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EFFECTS OF PLATELET-RICH PLASMA INFUSION ON PREGNANCY OUTCOMES IN WOMEN UNDERGOING IVF: A META-ANALYSIS

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ABSTRACT

Background This meta-analysis aims to evaluate the effects of platelet-rich plasma (PRP) infusion on pregnancy outcomes of women undergoing *in-vitro* fertilization (IVF) through a statistical analysis of previously conducted clinical trials. **Methods** A systematic search of English literature on PubMed, Springer, and Cochrane Library was conducted to identify studies that evaluated the role of PRP during the IVF procedure. The studies that were considered for statistical analysis included randomized control trials, clinical trials, comparative studies, and evaluation studies. The parameters like total implantation, clinical pregnancy, live birth, chemical pregnancy, ongoing pregnancy, multiple pregnancies, miscarriage, and abortion rate were analyzed from these studies. Risk of bias assessment and statistical analysis of the data was carried out using the RevMan (Review Manager v5.4.1) software, wherein the random effects model was utilized to determine the Odds Ratio (OR) of each trial. **Results** A total of eleven relevant studies including 1059 participants reporting the effects of PRP infusion in women undergoing IVF treatment were analyzed for a total of eight parameters. All the parameters showed clinical improvement after PRP treatment when compared with the patient groups under the routine care of IVF. Parameters like clinical pregnancy, chemical pregnancy, and ongoing pregnancy showed statistically significant results in improving pregnancy outcomes after PRP treatment. However, statistical analyses of total implantation, live birth, multiple pregnancies, miscarriage, and abortion rates were insignificant (p-value> 0.05 at a confidence interval of 95%) with clinically significant results. **Conclusion** The present meta-analysis demonstrated the effectiveness of PRP infusion in improving the pregnancy outcomes in women undergoing IVF treatment as compared to those undergoing routine IVF procedures. However, to arrive at a definitive conclusion, high-quality RCTs with a larger sample size will be necessary to establish the effectiveness of PRP usage in IVF.

KEYWORDS : Platelet-rich plasma, in-vitro fertilization, repeated implantation failure, infertility

INTRODUCTION

More than 17% of couples worldwide suffer from infertility. Ovulation disorders, fallopian-related disorders, repeated implantation failure (RIF), endometriosis, and unexplained infertility contribute to the common causes of female infertility.[1] More than 8 million babies have been born worldwide since the introduction of IVF. The live birth rate per initiated cycle remains between 19-22% even after the improvements in the protocols and advanced laboratory techniques.[2]

However, low live birth and pregnancy rates after IVF treatment remain difficult challenges for this treatment. 50-75% of IVF procedures fail due to implantation failure.[3,4] Reproductive specialists continue to face challenges in understanding the causes and treatments of RIF despite the rapid development of assisted reproductive technology (ART) in recent years. In the context of reproductive medicine, RIF is a condition that occurs when women undergo IVF procedures using high-quality embryos but fail to achieve pregnancy even after three attempts. This phenomenon can result in significant distress for both patients and healthcare providers.[5]

PRP is a preparation obtained by the centrifugation of freshly obtained autologous blood. This process results in a concentration of platelets that is four to five times higher than that found in plasma. The alpha granules of these platelets contain a variety of cytokines and growth factors, including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), angiopoietins, transforming growth factor-beta (TGF-□), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF).[6]

PRP is used in various fields including tissue regeneration. During the healing process, the alpha granules within platelets secrete growth factors, cytokines, and chemokines.[7,8] These secreted proteins exert paracrine effects on various cell types, such as myocytes, tendon cells,[9] mesenchymal stem cells of different origins,[10] chondrocytes, osteoblasts, fibroblasts, and endothelial cells.[11-14] These effects include stimulation of cell migration, cell proliferation, and angiogenesis, which ultimately leads to tissue regeneration.[15] Research has shown that PRP contains significant concentrations of growth factors and cytokines, which are vital for processes such as cell proliferation, chemotaxis, cell differentiation, regeneration, and angiogenesis.[16] PRP has been shown to enhance the growth rate and cellular survival of follicles from the earliest stages (primordial or primary) to the pre-antral stage, leading to improved ovarian function, as well as increased rates of pregnancy and live births.[17]

The present meta-analysis aims to evaluate the pregnancy outcomes in a group of women undergoing IVF with PRP infusion (study group) as compared to the group of women undergoing IVF with routine care (control group).

