Efficacy of Granulocyte Colony Stimulating Factor (G-CSF) for Improving Endometrial Thickness in IVF/ICSI Patients with thin Endometrium: A Meta-Analysis and Systematic Review

Original Article

Amr Sobhy Sweed[1], Ahmed Sherif Abdel hamid[1], Maram Salaeldeen Mahmoud[2], Hanan Shehata[1], Suzy Abdel Aziz[3] and Mohamed I. Taema[1]

Department of Obstetrics and Gynecology, Faculty of Medicine, [1]Ain Shams University, [2]Fayoum University, [3]Cairo University, Egypt

ABSTRACT

Background: To investigate how women seeking assisted reproduction respond to granulocyte colony-stimulating factor (G-CSF) on their poor endometrium.

Materials and Methods: Along with to a manual search, we conducted a systematic search from its founding to May 2024 in a number of databases, as PubMed, Cochrane Library, Embase, WOS, and Scopus. We located all the journals that discussed G-CSF's impact on endometrial thinness. Two research assistants worked separately on the selection of investigations, data collection, and risk of bias assessment under specific exclusion and inclusion requirements. For the purpose of conducting the meta-analysis of eligible investigations, we used the Revman 5.3 program.

Results: Eight research investigations totaling 673 candidates were enrolled in this meta-analysis, comprising two non-randomized controlled investigations and six randomized controlled trials. The results of the meta-analysis disclosed that G-CSF significantly increased the clinical pregnancy rate (RR = 1.73, 95% CI (1.22, 2.45), p = 0.002) and the embryo implantation rate (RR = 1.91, 95% CI (1.26, 2.91), in contrast to the placebo group. The endometrial thickness in the G-CSF arm had an insignificant rise in comparison to that of the placebo arm (mean difference (MD) = 0.81, 95% CI (–0.04, 1.67), p = 0.06.

Conclusions: G-CSF has the ability to thicken the endometrium in women with poor endometria and boost implantation and clinical pregnancy rates in IVF/ICSI cycles. Given their small number and quality, the findings of the studies that were incorporated should be interpreted cautiously, and more research of a better caliber is required to support these conclusions.

Key Words: Granulocyte Colony Stimulating Factor, IVF/ICSI, thin endometrium.

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Corresponding Author: Amr Sobhy Sweed, Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Egypt, **Tel.:** +96654805146, **E-mail:** sobhyamr@yahoo.com

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INTRODUCTION

Throughout the last few years, assisted reproductive technology, or ART, has been utilized extensively to treat sterility[1,2]. Both endometrial response and high-quality embryos are essential for a healthy pregnancy; nevertheless, endometrial receptivity may be a major restricting determinant of ART pregnancy rates. Endometrial thickness is a significant indicator of endometrial responsiveness; after embryo transfer, an underdeveloped endometrium is strongly linked to a negative pregnancy outcome[3,4,5].

1–2% of women receiving reproductive treatment had very thin endometrium, which is commonly described in ART as thickness of the endometrium less than 7 mm[5,6,7]. One of the most important challenges for individuals receiving ART is caring for patients with thin endometriums. In clinical terms, a variety of methods, such as aspirin, sildenafil, estrogen, antioxidant, vitamin E, pentoxifylline and others, are thought to be beneficial in treating patients with weak endometrium. Depending on the kind of embryo transfer (ET) that is being scheduled, these therapies are chosen. However, it is necessary to frequently cancel embryo transfer cycles because some women' endometrium remains insensitive even after utilizing these treatments, and even successfully implanted embryos may not attach[8].

Previous research has demonstrated the critical role that G-CSF plays in development of the endometrium and conception. By controlling decidual macrophages and the Th2 response, G-CSF may perform an essential variable in embryo implantation[9,10], promote the instructed distinction of stem cells at the area of injury and thicken the endometrium in animal models[11], and enhance the growth of endometrial epithelial cells. G-CSF may

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therefore be a useful treatment for thin endometrium. The implementation of G-CSF for the therapy of cases with delicate endometrium has been the subject to numerous clinical investigations[12,13,14,15,16].

