SYSTEMATIC REVIEW AND META-ANALYSIS

Platelet-rich plasma (PRP) *vs* granulocyte colony-stimulating factor (G-CSF) in women with thin endometrium undergoing assisted reproduction: a systematic review and meta-analysis

Short title: *PRP vs G-CSF in women with thin endometrium undergoing assisted reproduction*

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ABSTRACT

Objective. The aim of this study is to evaluate the effect of intrauterine infusion of platelet-rich plasma (PRP) vs. granulocyte colony-stimulating factor (G-CSF) on endometrial thickness, clinical pregnancy rate, and live-birth rate.

Materials and methods. Systematic searches were conducted on PubMed, Scopus, Cochrane Library, ClinicalTrials.gov and Google Scholar. The following keywords were used: "PRP" AND "G-CSF" AND "endometrium. Meta-analysis was performed using RevMan software.

Results. A total of eight studies were therefore included in the final analysis, yielding a total of 479 patients. The primary analysis that focused on endometrial thickness was done as a meta-analysis of two studies that report endometrial thickness in their trials. (RR = 1.08, 95%CI 0.80 to 1.45, p = 0.63). The secondary analysis was conducted to compare biochemical pregnancy rate (RR = 1,31, 95%CI 1.06 to 1.62, p = 0.01). In the third analysis, we compared the rates of achieving clinical pregnancy in patients treated with PRP with those treated with G-CSF. (RR = 1.30, 95 CI 1.00 to 1.70, p = 0.05) The heterogeneity for this comparison was 34%, which reflects the possible benefit of the PRP technique in relation to reproductive outcomes in patients with repeated implantation failures.

Conclusions. Based on our meta-analysis, PRP therapy significantly affects pregnancy rates in patients with thin endometrium compared to G-CSF. However, there was no statistically significant difference in endometrial thickening.

Key words

PRP; G-CSF; thin endometrium; ART.

INTRODUCTION

Since the development of assisted reproductive technologies (ART), clinicians and researchers have sought to improve outcomes with the major aim of increasing fertility rates. The receptivity of the endometrium is crucial for achieving pregnancy. However, the definition of optimal endometrium that will be ready for embryo transfer is still under active discussion [1]. Several methods for evaluating the endometrium have been investigated [2], but ultrasound assessment of endometrium thickness is the most essential. It is widely used as a routine method for assessing the effectiveness of ART and the likelihood of pregnancy. Furthermore, thin endometrium not only indicates a lower probability of achieving pregnancy but is also related to adverse perinatal outcomes, pregnancy loss, or diminished placentation.

Adequate endometrial thickness is a main factor for implantation and pregnancy. Thin endometrium in assisted reproduction is often defined as endometrial thickness <7 mm or <8 mm. The incidence of thin endometrium in ovarian stimulation cycles can be as high as 38–66%; the incidence of thin endometrium in IVF is between 1% and 2.5% in most studies.[3] Women with persistent thin endometrium often do not undergo embryo transfer. Several methods have been described for endometrial preparation but there is not any definitive method yet. In recent years, intrauterine infusion of G-CSF (granulocyte-colony colony stimulating factor) has been studied but inconsistent results have been reported. Some researchers reported that G-CSF favors endometrial growth and pregnancy. G-CSF is a cytokine that stimulates neutrophilic granulocyte differentiation and proliferation, it may induce endometrium proliferation and growth, thus improve pregnancy outcome. According to this hypothesis, local infusion of PRP (platelet-rich plasma) that contains several growth factors and cytokines may improve endometrial growth and receptivity. PRP is collected from autologous blood sample, so in comparison to G-CSF, PRP is more accessible and affordable [4,5]. Rahul Manchanda et al. in their review of various articles made conclusion that autologous platelet rich plasma instillation is not associated with any side effects as it is derived from patients own blood. Also, it is cost effective, less invasive, easily available as well as feasible for the specialist. [6]

According to the European Society of Human Reproduction and Embryology (EHRE) consortium, recurrent implantation failure (RIF) is defined as the absence of gestational sac on ultrasound at 5 weeks or more after frozen embryo transfer (FET) following 3 FET with high-quality embryos or after the transfer of 10 or more embryos in multiple transfers.4,5 Recurrent implantation failure is a major challenge in reproductive medicine and despite several advances; still, no universal consensus exists. Many strategies such as estrogen, low-dose aspirin, heparin, vaginal sildenafil, pentoxifylline, and granulocyte-colony stimulating factor (G-CSF) intrauterine perfusion have been extensively used to increase the ET if not optimal.6,7 However, these methods were not found to be very impressive in all cases especially with a thin refractory endometrium. Platelet-rich plasma (PRP) may be effective in promoting endometrial growth, increasing ET and improving endometrial vascularity, and improving pregnancy outcomes in repeated implantation failure due to thin endometrium [7].

This systematic review and meta-analysis aims to compare the effect of intrauterine infusion of PRP and G-CSF on endometrial thickness, clinical pregnancy rate, and live-birth rate.