MATERIALS AND METHODS

Search strategy

A systematic literature review was conducted independently by two authors (Fig. 1) to identify RCTs, clinical trials, and comparative and evaluation studies assessing the impact of PRP on pregnancy outcomes in women undergoing IVF. The search was performed on databases such as PubMed and Springer, utilizing a combination of MeSH terms, including "Platelet-rich plasma", "*in-vitro* fertilization", "Repeated implantation failure", and "Thin endometrium", and Boolean

operators such as "AND" and "OR". The Cochrane Central Database was also searched, yielding a limited number of results that were obtained from previous searches. Additional sources, including Google Scholar and other open sources, were searched for relevant studies.

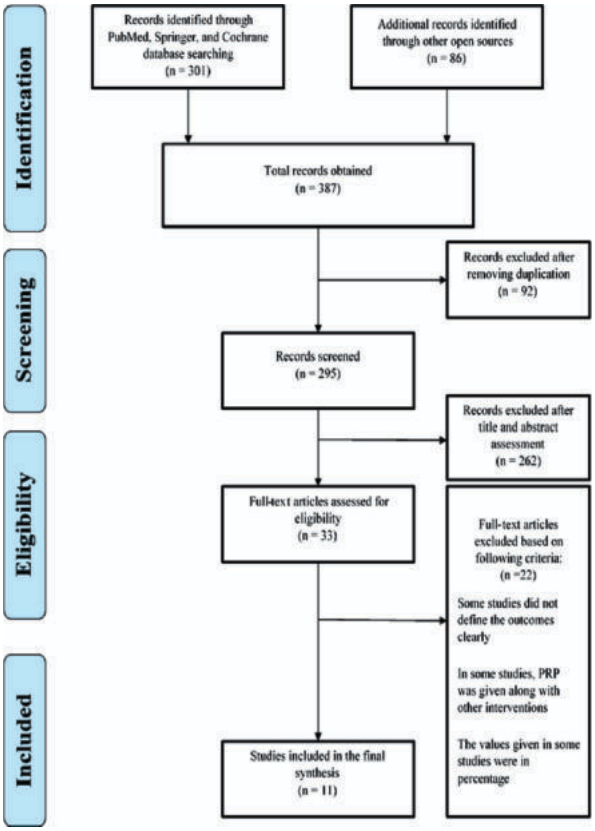

Fig 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study selection.

Study selection

Potentially relevant articles were obtained based on the titles and abstracts through the described search strategy (Fig. 1). After screening the articles for titles and abstracts, all the duplicates were removed.

The inclusion criteria were as follows:

- The study involved the patient population undergoing IVF treatment
- Treatment involved the use of PRP during IVF
- The study reported at least one standard parameter of pregnancy evaluation
- Only published studies were considered and only those written in the English language were included

Duplicates were removed, and in the event of overlapping patient populations, only the most recent study was selected for inclusion.

Data extraction

Extracted data included pregnancy outcomes with PRP treatment (study group) against routine treatment (control group) during IVF. The extracted data included: the first author, the number of participants in the study and the control group, categories of patient groups (control and study population), and values of the pregnancy outcome parameters *viz* total implantation, clinical pregnancy, live birth, chemical pregnancy, ongoing pregnancy, multiple pregnancies, miscarriage, and abortion.

