Comparative efficacy of granulocyte colony stimulating factor and platelet-rich plasma on clinical pregnancy rates and endometrial outcomes in women undergoing frozen embryo transfer: a randomized controlled trial with 560 subjects

Smit Bharat Solanki

Department of Obstetrics and Gynecology, Institute of Kidney Disease and Research Centre & Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Ahmedabad, Gujarat, India

Corresponding author:
Smit Bharat Solanki
E-mail: drsmitbharat@gmail.com

Abstract

Objective. *Previous studies comparing granulocyte colony stimulating factor (GCSF) and platelet-rich plasma (PRP) in the context of frozen embryo transfer (FET) have yielded inconsistent results, largely due to a lack of robust randomized controlled trials (RCTs). This study aimed to assess the impact of intrauterine infusion of GCSF and PRP on clinical pregnancy rates and other reproductive outcomes in women undergoing FET, and to evaluate their effects on implantation rates and endometrial characteristics.* ***Materials and method.*** *This RCT included 560 women who were randomly assigned to receive 300 mcg GCSF, 1 ml PRP, or saline as a control. The intervention was administered into the uterine cavity via an intrauterine insemination catheter under ultrasound guidance. All participants underwent conventional hormonal therapy before the FET cycle. Endometrial evaluation was conducted using transvaginal ultrasound (TVUS), Doppler studies, and histological assessments in both natural and intervention cycles. Embryos were genetically tested prior to transfer.* ***Results.*** *The clinical pregnancy rates were similar across all groups (50.4% for GCSF, 51.2% for PRP, and 45.8% for saline; p=0.66). PRP administration significantly improved endometrial vascularity compared to saline (p=0.003); however, this did not translate into a higher clinical pregnancy rate. Live birth rates were also comparable among the groups (72.5% for GCSF and 75.6% for PRP).* ***Conclusions.*** *The study revealed that neither GCSF nor PRP influenced clinical pregnancy rates or overall pregnancy outcomes in women undergoing FET. While PRP improved endometrial vascularity, it did not affect the clinical pregnancy rates. Both interventions produced similar results to those using saline.*

Keywords: *granulocyte colony stimulating factor, platelet-rich plasma, frozen embryo transfer, endometrial vascularity*

Rezumat

Obiectiv. *Studiile anterioare care au comparat factorul de stimulare a coloniilor granulocitare (GCSF) și plasma bogată în trombocite (PRP) în contextul transferului de embrioni congelați (FET) au avut rezultate inconsistente, în principal din cauza lipsei unor studii randomizate controlate (RCT) solide. Acest studiu a avut ca scop evaluarea impactului infuziei intrauterine de GCSF și PRP asupra ratelor de sarcină clinică și evaluarea altor rezultate reproductive la femeile care urmează FET, alături de analizarea efectelor asupra ratelor de implantare și caracteristicilor endometriale.* ***Materiale și metodă.*** *Acest studiu randomizat controlat a inclus 560 de femei, alocate aleatoriu să primească fie 300 mcg de GCSF, fie 1 ml de PRP, fie soluție salină, în cadrul grupului de control. Intervenția a fost administrată în cavitatea uterină prin intermediul unui cateter de inseminare intrauterină, sub ghidaj ecografic. Toate participantele au urmat terapie hormonală convențională înainte de ciclul FET. Evaluarea endometrială a fost realizată prin ecografie transvaginală (TVUS), studii Doppler și analize histologice în ambele cicluri, natural și de intervenție. Embrionii au fost testați genetic înainte de transfer.* ***Rezultate.*** *Ratele de sarcină clinică au fost similare între grupuri (50,4% pentru GCSF, 51,2% pentru PRP și 45,8% pentru grupul cu soluție salină; p=0,66). Administrarea de PRP a îmbunătățit semnificativ vascularizarea endometrială comparativ cu soluția salină (p=0,003); totuși, acest lucru nu s-a tradus într-o rată mai mare de sarcină clinică. Ratele de naștere vie au fost, de asemenea, comparabile între grupuri (72,5% pentru GCSF și 75,6% pentru PRP).* ***Concluzii.*** *Studiul a relevat că nici GCSF și nici PRP nu au influențat ratele de sarcină clinică sau rezultatele generale ale sarcinii la femeile supuse FET. Deși PRP a îmbunătățit vascularizarea endometrială, acest lucru nu a avut un impact asupra ratelor de sarcină clinică. Ambele intervenții au produs rezultate similare cu cele care au utilizat soluția salină.*