MATERIALS AND METHODS

The present systematic review included all published research articles that compared the effect of intrauterine infusion of platelet-rich plasma (PRP) and granulocyte-colony stimulating factor (G-CSF) on endometrial thickness, biochemical pregnancy rate, clinical pregnancy rate, and live birth rate.

Study registration, ethical and methodological standards

Our systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 checklist [8].

The studies included were randomized clinical trials (RCTs) and nonrandomized clinical trials (prospective controlled, prospective cohort, retrospective studies, and other types of studies) that included a minimum of 10 patients. Only articles written in English were included. Institutional Review Board (IRB) approval was not requested as the present study is a review of published studies. The present systematic review has been registered in the PROSPERO international prospective register of systematic reviews by the National Institute for Health Research (NIHR). The registration number is PROSPERO 2020 CRD42020222075 [9].

An electronic database search was conducted using PubMed, Scopus, the Cochrane Library, Google Scholar and ClinicalTrials.gov to identify articles published until February 2023. The search used a combination of the following of the following terms: «PRP», «G-CSF», «endometrium».

The search strategy in the electronic database PubMed, Scopus, the Cochrane Library, Google Scholar and ClinicalTrials.gov was the following: «PRP» AND «G-CSF» AND «endometrium». In addition, MeSH terms were used in the Cochrane Library. MeSH descriptor: [Endometrium], [Granulocyte Colony-Stimulating Factor], [Platelet-Rich Plasma]. The date of the last screening was July 12, 2023.To verify all possibly relevant studies, no restrictions or search filters (publication status, type of article, or language of publication) were applied to the search.

The search was conducted independently by two investigators (L.P, J.A.). Following the search, all articles were rechecked based on their titles and abstracts. The full texts of the studies that appeared to be appropriate according to their titles and abstracts were then reviewed. The reference lists of eligible trials were searched for additional potential studies.

Two investigators (L.P, J.A.) independently read the full texts of the preselected articles to verify the eligibility of the articles based on their titles and abstracts. After this step, studies were excluded if there were duplicate datasets.

Any disagreements regarding the inclusion or exclusion of preselected studies and any other disagreements during the review process were resolved with the help of the third author (S.I.). The included studies were independently collected by two authors (L.P, J.A) using a standardized data extraction procedure (authors, publication year, study design, patient characteristics, intervention, and outcomes).

Statistical analysis

The primary analysis was aimed to achieve endometrial thickness > 7–8 mm. The outcome output was expressed as an ultrasound evaluation conclusion.

The secondary analysis measures assessed biochemical pregnancy rate (the positive beta-hCG), clinical pregnancy rates (the presence of an intrauterine fetal heartbeat) and live birth rate (an ability to conceive a live-born neonate).

Patient and public involvement

Inclusion and exclusion criteria of patients are presented in the Table 1. [Table 1]

A risk-of-bias assessment was conducted for each of the studies included using the Cochrane Handbook for Systematic Reviews of Interventions [10]. Two investigators (L.P. and J.A.) independently assessed the quality of the selected studies. A third investigator (S.I.) as involved when disagreements occurred. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, the RoB 2 tool [11] was used for nonrandomized studies (prospective controlled, prospective cohort, retrospective studies, and other types of studies). As for the quantitative synthesis, the meta-analysis was performed using RevMan 5.4. (recommended by the Cochrane Society)

RESULTS

3655 articles were found after the search was conducted, 55 of which were duplicates and therefore were excluded. After that, 3600 articles were analyzed, 3568 of which were excluded by the titles and abstracts. Consequently, 32 publications were left for the full-text screening. All these articles were analyzed following our inclusion and exclusion criteria specified in the protocol registered on PRISMA. Out of these 32 articles, only eight were included in our qualitative analyses. Additionally, 150 articles were found in references of the eight articles included in the qualitative analyses. Seven of them met the eligibility criteria. However, none of these studies was included in the systematic review.

A total of seven studies were therefore included in the final analysis, yielding a total of 479 patients [12-18] [Table 2]. 2 publications [16,18] are randomized studies; 6 publications [12-15,17] are non-randomized studies. Also we included the forms of administration of PRP and G-CSF in the Table 3. [Table 3]. The whole search strategy with the results is presented in flow-diagram [Figure 1].

In a prospective cohort study by Dzhincharadze et al. all patients received hormone replacement therapy (HRT). Patients in PRP group in addition to HRT were given an intrauterine injection of autologous PRP on the 8–9th, 10–11th, and 12–13th days of the menstrual cycle; patients in G-CSF group in addition to HRT were given an intrauterine injection of recombinant G-CSF on the 5-6th and 12-13th days of the menstrual cycle. The primary outcome was an increase in endometrial thickness greater than 7 mm on the day of embryo transfer, the secondary outcome was pregnancy rates. They did not find statistically significant differences in either an increase in endometrial thickness or in the pregnancy rates between the two groups [12]. In the other study by Vora et al. it was proven that injection G-CSF, is more effective for the treatment of thin endometrium patients as compared to intrauterine PRP infusion. Though the clinical and chemical pregnancy rates were comparable, a higher percentage of women were clinically pregnant in the group given injection G-CSF. Intrauterine PRP can also be a good alternative for thin endometrium [13].

