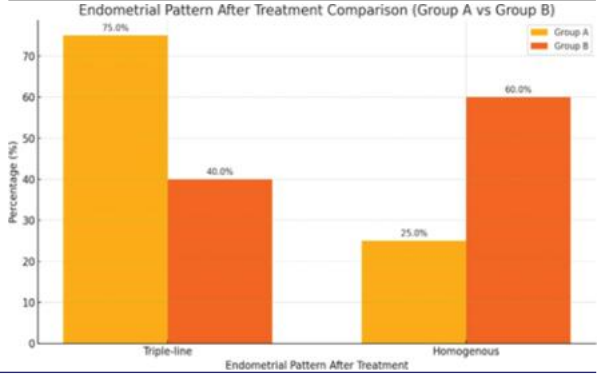


Table-47 Distribution of Patients According to Endometrial Pattern After Treatment in Group A and Group B (n=40)

	Group A	Group B
Endometrial Pattern	Number of Patient (n=40)	Percentage (%)
Triple-line	30(75.0%)	16(40.0%)
Homogenous, Hyperechoic	10(25.0%)	24(60.0%)
Total	40(100%)	40(100%)



After treatment, a significant improvement in the endometrial pattern was observed in Group A compared to Group B. A favorable triple-line pattern was seen in 75% of patients in Group A versus 40% in Group B, while a homogenous, less favorable pattern was present in 25% of Group A compared to 60% of Group B. These findings indicate that treatment significantly enhanced endometrial morphology in Group A, with comparatively limited improvement in the control group. A favorable trilaminar (triple-line) endometrial pattern was observed significantly more often in the G-CSF group (75%) compared to the estrogen group (40%). This difference was statistically significant (p = 0.01), indicating improved structural endometrial receptivity following G-CSF instillation.

Endometrial and Subendometrial Vascularity

Table-42 Distribution of Patients According to Endometrial Vascularity Before Treatmentin Group A and Group B (n=40)

Endometrial Vascularity (Zones)	Number of Patients (n=40)	Percentage (%)
Group A		
ZoneI–II	28	70.00%
ZoneIII–IV	12	30.00%

Table-48 Distribution of Patients According to Endometrial Vascularity After Treatment In Group A and Group B (n=40)

	Group A	Group B
Endometrial Vascularity (Zones)	Number of Patients (%)	Number of Patients (%)
ZoneI–II	35(87.50%)	34(85.0%)
ZoneIII–IV	5(12.50%)	6 (15.0%)
Total	40(100%)	40(100%)

Endometrial vascularity in zones I–II was comparable between the two groups (87.5% in Group A vs. 85% in Group B; p = 0.312).

However, subendometrial blood flow showed significant improvement in the G-CSF group. The mean resistance index (RI) was significantly lower in Group A (0.63) compared to Group B (0.66), indicating enhanced endometrial perfusion (p = 0.038).

Table-45 Distribution of Patients According to Sub-endometrial Resistance Index Before Treatment In Group B (n=40)

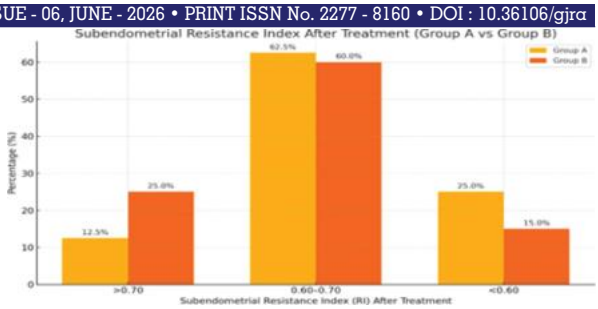
	Group B	
Subendometrial RI	Number of Patients (n)	Percentage (%)
>0.70	12	30.00%
0.60–0.70	22	55.00%
<0.60	6	15.00%

Table-47 Distribution of Patients According to Endometrial Pattern After Treatment in Group A and Group B (n=40)

	Group A	Group B
Endometrial Pattern	Number of Patient (n=40)	Percentage (%)
Triple-line	30(75.0%)	16(40.0%)
Homogenous, Hyperechoic	10(25.0%)	24(60.0%)
Total	40(100%)	40(100%)

Table-49 Distribution of Patients According to Sub-endometrial Resistance Index After Treatment in Group A and Group B (=40)

	GROUP A		GROU P B	
Sub endometrial Resistance Index	Number	Percentage (%)	Number	Percentage (%)
>0.70	5	12.50%	10	25.00%
0.60–0.70	25	62.50%	24	60.00%
<0.60	10	25.00%	6	15.00%
Total	40	100%	40	100%



After treatment, differences were observed in the distribution of subendometrial resistance index (RI) between Group A and Group B. An RI >0.70 was present in 12.5% of Group A compared to 25% of Group B. An RI between 0.60–0.70 was observed in 62.5% of Group A and 60% of Group B. An RI <0.60 was noted in 25% of Group A patients compared to 15% in Group B. Overall, Group A demonstrated a more favorable post-treatment RI distribution than Group B.

Overall Endometrial Receptivity

Assessment using the USSR scoring system demonstrated better overall endometrial receptivity in women receiving intrauterine G-CSF compared to those receiving standard estrogen therapy, driven primarily by improvements in endometrial pattern and subendometrial blood flow.

DISCUSSION

The present study demonstrates that intrauterine G-CSF instillation significantly improves qualitative parameters of endometrial receptivity, including endometrial pattern and subendometrial blood flow. These findings support the hypothesis that G-CSF enhances endometrial receptivity through angiogenic and immunomodulatory mechanisms [3,6].

Previous studies by Gleicher et al. and Kunicki et al. have reported improved endometrial thickness and pregnancy outcomes following G-CSF administration in women with thin endometrium [7,8]. While the present study did not evaluate pregnancy outcomes, the observed improvement in receptivity parameters suggests a potential clinical benefit. Compared to estrogen therapy alone, G-CSF appears to exert a more pronounced effect on endometrial quality rather than thickness alone.

The strengths of this study include its prospective design and objective assessment of endometrial receptivity using Doppler indices. However, the absence of pregnancy outcome data and the relatively small sample size limit the generalizability of the findings.

Limitations

- Single-center study
- Relatively small sample size
- Pregnancy outcomes were not assessed

CONCLUSION

Intrauterine instillation of granulocyte colony-stimulating factor is a promising adjunctive therapy for improving endometrial receptivity in women undergoing ovulation induction, particularly in cases of thin endometrium. Further large-scale randomized controlled trials are required to confirm its role and establish standardized treatment protocols.

Declarations

Ethical Approval: Obtained from Institutional Ethics Committee
Informed Consent: Obtained from all participants
Funding: None
Conflict of Interest: The authors declare no conflict of interest

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