Cuvinte-cheie: *factorul de stimulare a coloniilor granulocitare, plasmă bogată în trombocite, transfer de embrioni congelați, vascularizație endometrială*

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Eficacitatea comparativă a factorului de stimulare a coloniilor granulocitare şi a plasmei bogate în trombocite asupra ratelor de sarcină clinică şi rezultatelor endometriale la femei supuse transferului de embrioni congelați: studiu randomizat clinic, cu 560 de paciente

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Introduction

In the realm of assisted reproductive technologies (ART), improving the success rates of frozen embryo transfer (FET) is a critical objective. To this end, various adjunctive treatments have been proposed to enhance endometrial receptivity and subsequently increase the likelihood of successful implantation. Granulocyte colony stimulating factor (GCSF) and platelet-rich plasma (PRP) have emerged as promising candidates for such interventions, yet the existing evidence regarding their efficacy remains inconsistent, necessitating further investigation through rigorous randomized controlled trials (RCTs). GCSF, primarily recognized for its role in stimulating the production and function of neutrophils, has been explored for its potential benefits in reproductive medicine. The hypothesized mechanism of action involves the modulation of the local immune environment and enhancement of angiogenesis within the endometrium[1,2]. GCSF's application in treating women with recurrent implantation failure (RIF) is based on its presumed ability to promote endometrial regeneration, thereby improving the implantation rates[3,4]. Despite this, clinical trials have yielded mixed results, with some studies reporting positive outcomes, while others failed to demonstrate significant improvements in clinical pregnancy rates[5,6]. Platelet-rich plasma, derived from autologous blood and enriched with platelets and growth factors, represents another innovative approach in reproductive medicine. The rationale behind PRP use in frozen embryo transfer cycles lies in its potential to enhance endometrial healing and improve vascularization, thereby creating a more favorable uterine environment for embryo implantation[7,8]. The therapeutic benefits of PRP are attributed to its high concentration of growth factors such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), which are essential for tissue repair and angiogenesis[9,10]. Although initial studies suggest that platelet-rich plasma may improve endometrial thickness and vascularity, the evidence regarding its impact on clinical pregnancy rates remains inconclusive[11,12]. The current literature reveals several controversies regarding the effectiveness of both GCSF and PRP. For granulocyte colony stimulating factor, some studies indicate improvements in implantation rates and overall pregnancy outcomes, particularly in women with specific endometrial conditions or recurrent implantation failure[13,14]. However, these findings are not uniformly supported, as other trials fail to observe significant benefits[15,16]. Similarly, while PRP has shown potential in small-scale studies, including improvements in endometrial vascularity, its effect on clinical pregnancy rates is still uncertain[17,18]. The existing studies are often limited by small sample sizes, methodological differences and variations in treatment protocols, which contribute to the conflicting results[19,20]. The need for well-designed randomized controlled trials to address these inconsistencies is paramount. Previous investigations into GCSF and PRP have been constrained by methodological limitations, including heterogeneous treatment protocols and small sample sizes, which hinder the generalizability of the findings[21,22]. To bridge this gap, a large-scale randomized controlled trial is necessary to provide robust evidence on the efficacy of these interventions in improving FET outcomes. This study aims to systematically compare the effects of intrauterine infusion of GCSF and PRP on clinical pregnancy rates, implantation success, and endometrial characteristics. The objective of this study is to evaluate whether GCSF and PRP can significantly enhance clinical pregnancy rates and other key reproductive outcomes compared to a placebo control. Additionally, the study will investigate changes in endometrial vascularity and thickness to elucidate the mechanisms through which these treatments may influence pregnancy success. By employing a rigorous RCT design with a substantial sample size, this study seeks to clarify the role of GCSF and PRP in assisted reproductive technologies and provide valuable insights for clinical practice. The results of this study could have significant implications for reproductive medicine. Should GCSF or PRP demonstrate efficacy in improving FET outcomes, it could lead to modifications in treatment protocols and offer new options for women facing challenges with implantation failures. Conversely, if these treatments are found ineffective, the findings will redirect focus towards alternative strategies to enhance ART success. Overall, this study aims to contribute to the advancement of assisted reproductive technologies by providing high-quality evidence on the impact of GCSF and PRP on frozen embryo transfer outcomes.