Risk of bias assessment

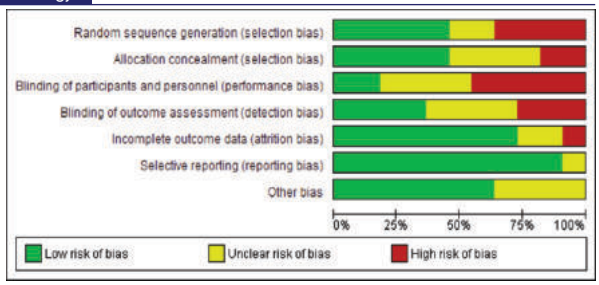

Fig 2. Risk of bias assessment for included studies in the meta-analysis

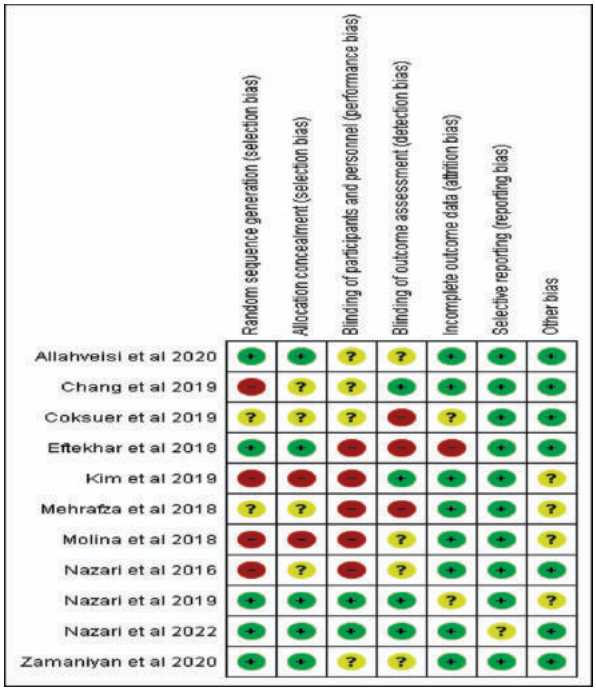

Fig 3. Summary of risk of bias for studies considered in the meta-analysis

Risk of bias assessment (Fig 2., Fig 3.) was carried out by two authors independently using RevMan (Review Manager v5.4.1) software.

Statistical analysis procedure

Data from all the relevant articles were imported and analyzed using RevMan to obtain the forest plots of necessary parameters. The random effects model was utilized to determine the Odds Ratio (OR) of each trial. The pregnancy outcomes data from the relevant studies were imported into the RevMan software for conducting the statistical analysis. The confidence interval (CI) was maintained at 95% and the statistical significance of the p-value was considered less than 0.05.

RESULTS

PRP in IVF and total implantation

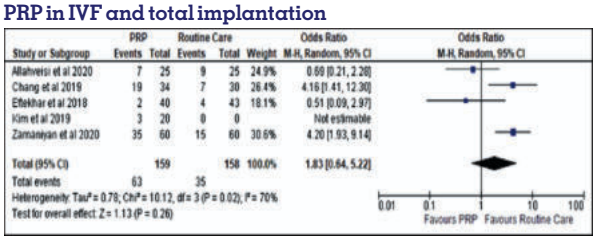

Fig 4. Effects of PRP in IVF on total implantation

(CI= Confidence Interval, df= Degrees of Freedom, I^2 = Heterogeneity, OR= Odds Ratio, M-H= Mantel-Haenszel analysis)

Fig 4. shows the effectiveness of PRP on IVF pregnancy outcomes in women. Five studies were analyzed using the random effects model to compare the implantation rate of women undergoing IVF with PRP (n=159) to those undergoing routine treatment (n=158). The statistical analysis found that the PRP group had a higher implantation rate (39.6%) than the routine care group (20.83%) (OR= 1.83, 95% CI 0.64-5.22, p=0.26, I^2 = 70%), indicating that PRP may improve implantation during IVF.

PRP in IVF and clinical pregnancy

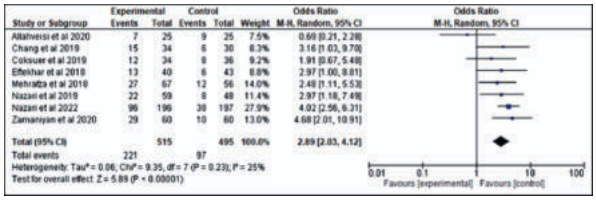

Fig 5. Effects of PRP in IVF on clinical pregnancy

(CI= Confidence Interval, df= Degrees of Freedom, I^2 = Heterogeneity, OR= Odds Ratio, M-H= Mantel-Haenszel analysis)

The clinical pregnancy rate was reported in eight studies with a total of 1010 participants (Study group= 515 and control group=495). The results of the random effects model showed a higher clinical pregnancy rate in the PRP group (42.91%) than in the control group (19.59%) (OR= 2.89, 95% CI 2.03-4.12, p=0.00001, I^2 = 25%) (Fig 5.). This statistical analysis suggests that PRP administration during IVF may significantly improve the clinical pregnancy rate.