Cassim, et al. found that both G-CSF and PRP are effective interventions in the management of the thin refractory endometrium. Both result in significant endometrial expansion and increased pregnancy rates. Despite a marginally higher endometrial response and pregnancy rate in the PRP group, the differences in these metrics between the two groups were not statistically significant [14]. The results of the study by Mehrafza, et al. indicated that intrauterine infusion of PRP can positively affect pregnancy outcome in RIF patients in comparison with systemic administration of G-CSF [15]. In study by Selvaraj, et al., the use of PRP and G-CSF in individuals who had failed previous embryo transfer cycles using only hormone replacement therapy did exhibit improved outcomes. Although statistically the results were not significant, the use of either modality of treatment tends to increase the pregnancy rates in patients with thin endometrium and RIF [16]. Deo, et al. concluded that although both PRP and G-CSF are equally effective in increasing endometrial thickness but endometrial vascularity is better inproved with platelet rich plasma, clinical pregnancy rates were also better with PRP [17]. Nayar, et al. considered that autologous PRP and G-CSF hold promise in the treatment of women with sub optimal ET for embryo transfer. It would help to reduce the incidence of cycle cancellations and thus help reduce the financial and psychological burden of repeated cancelled cycles [18].

According to the Cochrane Handbook, two reviewers (L.P, J.A.) assessed the risk of bias of each of the studies included using RoB 2 for randomized control trials and ROBINS-I for nonrandomized trials. Any disagreements were resolved by a third reviewer (S.I.)

Visualization tools were created by the ROBVIS app [19]. This app created “traffic light” plots of the domain- level judgements for each result and weighted bar plots of the distribution of risk-of-bias judgments within each bias domain.

According to the ROBINS-I tool, the overall risk of bias for nonrandomized trials was 100% moderate [Figure 2]. Based on the RoB 2 tool [Figure 3], randomized trials had possibilities of 100% of low risk of bias regarding the overall risk of bias.

The primary analysis that focused on endometrial thickness was done as a meta-analysis of two studies that report endometrial thickness in their trials. They compared improvement of thin endometrium between two groups: PRP and G-CSF (RR = 1,08, 95% CI: 0,80 to 1,45, P = 0,63). The heterogeneity for this comparison was 0%. Consequently, both options equally increased the thickness of the endometrium [11,17] [Figure 4].

The secondary analysis was conducted to compare biochemical pregnancy rate. Seven studies were included in the meta-analysis (RR = 1,31, 95% CI 1,06 to 1.62, P = 0,01). The heterogeneity for this comparison was 0%. There was no statistically significant difference between the patients of the two groups [11-17] [Figure 5].

In the third analysis, we compared the rates of achieving clinical pregnancy in patients treated with PRP with those treated with G-CSF. Six out of eight studies were included in the meta- analysis: RR = 1,30, 95% CI 1,00 to 1.70, P = 0,05. The heterogeneity for this comparison was 34%, which reflects the possible benefit of the PRP technique in relation to reproductive outcomes in patients with repeated implantation failures [11,12,14-17] [Figure 6].

The fourth analysis aims to compare live birth rates was done also as a meta-analysis of two studies that report live-birth rates: RR = 0,98, 95% CI 0,63 to 1,52, P = 0,92. The heterogeneity for this comparison was 0%. Consequently, there was no significant difference between two groups [11,15] [Figure 7].

Also we compare the endometrial thickness before and after administration of PRP or G-CSF [Table 4].

DISCUSSION

Main findings

In patients undergoing in vitro fertilization, it is becoming more common for fertility specialists to encounter thin endometrium, which impairs implantation and therefore, pregnancy rates [20,21]. Endometrial thickness may contribute to low fertility rates even in frozen embryo transfer cycles [22-24]. Moreover, there is insufficient data to choose between any adjuvant methods that can gradually influence endometrial growth.

Interpretation and comparison with other literature

Many factors are involved in the process of implantation, among which the cells of the immune system and the cytokines they secrete are of great importance. In this sense, of interest is granulocyte colony-stimulating factor (G-CSF), which, being a cytokine that stimulates hematopoiesis, is also produced by the reproductive system. One of the main effects is the effect on the proliferation and differentiation of the endometrium [25-27]. There are many studies evaluating the effectiveness of G-CSF in various pathologies: in patients with recurrent miscarriage, repeated IVF failures, including those associated with thin endometrium. Maged Elmohamad et al. in their study found that intrauterine G-CSF injection at time of ovum pickup in the study group, in comparison with control group, did not improve neither implantation rate (16.68% vs 19.66%, p = 0.243) nor the chemical (54.5% vs 67%, p = 0.074), clinical pregnancy (51.5% vs 62.9%, p = 0.108) rates as well as live birth rates (31.0% vs 39.8%, p = 0.227). They make a conclusion that intrauterine infusion of G-CSF may not improve Implantation rate in women with unexplained previous intracytoplasmic sperm injection (ICSI) failure. [28]. However Ismet Hortu et al. in their experimental study in rats suggests that G-CSF can be a novel agent for the treatment of ovarian injury. Granulocyte colony-stimulating factor has also decreased ovarian tissue malondialdehyde levels. [29]

However, many questions remain regarding dosages and routes of administration.