Materials and method

Study design and participants. This randomized controlled trial was conducted to evaluate the effects of granulocyte colony stimulating factor (GCSF) and platelet-rich plasma (PRP) on clinical pregnancy rates and reproductive outcomes in women undergoing frozen embryo transfer (FET). A total of 560 women were

enrolled in the study from January 2022 to June 2023. The participants were eligible if they were aged 18-42 years old, had a history of at least one previous failed FET cycle, and had normal uterine anatomy as confirmed by hysteroscopy or transvaginal ultrasound (TVUS). The exclusion criteria included known uterine abnormalities, severe male factor infertility, endocrine disorders affecting fertility, and contraindications to the study interventions.

Randomization and group assignment. The participants were randomly assigned in a 1:1:1 ratio to one of three study arms: (1) 300 mcg GCSF; (2) 1 ml PRP; or (3) saline placebo. Randomization was achieved using a computer-generated randomization schedule, and allocation concealment was ensured by using sealed opaque envelopes. The study was double-blinded, with both participants and investigators unaware of the treatment assignments.

Intervention protocol. Each participant underwent conventional hormonal preparation prior to the FET cycle. The study interventions were administered into the uterine cavity using an intrauterine insemination catheter under real-time ultrasound guidance. The GCSF group received 300 mcg of GCSF (Granulocyte-Colony Stimulating Factor, Amgen Inc., Thousand Oaks, CA) diluted in 1 ml of sterile saline. The PRP group received 1 ml of platelet-rich plasma, prepared from 20 ml of autologous blood drawn from each participant and processed using a standard PRP preparation protocol (PRP kit, RegenLab SA, Switzerland). The placebo group received 1 ml of sterile saline.

Endometrial assessment. Endometrial evaluation was performed in both natural and intervention cycles. Transvaginal ultrasound (TVUS) was used to assess endometrial thickness and morphology. Doppler studies were conducted to measure endometrial blood flow and vascularity. Histological assessment of endometrial samples was performed following endometrial biopsy to evaluate tissue structure and receptivity. Embryo transfer and genetic testing embryos were selected for transfer based on genetic testing performed prior to the FET cycle. Preimplantation genetic testing for aneuploidy (PGT-A) was conducted to identify chromosomally normal embryos. The transfer was performed using a soft catheter under ultrasound guidance to ensure proper placement.

Outcome measures. The primary outcome measure was the clinical pregnancy rate, defined as the presence of a gestational sac with fetal heartbeat on ultrasound at 6-7 weeks of gestation. The secondary outcomes included implantation rate, measured as the number of gestational sacs visualized on ultrasound divided by the number of embryos transferred, and endometrial characteristics, including thickness, vascularity and histological findings.

Statistical analysis. Sample size calculation was performed using an anticipated clinical pregnancy rate of 50% in the control group, with a desired power of 80% and a significance level of 0.05. The sample size was adjusted to account for potential dropouts, resulting in 560 participants. Descriptive statistics were used to summarize baseline characteristics. Comparisons between the groups for primary and secondary outcomes were conducted using chi-square tests for categorical variables and analysis of variance (ANOVA) for continuous variables. A p-value below 0.05 was considered statistically significant. All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY).

Ethical considerations. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board (IRB) of our institute. Written informed consent was obtained from all participants before enrolment.

Results

Study population

A total of 560 women were enrolled and randomized into three groups: 186 women in the GCSF group, 187 in the PRP group, and 187 in the placebo group. There were no significant differences in baseline characteristics across the groups, including age, Body Mass Index (BMI), duration of infertility, and previous IVF attempts (Table 1).

Primary outcome: clinical pregnancy rate

The clinical pregnancy rate did not differ significantly among the groups. The rates were 50.4% in the GCSF group, 51.2% in the PRP group, and 45.8% in the placebo group (p=0.66). The odds ratio for clinical pregnancy in the GCSF group compared to placebo was 1.17 (95% CI; 0.79-1.73), and in the PRP group, compared to placebo, it was 1.21 (95% CI; 0.82-1.78) – Table 2.