PRP in IVF and live birth

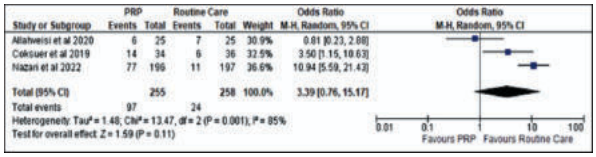

Fig 6. Effects of PRP in IVF on live birth

(CI= Confidence Interval, df= Degrees of Freedom, I^2 = Heterogeneity, OR= Odds Ratio, M-H= Mantel-Haenszel analysis)

Fig 6. shows three studies that evaluated the outcomes of PRP on live birth rate with a total study population of 513 (PRP group= 255 and control group=258). A higher live birth rate was observed in the PRP group (38.03%) than in the group undergoing routine care (9.3%) (OR= 3.39, 95% CI 0.76-15.17, p=0.11, I^2 = 85%). This statistical analysis concluded that PRP might improve the live birth rate with IVF treatment.

PRP in IVF and chemical pregnancy

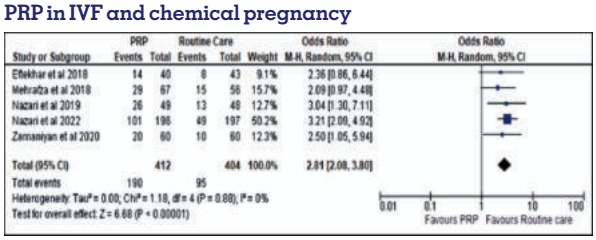

Fig 7. Effects of PRP in IVF on chemical pregnancy

(CI= Confidence Interval, df= Degrees of Freedom, I^2 = Heterogeneity, OR= Odds Ratio, M-H= Mantel-Haenszel analysis)

Five studies reported the outcomes of PRP treatment during IVF with a patient population of 816 (PRP group=412 and control group=404) as shown in Fig 7. All five clinical trials had a significant effect favouring the routine care scenario (OR>1). Chemical pregnancy rates were found to be higher in the case of the PRP group (46.11%) than the group of patients undergone routine care (23.51%) (OR= 2.81, 95% CI 2.08-3.80, p<0.00001, I^2 = 0%). The pooled effect of this statistical analysis showed that chemical pregnancy might increase with the treatment of PRP in IVF significantly.

PRP in IVF and ongoing pregnancy

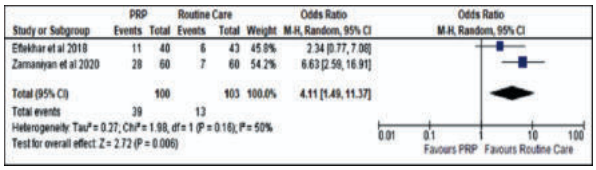

Fig 8. Effects of PRP in IVF on ongoing pregnancy

(CI= Confidence Interval, df= Degrees of Freedom, I^2 = Heterogeneity, OR= Odds Ratio, M-H= Mantel-Haenszel analysis)

Fig 8. represents the results of two clinical trials that evaluated ongoing pregnancy on a cumulative patient population of 203 (PRP group= 100 and control group= 103). Both studies significantly favoured routine care (OR>1). The PRP group showed higher ongoing pregnancy rates (39%) than the routine care group (12.62%) (OR= 4.11, 95% CI 1.49-11.37, p=0.006, I^2 = 50%). The pooled analysis indicated that the ongoing pregnancy rates can be significantly improved using PRP as an adjuvant during IVF.