On the other hand, conflicting findings about the impact of uterine G-CSF on the occurrence of conception have been documented in clinical investigations. Pregnancy rates have improved, according to some research[12,13,14], but not in others[15,16].

In order to gather important information on the manner to set up the endometrium for transfer of embryos for people with a weak endometrial, we did a meta-analysis in the present research to examine the influence of G-GSF on poor endometrium throughout ART.

MATERIALS AND METHODS

Search Strategy

In addition to a manual search, we checked PubMed, the Cochrane Library, Embase, Scopus, and WOS to May 2024. Here was the search approach: (("Reproductive Techniques, Assisted") OR (IVF) OR (ICSI) OR OR (FET) OR (ET) OR (Embryo Transfer) AND ((thin endometrium) OR (endometrial thickness)) AND (Granulocyte Colony-Stimulating Factor) OR (Granulocyte Colony Stimulating Factor) OR (GCSF) OR (neupogen) OR (filgrastim).

Study Selection

Inclusion Criteria

1. The investigation was conducted as either a non-RCT or a randomized controlled trial (RCT).
2. Patients receiving ART whose ET was less than 7 mm.
3. Uterine injection or SC injection of G-CSF were the intervention measures used in the treatment group, whereas normal saline or a blank control were used in the control group.
4. The study's findings comprised the ET on the day of embryo transfer, the clinical pregnancy rate, and the embryo implantation rate.

Exclusion Criteria

1. The research investigation was conducted in one of the following styles: observational, descriptive, retrospective, case report, or review.
2. Animals served as the research's participants.
3. There was an inconsistency in the intervention group's and the reference group's baseline.
4. Trials included a poor design or inadequate statistical methodologies and could not be remedied.
5. Repetitive research.

Data Extraction

Separately, two authors chose the publications and retrieved the data. Initially, the editors reviewed the abstract and headline of each appropriate study before evaluating it. After that, they went over the entire investigation to determine if it satisfied the requirements for inclusion. Both investigators subsequently assessed their findings; in the event that they weren't in agreement, an additional reviewer who was an authority in the subject would be consulted. Lastly, using a previously created information gathering table, the reviewers collected data from each chosen study. Anytime there was an insufficient dataset, the relevant researcher was approached to gather more information. The authors of the review gathered a variety of information: The research design; the number of therapy and control groups; the country; the participant's age; the duration, approach, and amount of uterine G-CSF infusion; (5) details concerning intervention techniques; (6) endometrial thickness; (5) fundamental information, such as the name of the first author and the publishing date; (5) basic data, including the study's essential data; (6) variables used to evaluate the probability of bias; (7) vital patient information.

Bias Risk Assessment

The Cochrane risk-of-bias tool[17] was used to evaluate the likelihood of bias for the RCTs that were part of this meta-analysis. In addition, we used the Methodology Assessment for Non-Randomized Studies (MINORS) to assess the bias risk associated with non-RCTs[18].

Statistical Analysis

Review Manager 5.3 (Cochrane Collaboration, Copenhagen, Denmark) was used to conduct the meta-analysis[19]. Relative risk (RR) was utilized to display categorical variables, and mean differences (MD) were employed to depict continuous variables. For every outcome scale, we computed 95% confidence intervals (CIs) and point estimates. Based on the I22 statistic, random and fixed effects models were used for the meta-analysis. Since this meta-analysis only contained eight papers, funnel plots were not produced.

RESULTS

Study Selection

Eight studies: six RCTs[12,13,14,20,21,22] and two non-

RCTs[15,16] were ultimately chosen for the meta-analysis after rigorous selection and evaluation of the inclusion and exclusion rules. In all, 673 individuals were involved in this study. The number of chosen studies is displayed in (Figure 1).