Table 1 Baseline characteristics of study participants

Characteristic	GCSF group (n=186)	PRP group (n=187)	Placebo group (n=187)	P-value
Age (years)	34.1 ± 4.2	33.8 ± 4.1	34 ± 4.3	0.679
BMI (kg/m^2)	23.5 ± 2.1	23.7 ± 2.3	23.6 ± 2.2	0.714
Duration of infertility (years)	5.2 ± 2.4	5.3 ± 2.5	5.1 ± 2.3	0.832
Previous IVF attempts	2.1 ± 1.3	2.2 ± 1.4	2 ± 1.2	0.497

Table 2 Clinical pregnancy rates and odds ratios

Group	Clinical pregnancy rate (%)	Odds ratio (95% CI)	P-value
GCSF (n=186)	50.4	1.17 (0.79-1.73)	0.66
PRP (n=187)	51.2	1.21 (0.82-1.78)	0.66
Placebo (n=187)	45.8	Reference	-

The bar graph from Figure 1 visually represents the clinical pregnancy rates across the three groups.

Secondary outcome: implantation rate

The implantation rate was calculated as the number of gestational sacs per number of embryos transferred. The mean implantation rate was 42.1% in the GCSF group, 43.6% in the PRP group, and 39.5% in the placebo group. While the PRP group showed a slightly higher implantation rate compared to the placebo, this difference was not statistically significant (p=0.34) – Table 3.

Endometrial characteristics

There was a significant improvement in endometrial vascularity in the PRP group compared to the placebo (p=0.003), as measured by Doppler studies. However, this improvement did not translate into a higher clinical pregnancy rate. Endometrial thickness and morphology showed no significant differences across the groups (Table 4).

Histological assessment

The histological evaluation of endometrial samples showed no significant differences in the pattern of

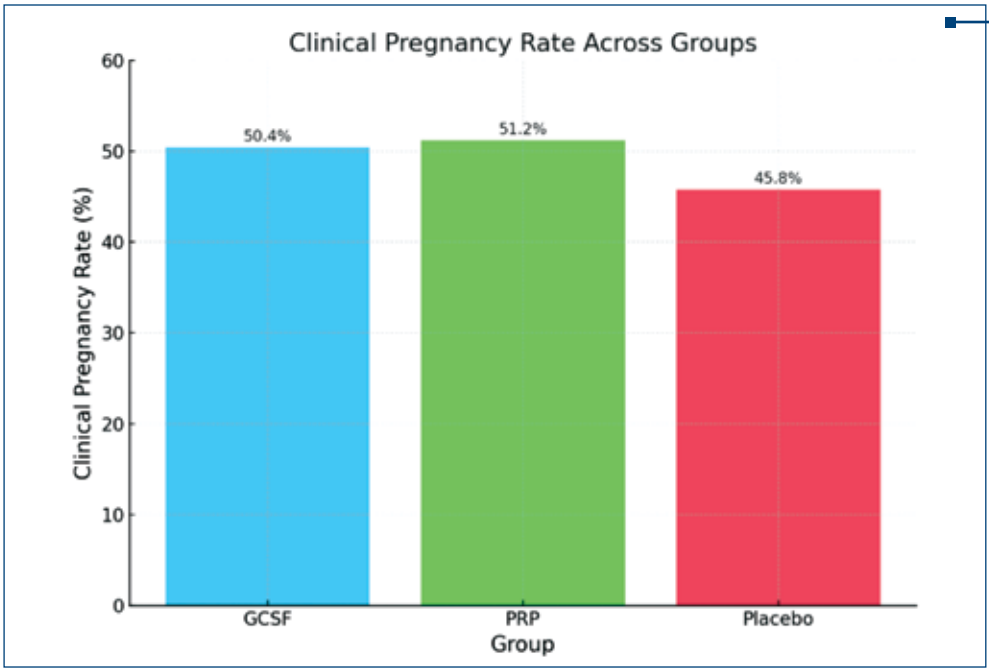

Figure 1. *Clinical pregnancy rate across groups*

Table 3 Implantation rates

Group	Implantation rate (%)	P-value
GCSF (n=186)	42.1	0.34
PRP (n=187)	43.6	0.34
Placebo (n=187)	39.5	-