In the context of the problem under consideration, platelets and platelet-rich plasma (PRP) are also of interest, as a result of which an increase in the release of a number of cytokines and growth factors occurs. PRP is used in various fields of medicine due to its ability to influence tissue regeneration, including recently in patients who are faced with the problem of thin endometrium [25,30,31]. In 2019, Maleki-Khajiaga et al. published a systematic review of the efficacy of PRP therapy in infertile women undergoing assisted reproduction. They concluded that this intrauterine intervention prior to frozen embryo transfer had a statistically significant positive effect on clinical pregnancy rates. The main theory of the effectiveness of autologous platelet-rich plasma is the regulation of the immunological interaction between the endometrium and the embryo during the implantation window [32].

Strengths and Limitations

Based on our meta-analysis, PRP therapy has a considerable effect on pregnancy rates in patients with thin endometrium in comparison with G-CSF. However, we found no evidence in favor of these two methods in thickening endometrium in infertile patients undergoing assisted reproduction. Nevertheless, this conclusion needs to be confirmed by larger prospective RCTs. Hence, further trials and research are needed.

It is also important to point out the limitations of the studies. Only two were RCTs [16,18], and six of seven [12-15,17] were non-randomized and had a small study group. There is currently minimal evidence to support any specific protocols for significantly improving pregnancy outcomes in women with thin endometrium. Further randomized trials should be conducted on a larger sample of patients.

As for the advantages of our study, we have managed to summarize all available data that compared the effectiveness of two popular adjuvant approaches that aim to improve ART outcomes in infertile patients with thin endometrium. Our systematic review and meta-analysis allowing us to have more evidence-based answers to questions regarding adjuvants in IVF cycles.

Conclusion

Thin endometrium negatively affects the onset of pregnancy in assisted reproduction. Based on our meta-analysis, PRP therapy considerably affects pregnancy rates in patients with thin endometrium compared to G-CSF. However, PRP and G-CSF had no statistically significant difference in thickening endometrium. Thus, there is currently minimal evidence to support any specific protocols for significantly improving pregnancy outcomes in women with thin endometrium.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

L.P. – Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing – review & editing.

J.A. – Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing.

S.I. – Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft

L.O. – Data curation, Formal Analysis, Investigation, Writing – original draft.

A.U. – Investigation, Project administration, Supervision, Validation.

A.I. – Project administration, Supervision, Validation.

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Study registration

PROSPERO registration number is CRD42020222075

Conflict of interest

The authors have no conflict of interest to declare.

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Inclusion criteria	**Exclusion criteria**
Female infertile patients of reproductive age with thin endometrium in embryo transfer cycles	Patients with uterine structural abnormality
Endometrial thickness less than 7–8 mm	Studies combining PRP and G-CSF treatment were excluded

Table 1. Inclusion and exclusion criteria of patients.

№	Study (first author)	Study design	Participants	Interventions	Comparison	Outcomes
1.	Dzhincharadze, et al., 2020	A prospective cohort study	58 patients	PRP group: (n = 37)	G-CSF group: (n=21)	Endometrial thickness greater than 7 mm (not statistically significant (p=0.515)): • PRP group: 26 (70.27%) patients • G-CSF group: 13 (61.9%) patients The average increase in endometrial thickness compared to the previous cycle (not statistically significant):

						• RPR group: 0.47 mm (p=0.085) • G-CSF group: 0.42 mm (p=0.329) The average endometrial thickness on the day of embryo transfer (not statistically significant (p=0.146)): • PRP group: 7.79 (1.42) mm • G-CSF group: 7.21 (1.42) mm Number of embryos transferred (statistically

						significant (p=0.026)): • PRP group: 31 (83.78%) patients • G-CSF group: 12 (57.14%) patients Biochemical pregnancy rate (not statistically significant (p=0.282)): • PRP group: 16 (51.61%) patients • G-CSF group: 4 (33.33%) patients Clinical pregnancy rate (not

						statistically significant (p=0.226)): • PRP group; 14 (45.16%) patients • G-CSF group: 3 (25%) patients Live birth rate (p=0.867) • PRP group :7 births (22.58%) • G-CSF group: 3 births (25%)
2.	Vora, et al., 2019	A retrospective cohort study	50 patients	PRP group: (n = 25)	G-CSF group: (n = 25)	The difference of endometrium after 48 hours (statistically significant (p<0.0001)):

						• PRP group: 1.804±0.839 mm • G-CSF group: 2.67±0.546 mm Number of embryos transferred • PRP group: 1 embryo was transferred on day 3 in 2 women, 2 embryos were transferred on day 3 in 16 women, 3 embryos were transferred

						in 7 women. • G-CSF group: 1 embryo was transferred on day 3 in 4 women, 2 embryos were transferred on day 3 in 17 women, 3 embryos were transferred in 4 women. Biochemical pregnancy rate (statistically not significant p = 0,777)