Fundamental Features and Bias Analysis Risk

(Table 1) lists the features of the research included in the analysis, such as the number of individuals, country, mean age, initial ET, strategies, and outcome measures for every research. Six nations were included in these studies: Portugal, Spain, Poland, India, Iran, and China. Eight qualifying studies in all have been incorporated in this meta-analysis. Four studies examined endometrial thickness, seven eligible research described the clinical pregnancy rate, and five studies reported the embryo implantation rate (Figure 2).

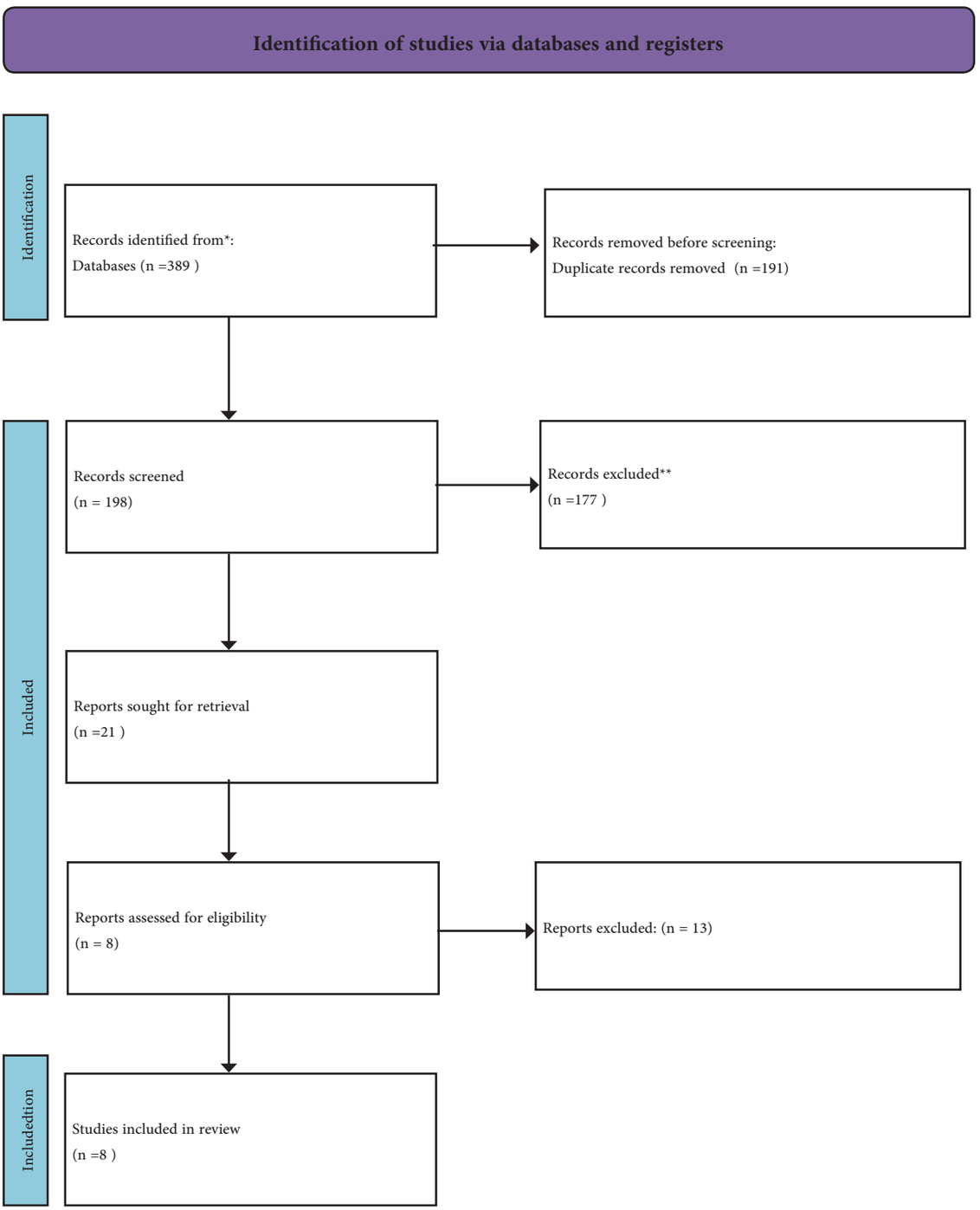

Fig. 1: Flow chart showing study selection

Table 1: Base-line data of enrolled studies

Study	Patients No.	Mean age	Baseline EM	EM after	Interventions	Outcome measures
Singh R 2015[12]	28	<40	6.49 ± 1.65	8.79 ± 1.57	Inutero 300 µg/1 mL G-CSF on the day of trigger vs. intrauterine perfusion of placebo (1 mL saline solution)	Implantation Rate, Clinical Pregnancy Rate
Sarvi F 2017[13]	48	31.4±3.3	4.1 ± 1.8	9.1 ± 1.5	In utero 300 µg/1 mL G-CSF on the day of trigger; if ET < 6 mm, a 2nd injection infused 2–3 days after oocyte retrieval vs. placebo	End.thickness, Implantation Rate, Clinical Pregnancy Rate
Singh R 2018[14]	112	-------	6.23 ± 1.45	8.46 ± 1.27	In utero or SC G-CSF 300 µg/1 mL on the day of Trigger; a 2nd G-CSF after oocyte retrieval in some patients vs. placebo	Implantation Rate, Clinical Pregnancy Rate
Eftekhar M 2014[15]	68	30.8±4.7	5.63 ± 0.78	7.91 ± 0.55	In utero 300 µg/1 mL G-CSF at the 12th–13th day of FET, a 2nd dose of G-CSF given 2–3 day after 1st one vs. controls	End. thickness, Clinical Preg. Rate