PRP in IVF and multiple pregnancy rate

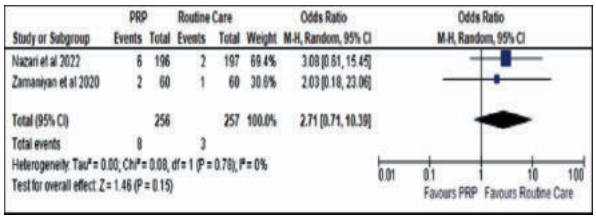

Fig 9. Effects of PRP in IVF on multiple pregnancy rate

(CI= Confidence Interval, df= Degrees of Freedom, I^2 = Heterogeneity, OR= Odds Ratio, M-H= Mantel-Haenszel analysis)

Multiple pregnancy rate outcomes after PRP treatment were reported in two studies with a total patient population of 513 (PRP group=256 and control group=257), both of which favoured routine care, significantly (OR>1). The multiple pregnancy rate was found to be higher in the PRP treatment group (3.12%) than in the routine care group (1.17%) (OR= 2.71, 95% CI 0.71-10.39, p=0.15, I^2 = 0%) as shown in Fig 9. The pooled effect of this statistical analysis suggested that the multiple pregnancy rates can be improved using PRP during the IVF treatment.

PRP in IVF and miscarriage

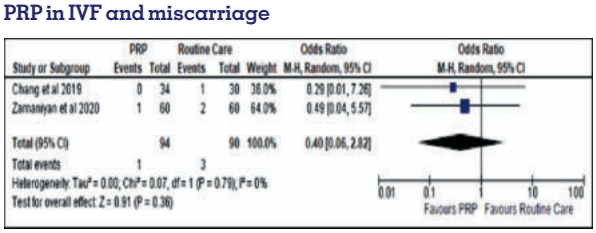

Fig 10. Effects of PRP in IVF on miscarriage

(CI= Confidence Interval, df= Degrees of Freedom, I^2 = Heterogeneity, OR= Odds Ratio, M-H= Mantel-Haenszel analysis)

Miscarriage rates after PRP treatment were reported by two studies (Fig 10.) with a cumulative patient population of 184

(PRP group=94 and control group=90). Both studies showed that miscarriage rates were lower in the PRP group as compared to the routine care group, however, the results were insignificant (OR<1). The miscarriage rates were 1.06% in the PRP group and 3.33% in the routine care group (OR= 0.40, 95% CI 0.06-2.82, p=0.36, I^2 = 0%). This statistical analysis suggested that PRP can be used during IVF treatment to lower miscarriage rates.

PRP in IVF and abortion

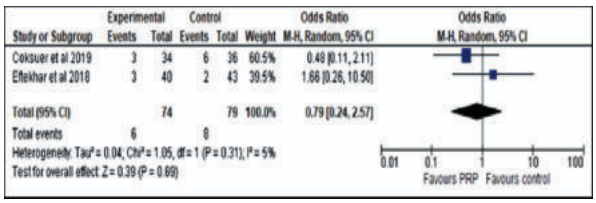

Fig 11. Effects of PRP in IVF on abortion
(CI= Confidence Interval, df= Degrees of Freedom, I^2 = Heterogeneity, OR= Odds Ratio, M-H= Mantel-Haenszel analysis)

The summary results of abortion rates after the PRP treatment for IVF were obtained from two studies having a patient population of 153 (PRP group=74 and control group=79). One study showed a lower abortion rate with the use of PRP; however, the results were insignificant (OR<1). The second clinical trial showed a lower abortion rate in routine care scenarios (OR>1). As shown in fig. 11, the comparative abortion rate indicated that the intrauterine infusion of PRP during IVF treatment had lower abortion rates (8.1%) than the control group (10.12%) (OR= 0.79, 95% CI 0.24-2.57, p=0.69, I^2 = 5%). This statistical analysis demonstrated that the use of PRP during IVF treatment may reduce the abortion rate.

DISCUSSION

In the present study, a meta-analysis was conducted on relevant articles stating the outcomes of PRP in women undergoing IVF treatment and comparing these results against the outcomes of routine care IVF. The statistical analysis of data on 3709 women undergoing IVF was conducted using the RevMan software. Random effects model was used to calculate the OR of all the studies and the forest plots were obtained.

The results showed that in the majority of parameters, there was a significant improvement in the pregnancy outcomes after PRP infusion during IVF when compared to the routine care in women undergoing IVF. Statistically significant results were obtained in parameters of clinical pregnancy, ongoing pregnancy, and chemical pregnancy. The pooled analysis for implantation rate, live birth rate, multiple pregnancy rate, miscarriage, and abortion rates was statistically insignificant. However, clinical improvement was observed in all the pregnancy outcome parameters evaluated in the present meta-analysis.