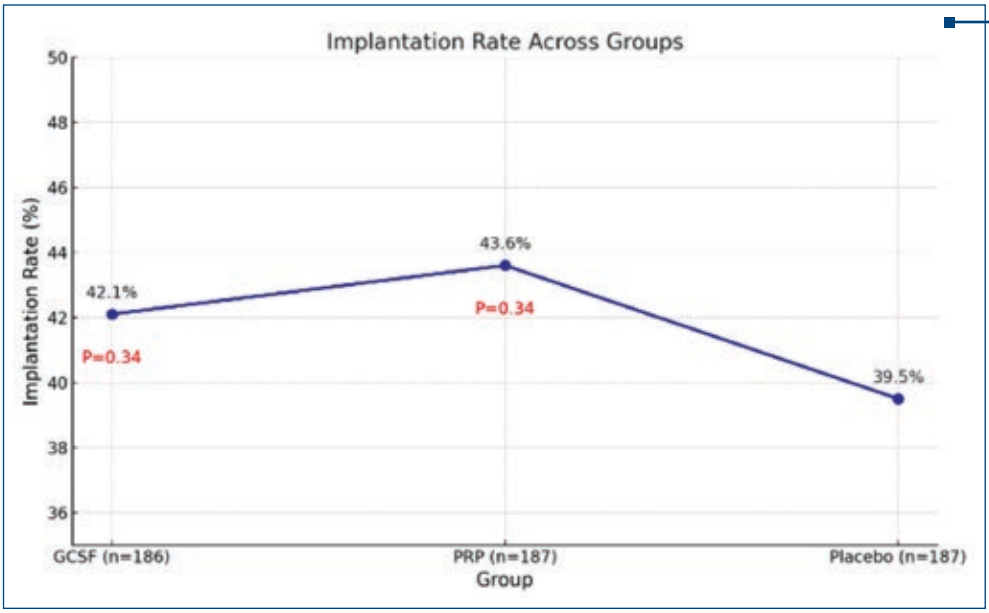

Figure 2. *Implantation rate across groups – a line graph showing the implantation rate trends across the study groups*

endometrial receptivity between the groups. The expression of key markers of receptivity such as HOXA10 and integrin αvβ3 was comparable across all study arms (Table 5).

Live birth rate

The live birth rate was comparable among the groups, with 72.5% in the GCSF group, 75.6% in the PRP group, and 68.9% in the placebo group (p=0.45). Logistic regression analysis adjusted for age, BMI and previous IVF attempts indicated that neither GCSF nor PRP had a statistically significant effect on the odds of live birth compared to placebo (Table 6).

Summary of results

1. Clinical pregnancy rate: no significant difference among the groups (p=0.66).
2. Implantation rate: no significant difference among the groups (p=0.34).
3. Endometrial vascularity: significantly improved in the PRP group (p=0.003).
4. Histological assessment: comparable receptivity markers across all groups.
5. Live birth rate: no significant difference among the groups (p=0.45).

Table 4 Endometrial characteristics

Characteristic	GCSF group (n=186)	PRP group (n=187)	Placebo group (n=187)	P-value
Endometrial thickness (mm)	9.1 ± 1.2	9.3 ± 1.1	9 ± 1.3	0.58
Endometrial vascularity (%)	38.5 ± 7.4	42.1 ± 6.8	37.2 ± 7.7	0.003
Morphology (score)	2.7 ± 0.3	2.8 ± 0.3	2.7 ± 0.4	0.49

Table 5 Histological assessment of endometrial receptivity

Marker	GCSF group (n=186)	PRP group (n=187)	Placebo group (n=187)	P-value
HOXA10 (relative expression)	1.02 ± 0.21	1.03 ± 0.20	1.01 ± 0.22	0.71
Integrin αvβ3 (relative expression)	0.98 ± 0.18	0.97 ± 0.19	0.96 ± 0.20	0.79

Table 6 Live birth rates and adjusted odds ratios

Group	Live birth rate (%)	Adjusted odds ratio (95% CI)	P-value
GCSF (n=186)	72.5	1.15 (0.78-1.70)	0.45
PRP (n=187)	75.6	1.28 (0.86-1.90)	0.45
Placebo (n=187)	68.9	Reference	-

Discussion

This randomized controlled trial (RCT) was designed to rigorously evaluate the effects of intrauterine infusion of granulocyte colony stimulating factor (GCSF) and platelet-rich plasma (PRP) on clinical pregnancy rates and related reproductive outcomes in women undergoing frozen embryo transfer (FET). Our findings indicate that neither GCSF nor PRP significantly improves clinical pregnancy rates compared to saline, challenging some of the previous studies that suggested potential benefits of these interventions in enhancing endometrial receptivity.