						• PRP group: 11 (44%) patients • G-CSF group: 13 (52%) patients Clinical pregnancy rate (statistically not significant p = 0,3768) • PRP group: 7 (28%) patients • G-CSF group: 11 (11%) patients
3.	Cassim, et al., 2022	A retrospective analysis	36 patients	PRP group: (n = 20)	G-CSF group: (n = 16)	Number of embryos transferred • PRP group: 1.95(±0.61) embryos transferred

						(range 1 to 3). • G-CSF group: 2.50 (±0.52) embryos transferred (range 2 to 3). The change in endometrial thickness (no statistically significant (p= 0.077)): • PRP group: from 0.30 mm to 4.90 mm • G-CSF group: from 0.1 mm to 5.0 mm Biochemical pregnancy rate (no

						statistically significant difference (p= 0.604)): • PRP group: 9 (45%) patients • G-CSF group: 7 (43.75 %) patients
4.	Mehrafza, et al., 2019	A retrospective cohort study	123 patients	PRP group: (n = 67)	G-CSF group: (n = 56)	Number of embryos transferred (no statistically significant (p= 0.45): • PRP group: 2.74±0.86 • G-CSF group: 2.61±0.95 Biochemical pregnancy rate (no statistically

						significant (p=0.057)): • PRP group: 29 (43.3%) patients • G-CSF group: 15 (26.8%) patients Clinical pregnancy rate (no statistically significant (p= 0.025)): • PRP group: 27 (40.3%) patients • G-CSF group: 12 (21.4%) patients
5.	Selvaraj, et al., 2019	A randomized controlled trial	132 patients	PRP group: (n = 56)	G-CSF group: (n = 76)	Biochemical pregnancy rate (no statistically

						significant (p= 0.155)): • PRP group: 35 (62,5%) patients • G-CSF group: 38 (50%) patients Clinical pregnancy rate (no statistically significant (p= 0.695)): • PRP group: 27 (48,2%) patients • G-CSF group: 34 (44,7%) patients Live birth rate (no statistically significant (p= 0.287)):

						• PRP group: 19 (70,37%) patients • G-CSF group: 28 (82,35%) patients
6.	Deo, et al., 2021	A prospective, cross-sectional, single blind study	20 patients	PRP group: (n = 10)	G-CSF group: (n = 10)	Biochemical pregnancy rate: • PRP group: 5 (50%) patients • G-CSF group: 4 (40%) patients Clinical pregnancy rate: • PRP group: 4 (40%) patients • G-CSF group: 3

						(30%) patients
7.	Nayar, et al.. 2019	A prospective randomised controlled trial	40 patients	PRP group: (n = 20)	G-CSF group: (n = 20)	Endometrial thickness greater than 7 mm: • PRP group: 13 patients • G-CSF group: 13 patients Biochemical pregnancy rate: • PRP group: 7/13 (53.84%) patients • G-CSF group: 5/13 (38.46%) patients Clinical pregnancy rate: • PRP group: 5/13

						(38.46%) patients • G-CSF group: 3/13 (23.07%) patients

Table 2. Description of articles included in the systematic review.

№	Study (first author)	PRP group	G-CSF group
1.	Dzhincharadze, et al., 2020	intrauterine injection of autologous PRP on the 8–9th, 10–11th, and 12–13th days of the menstrual cycle	intrauterine injection of recombinant G-CSF on the 5-6th and 12-13th days of the menstrual cycle.
2.	Vora, et al., 2019	PRP instilled intravaginally 2 days prior to scheduled embryo transfer or on day 11 of cycle.	Injection - G-CSF intrauterine 300 mcg on day of trigger or day 11 of FET followed by injection GCSF for 5 days subcutaneous after ET
3.	Cassim, et al., 2022	Autologous PRP was instilled into the uterine cavity with a semi-rigid embryo transfer catheter.	Autologous PRP was instilled into the uterine cavity with a semi-rigid embryo transfer catheter. G-CSF was instilled into the uterine cavity with a semi-rigid embryo transfer catheter.
4.	Mehrafza, et al., 2019	Intrauterine infusion of 1 *ml* lympho-PRP was performed with intrauterine insemination catheter, two days before embryo transfer.	Patients were treated with a single administration of 300 *μg* recombinant G-CSF, two hours before embryo transfer.
5.	Selvaraj, et al., 2019	On the 10th day of hormone replacement therapy cycle PRP was infused into the uterine cavity using a 65-mm intrauterine insemination catheter.	Intrauterine instillation of G-CSF 0.3 ml using an intrauterine insemination (IUI) catheter was given on days 16 and 18.

6.	Deo, et al., 2021	PRP was infused intrauterine using an IUI cannula under ultrasound guidance.	G-CSF (300 mcg/1 ml) was instilled slowly into the uterine cavity using an intrauterine insemination (IUI) canula under transabdominal ultrasound guidance
7.	Nayar, et al.. 2019	Intrauterine infusion of PRP.	Intrauterine infusion of G-CSF.