Kunicki M 2017[16]	62	33.7±4.6	6.50 (5.50–6.80)	7.90 (6.58–8.70)	In utero 300 µg/1 mL G-CSF at 9th day of FET cycle vs. control	Implantation Rate, Clinical Pregnancy Rate
Xu B 2015[20]	66	31.9±4.1	5.7 ± 0.7	8.5 ± 2.4	In utero G-CSF (100 µg/0.6 mL) on the day a follicle is dominant (12 mm) vs. control	Implantation Rate, Clinical Pregnancy Rate
Jindal PC 2021[21]	60	-------	5.9 ± 0.7	7.9 ± 0.5	In utero 300 µg/1 mL G-CSF on day 14 of FET cycle, a 2nd G-CSF after 48 hours if endometrium was < 7 mm vs. injection of G-CSF (300 mcg/1 mL) SC on 14th day onwards every other day for 2 times.	End. thickness
Zhang Y 2022[22]	229	31.7±4.2	5.50 ± 1.96	7.91 ± 2.12	Uterine effusion of 300 mg G-CSF vs. placebo	End. thickness

Figures provide an evaluation of the bias risk for the listed RCTs. In order to prevent selection bias, two RCTs[13,20,22] used a random sequence generation technique; one of these RCTs[13] also discussed the use of a "sealed envelope" to assure allocation concealment. The blinding of subjects and staff was covered in 4 RCTs[12,13,14,22], while the blinding of outcome evaluations was covered in 5 RCTs[12,13,14,21,22]. Yet the outcome dataset for 2 RCTs[12,14] was not full. Six randomized controlled trials[12,13,14,20,21,22] did not report on biased reporting or other types of bias. Every RCT was regarded as having a medium level of risk.

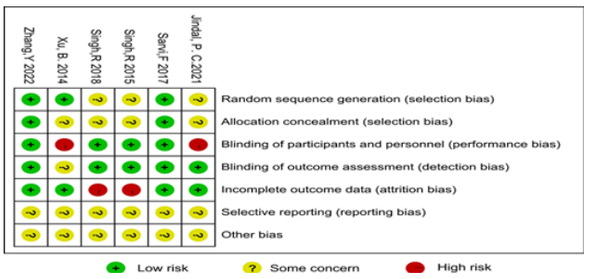

Fig. 2: Assessment of risk of bias for the included RCTs.