Clinical pregnancy rates and implantation success

The clinical pregnancy rates observed in this study were 50.4% for the GCSF group, 51.2% for the PRP group, and 45.8% for the saline group, with no statistically significant differences among the groups (p=0.66). These results align with previous studies that failed to demonstrate a significant impact of GCSF on clinical pregnancy rates, particularly in populations without recurrent implantation failure[22,23]. Similarly, the lack of a significant difference in the PRP group is consistent with other RCTs that reported no substantial improvement in clinical pregnancy rates with PRP administration[24,25]. Our findings suggest that, while both GCSF and PRP may have theoretical benefits in enhancing endometrial receptivity through immunomodulation and angiogenesis, these effects do not necessarily translate into higher clinical pregnancy rates.

The implantation rates, which were slightly higher in the PRP group (43.6%) compared to the GCSF group (42.1%) and the saline group (39.5%), did not reach statistical significance. These findings corroborate the hypothesis that the benefits of PRP in terms of endometrial vascularity might not be sufficient to improve implantation success significantly[26]. Previous studies have shown that, while PRP can improve endometrial thickness and vascularity, its impact on implantation rates remains inconclusive[27]. The current study adds to this body of evidence, suggesting that the improvements in endometrial characteristics observed with PRP administration do not necessarily lead to better implantation outcomes.

Endometrial vascularity and thickness

One of the key findings of this study is the significant improvement in endometrial vascularity observed in the PRP group compared to the saline group (p=0.003). This finding supports the notion that PRP may enhance endometrial receptivity by improving vascularization, a critical factor for successful embryo implantation[28]. However, the lack of a corresponding increase in clinical pregnancy rates indicates that improved vascularity alone may not be sufficient to overcome other barriers to implantation. This observation is consistent with earlier reports revealing that, while PRP can enhance endometrial characteristics, it does not always lead to improved reproductive outcomes[29].

The GCSF group did not show a significant improvement in endometrial vascularity compared to saline, which may explain the lack of difference in clinical pregnancy rates. Previous studies have suggested that GCSF may benefit certain subgroups of patients, particularly those with recurrent implantation failure or thin endometrium, by promoting endometrial regeneration and angiogenesis[30,31]. However, the results of our study, which included a broader population of women undergoing FET, suggest that GCSF may not have a universal effect on endometrial receptivity.

Live birth rates

The live birth rates in this study were comparable across the groups, with 72.5% for GCSF, 75.6% for PRP, and similar rates for saline. These findings are particularly important, as they underscore the notion that, while interventions like GCSF and PRP may improve certain intermediate markers of endometrial receptivity, such as vascularity, they do not necessarily translate into higher live birth rates. This is consistent with the concept that successful implantation and pregnancy outcome depend on a complex interplay of factors, and that improving one aspect of endometrial receptivity may not be sufficient to overcome other challenges[32,33].

Limitations and strengths

The strengths of this study include its large sample size, randomized controlled design, and the comprehensive evaluation of endometrial characteristics using transvaginal ultrasound, Doppler studies and histological assessments. However, several limitations should be considered. Firstly, while the study was adequately powered to detect differences in clinical pregnancy rates, it may not have been sufficiently powered to detect smaller but clinically relevant differences in live birth rates. Secondly, the study population was relatively heterogeneous, including women with varying causes of infertility and different FET protocols, which may have introduced variability in the results. Finally, while the study focused on short-term reproductive outcomes,

it did not assess long-term outcomes such as neonatal health, which could provide additional insights into the safety and efficacy of these interventions.

Implications for clinical practice

The findings of this study have significant implications for clinical practice. Given that neither GCSF nor PRP demonstrated a significant impact on clinical pregnancy rates or live birth rates, their routine use in FET cycles cannot be recommended based on the current evidence. While PRP showed some promise in improving endometrial vascularity, this did not translate into better reproductive outcomes, suggesting that clinicians should be cautious in using PRP as a routine intervention in ART. Similarly, the lack of benefit observed with GCSF suggests that its use should be limited to specific subgroups of patients where its efficacy has been more clearly demonstrated, such as those with recurrent implantation failure or thin endometrium[34].