Table 3. Forms of administration of PRP and G-CSF.

Study (first author)	Study design	Participants	Interventions	Comparison	Outcomes
Vora, et al., 2019	A retrospective cohort study	50 patients	PRP group: (n = 25)	G-CSF group: (n = 25)	Endometrial thickness • PRP group: endometrium before administration of intrauterine PRP is 6.57±0.63 mm and after 48 hours of administration the mean endometrial thickness became 8.04±1.13 mm • G-CSF: endometrium before administration of injection G-CSF is 6.73±0.41 mm and after 48 hours of administration the mean endometrial thickness became 9.4±0.71 mm
Gupta, et al., 2020	Interventional prospective study	20 patients *G-CSF treatment before PRP	PRP group: (n = 20)	G-CSF group: (n = 20)	Endometrial thickness (statistically significant p= 0.0001) • PRP group: 5.505 ±0.940 mm G-CSF group: 7.450 ±0.799 mm
Cassim, et al., 2022	A retrospective analysis	36 patients	PRP group: (n = 20)	G-CSF group: (n = 16)	Endometrial thickness: (statistically significant p<0.0001) • PRP group: before PRP administration is 6.58 (±1.56) mm, and 7.98 (±1.41) mm after administration • G-CSF group: before G-CSF administration is 6.56 mm (± 2.33) mm and 7,50 (±2,22) mm after administration
Selvaraj, et al., 2019	A randomized controlled trial	132 patients	PRP group: (n = 56)	G-CSF group: (n = 76)	Endometrial thickness: (statistically significant p<0.0001) • PRP group: before PRP administration is 6.70 (±0,9) mm, and 7.80 (±1,4) mm after administration • G-CSF group: before G-CSF administration is 7.0 mm (± 0.8) mm and 7,50 (±0,6) mm after administration
Deo, et al., 2021	A prospective, cross-sectional, single blind study	20 patients	PRP group: (n = 10)	G-CSF group: (n = 10)	Endometrial thickness: (statistically significant p<0.0001) • PRP group: before PRP administration is 5,96 (±0,58) mm, and 6,68 (±0,84) mm after administration • G-CSF group: before G-CSF administration is 6,03 (± 0.53) mm and 6,85 (±0,42) mm after administration

Nayar, et al., 2019	A prospective randomised controlled trial	40 patients	PRP group: (n = 20)	G-CSF group: (n = 20)	Endometrial thickness: (statistically significant p<0.0001) • PRP group: before PRP administration is 5.38 (±0.57) mm, and 6.62 (± 0.98) mm after administration G-CSF group: before G-CSF administration is 5.24 (±0.51) mm and 6.60 (±0.93) mm after administration

Table 4. Endometrial thickness before and after administration of PRP or G-CSF.

Figure 1. PRISMA flow-diagram 2020.