Meta-Analysis Results

Embryo Implantation Rate

The embryo implantation rate has been stated in a total of five investigations[12,13,14,16,20]. When the statistical findings were homogeneous (p = 0.87, I22 = 0%), a fixed-effects model was utilized. When comparing the G-CSF group to the control group, a meta-analysis showed a significantly greater embryo implantation rate [RR = 1.91, 95% CI (1.26, 2.91), p = 0.002] (Figure 3). Due to the sufficient homogeneity among the four contained RCTs (p = 0.95, I22 = 0%), a fixed-effect model was employed for the a subsection analyses[12,13,14,20]. Sub-group analysis revealed that the clinical pregnancy rate of the G-CSF group was considerably higher [RR = 2.08, 95% CI (1.33, 3.26), p = 0.001] in comparison to the placebo group (Figure 4).

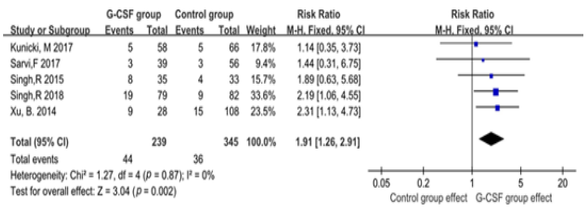

Fig. 3: Embryo implantation rate contrast between the G-CSF and placebo groups.

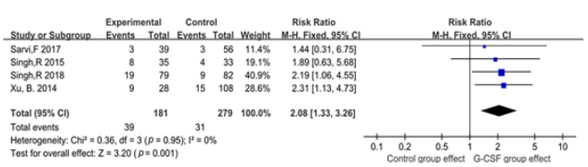

Fig. 4: Comparison of embryo implantation rate between G-CSF group and control group in RCTs.

Clinical Pregnancy Rate

While taking into account the clinical pregnancy rate, all seven of the qualifying trials were included[12,13,14,15,16,20,21]. Because there was sufficient homogeneity across studies (p = 0.81, I22 = 0%), we employed a fixed-effect model.

In comparison to the placebo group, the clinical pregnancy rate in the G-CSF group was considerably higher [RR = 1.73, 95% CI (1.22, 2.45), p = 0.002] (Figure 5). A subsection evaluation was carried out for the five included RCTs[12,13,14,20,21]. A fixed-effect model (p = 0.80, I22 = 0%) was used because there was enough homogeneity among these RCTs. In the analysis of subgroups, the clinical pregnancy rate in the G-CSF group was likewise significantly greater than in the placebo group [RR = 1.69, 95% CI (1.15, 2.49), p = 0.008]. (Figure 6)

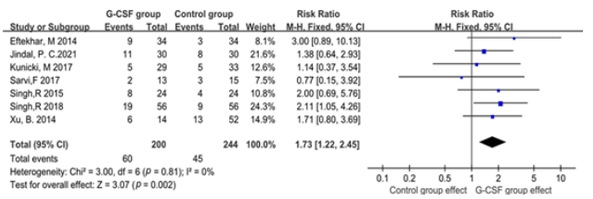

Fig. 5: Comparison of clinical pregnancy rate between G-CSF group and control group.

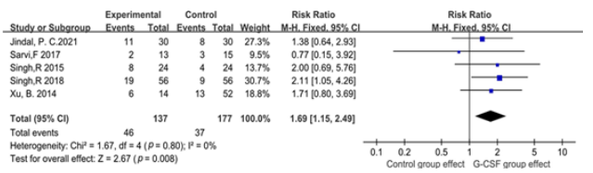

Fig. 6: Comparing the clinical pregnancy rate in RCTs between the G-CSF group and the placebo group is shown in Fig. 6.