Future research

Future research should focus on identifying the specific patient populations that may benefit from GCSF or PRP, as well as optimizing the timing, dosage and administration methods for these interventions. Additionally, further studies are needed to explore the molecular and cellular mechanisms underlying the effects of GCSF and PRP on endometrial receptivity, which could lead to the development of more targeted and effective therapies. Finally, long-term follow-up studies are essential to assess the impact of these interventions on neonatal outcomes and to ensure their safety and efficacy in assisted reproductive technologies.

Conclusions

This large-scale randomized controlled trial provides robust evidence that neither GCSF nor PRP significantly improves clinical pregnancy rates, implantation success, or live birth rates in women undergoing frozen embryo transfer. While platelet-rich plasma improves endometrial vascularity, this benefit does not translate into better reproductive outcomes, suggesting that its routine use in assisted reproductive technologies should be reconsidered. Further research is needed to identify the subgroups of patients who may benefit from these interventions and to explore alternative strategies for improving frozen embryo transfer outcomes. ■

References

1. Cavalcante MB, Cavalcante C, Sarno M, Barini R. Intrauterine perfusion immunotherapies in recurrent implantation failures: systematic review. Am J Reprod Immunol. 2020;83(6):e13242.
2. Demetri GD, Griffin JD. Granulocyte colony-stimulating factor and its receptor. Blood. 1991;78(11):2791–808.
3. Metcalf D. The granulocyte-macrophage colony-stimulating factors. Science. 1985;229(4708):16–22.
4. Nagata S, Tsuchiya M, Asano S, Kaziro Y, Yamazaki T, Yamamoto O, Hirata Y, Kubota N, Oheda M, Nomura H. Molecular cloning and expression of cDNA for human granulocyte colony-stimulating factor. Nature. 1986;319(6052):415–8.
5. Bonilla MA, Gillio AP, Ruggeiro M, Kernan NA, Brochstein JA, Abboud M, Fumagalli L, Vincent M, Gabrilove JL, Welte K. Effects of recombinant human granulocyte colony-stimulating factor on neutropenia in patients with congenital agranulocytosis. N Engl J Med. 1989;320(24):1574–80.
6. Tabbara IA, Ghazal CD, Ghazal HH. The role of granulocyte colony-stimulating factor in hematopoietic stem cell transplantation. Cancer Investig. 1997;15(4):353–7.
7. Lédée N, Gridelet V, Ravet S, et al. Impact of follicular G-CSF quantification on subsequent embryo transfer decisions: a proof of concept study. Hum Reprod. 2013;28(2):406–13.
8. Kamath MS, Kirubakaran R, Sunkara SK. Granulocyte-colony stimulating factor administration for subfertile women undergoing assisted reproduction. Cochrane Database Syst Rev. 2020;1(1):Cd013226.
9. Zhang L, Xu WH, Fu XH, Huang QX, Guo XY, Zhang L, Li SS, Zhu J, Shu J. Therapeutic role of granulocyte colony-stimulating factor (G-CSF) for infertile women under in vitro fertilization and embryo transfer (IVF-ET) treatment: a meta-analysis. Arch Gynecol Obstet. 2018;298(5):861–71.
10. Busnelli A, Somigliana E, Cirillo F, Baggiani A, Levi-Setti PE. Efficacy of therapies and interventions for repeated embryo implantation failure: a systematic review and meta-analysis. Sci Rep. 2021;11(1):1747.
11. Achilli C, Duran-Retamal M, Saab W, Serhal P, Seshadri S. The role of immunotherapy in in vitro fertilization and recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril. 2018;110(6):1089–100.
12. Li J, Mo S, Chen Y. The effect of G-CSF on infertile women undergoing IVF treatment: a meta-analysis. Syst Biol Reprod Med. 2017;63(4):239–47.
13. Xie Y, Zhang T, Tian Z, et al. Efficacy of intrauterine perfusion of granulocyte colony-stimulating factor (G-CSF) for infertile women with thin endometrium: a systematic review and meta-analysis. Am J Reprod Immunol. 2017;78(2):1–10.
14. Cavalcante MB, Costa Fda S, Barini R, Araujo Júnior E. Granulocyte colony-stimulating factor and reproductive medicine: a review. Iran J Reprod Med. 2015;13(4):195–202.