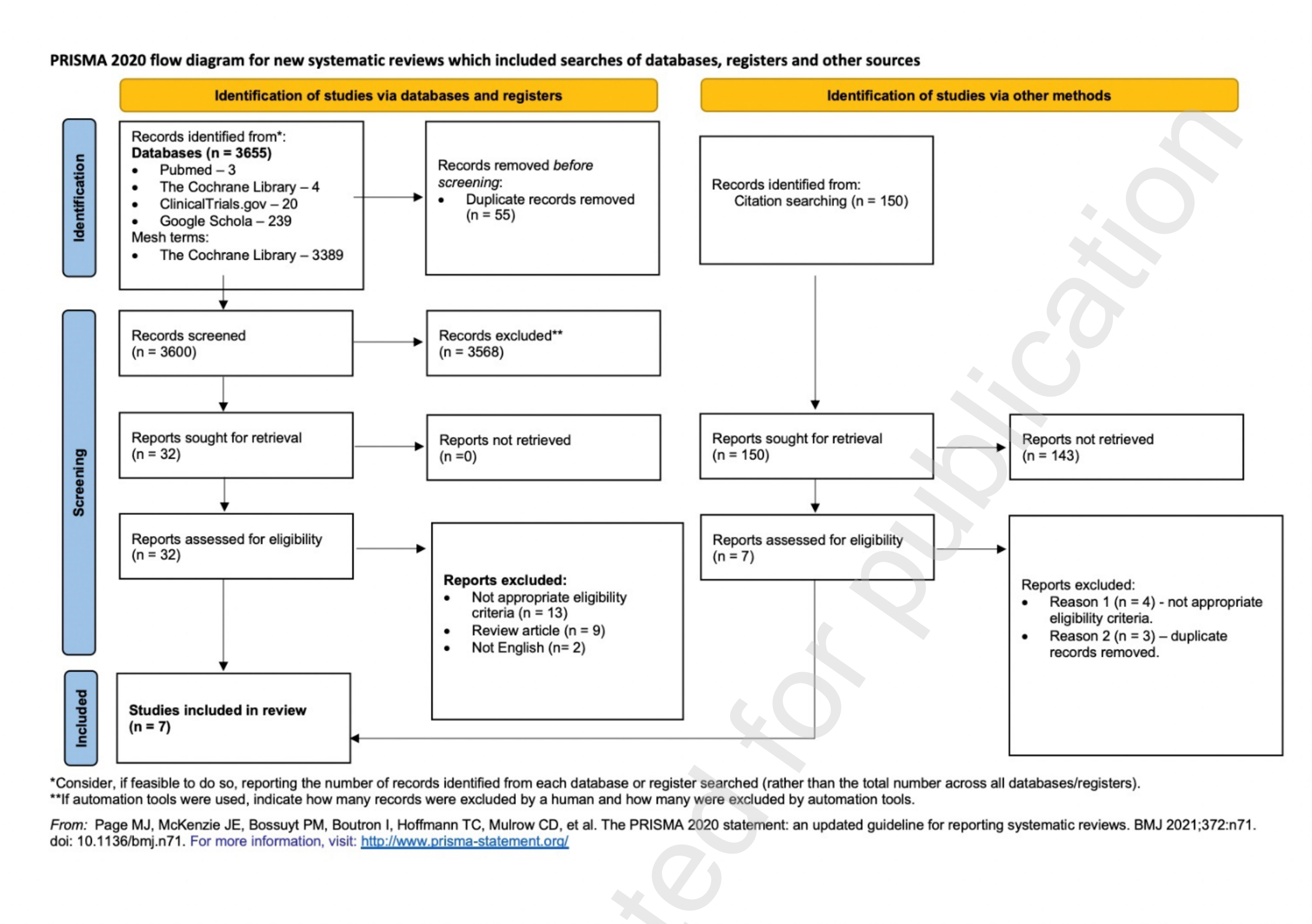

Figure 2. RoB2.0 tool for randomized trials - traffic light plot.

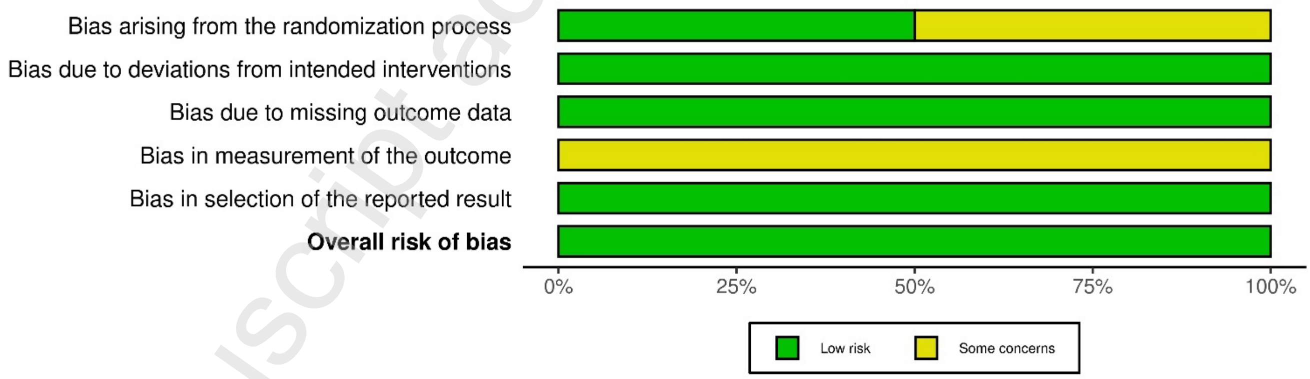

Figure 3. ROBINS-I for non-randomized trials - traffic light plot.

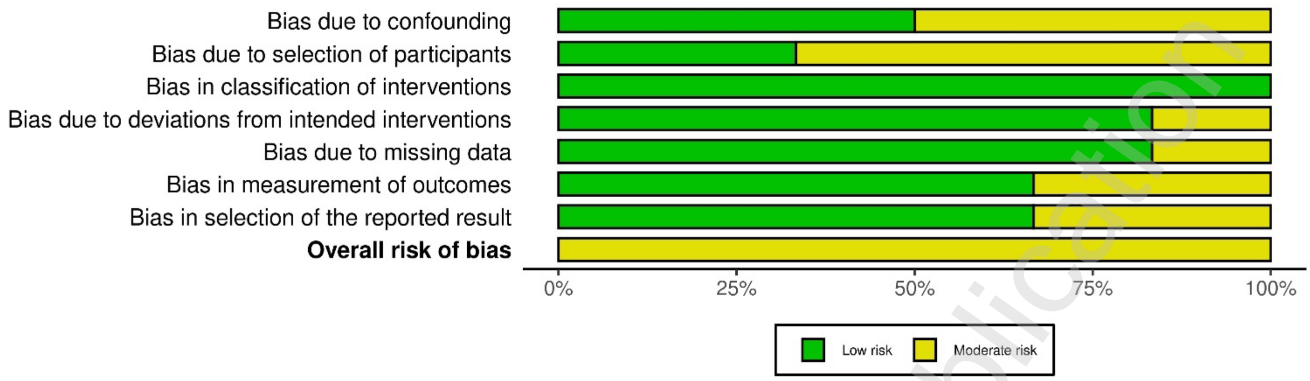

Figure 4. Meta-analysis of endometrial thickness in two groups.