Endometrial Thickness

Taking endometrial thickness into account, four research were considered[13,15,21,22]. Because of the statistical heterogeneity between these trials (p << 0.00001, I22 = 94%), a random-effect model was chosen. Comparing G-CSF treated women to the control group, there was an insignificant rise in endometrial thickness [MD = 0.81, 95% CI (–0.04, 1.67), p = 0.06] (Figure 7). Two of the included RCTs underwent subgroup analysis[13,21,22], and due to statistical heterogeneity among these RCTs (p = 0.03, I22 = 71%), a random-effect model was employed. As contrasted with the placebo group, the G-CSF group's endometrial thickness was substantially larger in the subgroup evaluation [MD = 1.13, 95% CI (0.56, 1.67), p<< 0.0001]. (Figure 8).

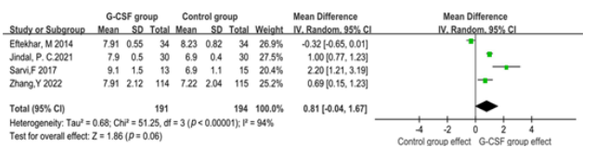

Fig. 7: Endometrial thickness contrast between the G-CSF and untreated groups.

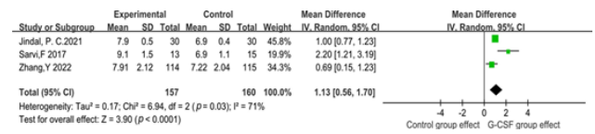

Fig. 8: Endometrial thickness in RCTs was compared with the G-CSF group and the untreated group.

DISCUSSION

A responsive endometrium is necessary for effective assisted reproduction; yet, research has revealed that women with thinner endometrium have substantially lower implantation rates[23]. The outcome of reproduction is adversely affected by an underdeveloped endometrium. Women with weak endometrium have been treated with a variety of techniques. Despite the wide range of available treatments, the majority of them only marginally alter endometrial thickness and the course of pregnancy. As a result, when weighing ART, treating women with delicate endometrium is extremely difficult[24].

According to earlier research, women with weak endometria may see a rise in the rate of embryo implantation and clinical pregnancy while using G-CSF. As a cytokine, G-CSF has the ability to impact decidual macrophages and bone marrow mesenchymal stem cells, which in turn affects endometrial development and expansion[25]. A prior work that used a rat model of thin endometrium demonstrated that endometrial receptivity might be enhanced by intrauterine infusion of G-CSF through the regulation of endometrial overgrowth and angiogenesis[26].

According to Zhao *et al*.[27], G-CSF can attract stem cells to the region of injury and heal tissue in animal models. In contrast to control groups, G-CSF caused the endometrium to visibly thicken and upregulate the production of vimentin and cytokeratin. As a chemical and mechanical stimulation, intrauterine perfusion of G-CSF is thought to cause the release of endogenous cytokines and trigger endocrine-paracrine pathways, resulting in an effective implantation of the embryo and subsequent pregnancy[15].

Moreover, G-CSF may aid in embryo implantation by fostering angiogenesis-related gene expression, cell migration, tissue remodeling, and embryonic adhesion[28,29]. It has been demonstrated that G-CSF plays a part in both the upkeep of pregnancy[31] and the maturation and growth of the embryo[30].

The application of G-CSF for the therapy of women with weak endometrium has been the subject of numerous clinical trials. The first reports of four infertile women with thin endometria who subsequently got pregnant by ART after intrauterine G-CSF perfusion were made in 2011 by Gleicher *et al*.[30]. The same study team then enlisted a second group of patients who had undergone intrauterine

G-CSF perfusion after failing conventional treatment and still had a persistently thin endometrium. Upon the intrauterine injection of G-CSF, these patients' clinical pregnancy rate was deemed to be modest but manageable by investigators[32].