15. Robert CA, Abbas MK, Zaidi ARZ, Thiha S, Malik BH. Mediator in the embryo-endometrium cross-talk: granulocyte colony-stimulating factor in infertility. Cureus. 2019;11(8):e5390.
16. Eftekhar M, Naghshineh E, Khani P. Role of granulocyte colony-stimulating factor in human reproduction. J Res Med Sci. 2018;23:7.
17. Jiang Y, Zhao Q, Zhang Y, et al. Treatment of G-CSF in unexplained, repeated implantation failure: a systematic review and meta-analysis. J Gynecol Obstet Hum Reprod. 2020;49:101866.
18. Mouhayar Y, Sharara FI. G-CSF and stem cell therapy for the treatment of refractory thin lining in assisted reproductive technology. J Assist Reprod Genet. 2017;34(7):831–7.
19. Rocha MNC, Florêncio RS, Alves RRF. The role played by granulocyte colony stimulating factor (G-CSF) on women submitted to in vitro fertilization associated with thin endometrium: systematic review. JBRA Assist Reprod. 2020;24(3):278–82.
20. Shah J, Welsh SJ. The clinical use of granulocyte-colony stimulating factor. Br J Hosp Med (Lond). 2014;75(2):C29–C32.
21. Toth B, Würfel W, Germeyer A, Hirv K, Makrigiannakis A, Strowitzki T. Disorders of implantation – are there diagnostic and therapeutic options?. J Reprod Immunol. 2011;90(1):117–23.
22. Würfel W. Treatment with granulocyte colony-stimulating factor in patients with repetitive implantation failures and/or recurrent spontaneous abortions. J Reprod Immunol. 2015;108:123–35.
23. Zhao J, Xu B, Xie S, Zhang Q, Li YP. Whether G-CSF administration has beneficial effect on the outcome after assisted reproductive technology? A systematic review and meta-analysis. Reprod Biol Endocrinol. 2016;14(1):62.
24. Lebovitz O, Orvieto R. Treating patients with "thin" endometrium – an ongoing challenge. Gynecol Endocrinol. 2014;30(6):409–14.
25. Mekinian A, Cohen J, Alijotas-Reig J, Carbillon L, Nicaise-Roland P, Kayem G, Daraï E, Fain O, Bornes M. Unexplained recurrent miscarriage and recurrent implantation failure: is there a place for immunomodulation?. Am J Reprod Immunol. 2016;76(1):8–28.
26. Turocy J, Williams Z. Novel therapeutic options for treatment of recurrent implantation failure. Fertil Steril. 2021;116(6):1449–54.
27. Hou Z, Jiang F, Yang J, Liu Y, Zha H, Yang X, Bie J, Meng Y. What is the impact of granulocyte colony-stimulating factor (G-CSF) in subcutaneous injection or intrauterine infusion and during both the fresh and frozen embryo transfer cycles on recurrent implantation failure: a systematic review and meta-analysis?. Reprod Biol Endocrinol. 2021;19(1):125.
28. Kamath MS, Chittawar PB, Kirubakaran R, Mascarenhas M. Use of granulocyte-colony stimulating factor in assisted reproductive technology: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2017;214:16–24.
29. Zeyneloglu HB, Onalan G. Remedies for recurrent implantation failure. Semin Reprod Med. 2014;32(4):297–305.
30. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160.
31. Barad DH, Yu Y, Kushnir VA, Shohat-Tal A, Lazzaroni E, Lee HJ, Gleicher N. 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. Fertil Steril. 2014;101(3):710–5.
32. Eftekhar M, Hosseinisadat R, Baradaran R, Naghshineh E. Effect of granulocyte colony stimulating factor (G-CSF) on IVF outcomes in infertile women: an RCT. Int J Reprod Biomed. 2016;14(5):341–6.
33. Jain S, Mahey R, Malhotra N, Kalaivani M, Sangeeta P, Bhatt A, Singh N, Kriplani A. Effect of intrauterine perfusion of granulocyte colony-stimulating factor on endometrial parameters and in vitro fertilization outcome in women undergoing in vitro fertilization/intracytoplasmic sperm injection cycles: a randomized controlled trial. J Hum Reprod Sci. 2018;11(3):254–60.
34. Sarvi F, Arabahmadi M, Alleyassin A, Aghahosseini M, Ghasemi M. Effect of increased endometrial thickness and implantation rate by granulocyte colony-stimulating factor on unresponsive thin endometrium in fresh in vitro fertilization cycles: a randomized clinical trial. Obstet Gynecol Int. 2017;2017:3596079.

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