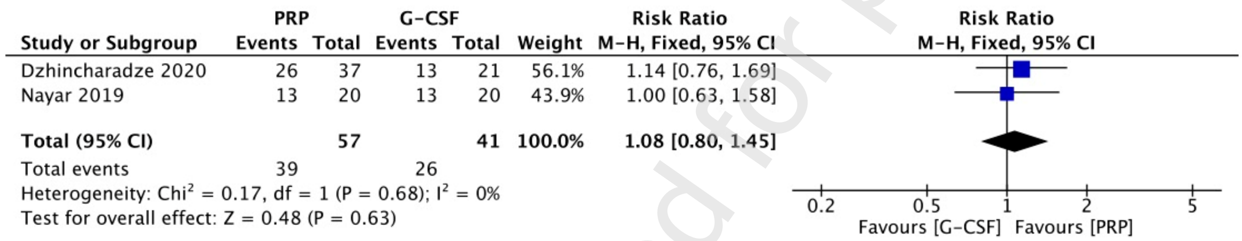

Figure 5. Meta-analysis of biochemical pregnancy rate in two groups.

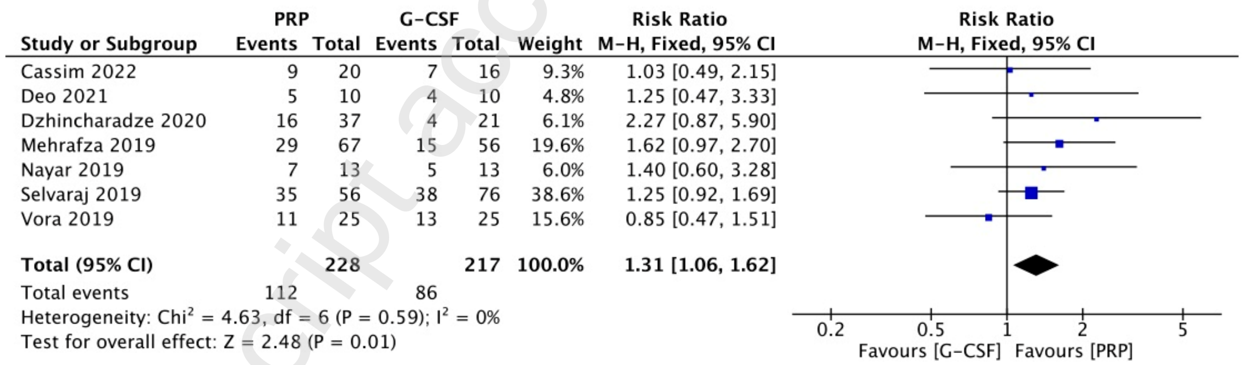

Figure 6. Meta-analysis of clinical pregnancy in two groups.

Study or Subgroup	PRP Events	PRP Total	G-CSF Events	G-CSF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Deo 2021	4	10	3	10	4.8%	1.33 [0.40, 4.49]
Dzhincharadze 2020	14	37	3	21	6.1%	2.65 [0.86, 8.17]
Mehrafza 2019	27	67	12	56	20.8%	1.88 [1.05, 3.36]
Nayar 2019	5	13	3	13	4.8%	1.67 [0.50, 5.57]
Selvaraj 2019	27	56	34	76	46.0%	1.08 [0.75, 1.56]
Vora 2019	7	25	11	25	17.5%	0.64 [0.30, 1.37]
Total (95% CI)		**208**		**201**	**100.0%**	**1.30 [1.00, 1.70]**
Total events	84		66			

Heterogeneity: $Chi^2 = 7.58$, df = 5 (P = 0.18); $I^2 = 34\%$
Test for overall effect: Z = 1.95 (P = 0.05)

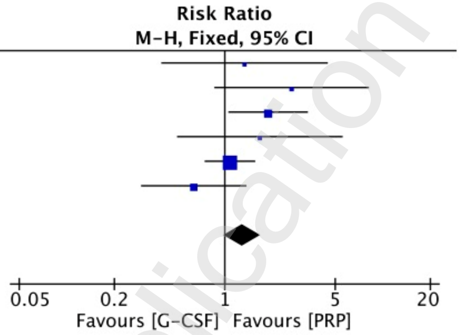

Figure 7. Meta-analysis of live-birth rates in two groups.

Study or Subgroup	PRP Events	PRP Total	G-CSF Events	G-CSF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dzhincharadze 2020	7	37	3	21	13.9%	1.32 [0.38, 4.59]
Selvaraj 2019	19	56	28	76	86.1%	0.92 [0.58, 1.47]
Total (95% CI)		**93**		**97**	**100.0%**	**0.98 [0.63, 1.52]**
Total events	26		31			

Heterogeneity: $Chi^2 = 0.29$, df = 1 (P = 0.59); $I^2 = 0\%$
Test for overall effect: Z = 0.10 (P = 0.92)