Since then, a number of research initiatives have looked into the treatment of women with thin endometria with G-CSF. These investigations' findings, meanwhile, were not always constant. For instance, Mishra *et al*.[33] revealed that while G-CSF did not raise the pregnancy rate in individuals with a refractory poor endometrium, it did cause a modest rise in ET in these patients. Only approximately one-third of cases with a refractory poor endometrium showed a boost in ET with G-CSF, according to a different study by Swati *et al*[34]. According to Kim *et al*.[35], G-CSF enhanced the likelihood of pregnancy and embryo implantation by thickening a thin endometrium without creating intrauterine adhesions. Because of this discrepancy, it became clear that a meta-analysis of the literature was required to ascertain whether G-CSF has any effect on ET and conception.

In this meta-analysis, we looked into a total of 8 papers, comprising 6 RCTs and 2 non-RCTs with 673 participants. Comparing the results with controls, we concluded that G-CSF via injection under the skin or uterine administration greatly enhanced the frequencies of clinical pregnancy and embryo implantation. Whether or not we were taking into account RCTs, the impact of G-CSF on the rate of clinical pregnancy and the rate of embryo implantation remained constant both before and after subgroup evaluation. Endometrial thickness was not significantly affected by the use of G-CSF. Endometrial thickness was examined in three studies: one non-RCT and two RCTs. Sub-group examination of two RCT studies' data led us to conclude that G-CSF did, in fact, thicken the endometrium.

Given the boosted risk of miscarriage associated with weak endometrium, patients should exercise caution when undergoing embryo transfer; it may be best to wait until the endometrial cycle thickens before proceeding with the transplant[36]. Consequently, by thickening the endometrium, G-CSF may enhance the success of the pregnancy. To properly validate our findings, further RCTs are significantly needed, as just two RCTs were included in this research.

In 2017, Kamath *et al*.[37] conducted a systematic review and meta-analysis on the utilization of G-CSF in ART; yet, this study contained only 1 non-RCT and 3 RCTs with inadequate data. Eight studies, six RCTs and two non-RCTs, were incorporated in the current meta-analysis; the quality of the proof for each investigation in our analysis was higher than that of the prior one, and there has been an upward trend in pertinent studies[37].

However, when G-CSF was administered to women with weak endometrium, there was an insignificant rise in endometrial thickness [MD = 0.47, 95% CI (1.36, 2.31), I22 = 82%]. These prior researchers stated a significantly higher clinical pregnancy rate following the application of G-CSF when contrasted to controls [RR = 2.43, 95% CI (1.09, 5.40), I22 = 0%][37]. These results align with those of another meta-analysis carried out by Zhao *et al*.[38]as well as our current findings. Analytical efficiency may have been impacted by the Zhao *et al*. study's[38] analysis of aggregated information from research with prospective and retrospective designs.

It is important to take into account the various restrictions that apply to our present investigation. Initially bias may have resulted from the small number of samples of our analysis, only five RCTs and two non-RCTs were included.

Given the small number of investigations, subgroup evaluations of the clinical pregnancy rate and embryo implantation rate, when categorized by RCTs against non-RCTs, yielded results that were in line with the overall aggregated analyses. Further research is now required to elucidate the genuine benefits of G-CSF therapy, as disparate findings on the influence of G-CSF on ET were found. Secondly, there was a tendency for the studies that were included to differ in terms of the root causes of thinner endometrium, the dosage, and the modes of giving of G-CSF. With the data at hand, an irrefutable conclusion could not be drawn because the available trials did not customize approaches to treatment based on distinct underlying reasons of fragile endometrium. Consequently, additional high-quality, well-designed RCTs with sizable sample sizes are required to corroborate our results. The present research is merely at the investigation phase, and there is no consistent guideline for dosage, timing, method, or times of treatment.

CONCLUSIONS

Our meta-analysis results suggest that while G-CSF may have a tendency to boost endometrial thickness, the rate of embryo implantation and clinical pregnancy among women who have fragile endometrium through ART. However, given the small number and poor quality of the studies comprised in this meta-analysis, variations in the causes of thin endometrium, and variations in the amount and method of G-CSF management, our conclusions should be interpreted with caution. It is now necessary to conduct extensive, high-quality, multi-center RCTs in order to completely clarify the advantages of G-CSF on weak endometrium.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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