Total implantation rate

In the present study, the effect of the pooled analysis showed that the total implantation rate had improved after PRP treatment during IVF when compared to routine care. Similar results were obtained by Maleki-Hajiagha et al. (2020).[18] In 2019, Chang et al. conducted a clinical trial to investigate the effects of PRP on the pregnancy outcomes of 64 patients. There was a significant improvement in the total implantation rate in patients who received PRP treatment than the control group (27.94% vs 11.67%, p<0.05).[19] A RCT was conducted by Eftekhar et al. in 2018 on 40 patients undergoing IVF treatment. The results of the study reported that there was a statistically significant improvement in the implantation rate of the patient group who received PRP during IVF treatment when compared to the control group (21% in the PRP group (n=40) and 9.37% in the control group (n=43), p<0.05).[20] In a pilot study conducted in 2019 by Kim et al., 24 women with repeated implantation failure (RIF) were treated with intrauterine infusion of PRP. The study outcome stated that the improvement in implantation rate was statistically significant in the patient group (0% in the control and 12.7% in the study group, p<0.05).[7]

Clinical pregnancy

As per the results of the current meta-analysis, the pooled effect of statistical analysis suggested significant improvement in clinical pregnancy after the administration of PRP during IVF against routine care. In a clinical trial by Chang et al. (2019), there was a significant improvement in clinical pregnancy for a group that received PRP during IVF when compared to the control group (44.12% and 20% respectively, p<0.05).[19] In a retrospective study performed by Coksuer et al. in 2019, intrauterine infusion of PRP was administered in 34 patients suffering from repeated implantation failure (RIF). The study outcomes were compared against the control group (n=36). The results of this retrospective study showed statistically significant improvement in the clinical pregnancy rates of the study group to the control group (35.2% and 22.2 %, p<0.05).[21]

In a randomized clinical trial conducted by Eftekhar et al. in 2018, similar results were obtained where the improvement of clinical pregnancy in the study group was 32.5% and in the control group, it was 14%. This improvement was stated to be statistically significant as well (p<0.05).[20] Similar outcomes were observed in a study conducted by Nazari et al. in 2019. In this randomized control trial, 97 women undergoing IVF treatment with a history of RIF were included. The statistical analysis confirmed that the clinical pregnancy rates can be improved significantly with the help of PRP infusion during IVF treatment. The control group had a clinical pregnancy rate of 16.66% (n=48) while the PRP group had a clinical pregnancy rate of 44.89% (n=49) (p<0.05).[22]

Live birth

The statistical analysis conducted for live birth through this meta-analysis was insignificant. However, clinically significant improvement was reported through the pooled analysis. In an RCT conducted by Allahveisi et al. in 2020 on 50 women who reported RIF, 25 patients were treated with PRP during IVF and 25 patients were included in the control group. The results of this study showed significant improvement in the live birth rate of patients who received PRP during IVF when compared to the control group (28% and 24%, p>0.05).[23]

In the study conducted by Kim et al., the improvement in the live birth rate after PRP treatment was clinically significant but when compared to the control group, the pooled analysis was statistically insignificant (p>0.05).[7] In a clinical trial conducted by Molina et al. in 2018, 19 patients with a history of RIF were treated with PRP during IVF treatment. Improved live birth rates were observed in 26.3% of the population.[24] Similarly, in a randomized trial conducted by Nazari et al. in 2021, 196 patients received PRP as an adjuvant during the IVF treatment while a control group of 197 patients received routine IVF care. The pooled analysis of this study showed statistically significant improvement in the live birth rates of the study group when compared to the control group (39.28% and 5.58% respectively, p<00001).[25]

Chemical pregnancy

The present study showed statistically significant outcomes after statistical analysis of relevant studies for a chemical pregnancy. The results showed that the chemical pregnancy improved significantly after PRP treatment compared to the

control group. Similar outcomes were reported by Eftekhar et al. where, in a randomized clinical trial of 83 women, the PRP group (n=40) showed chemical pregnancy was reported in 35%, and in the control group (n=43), the chemical pregnancy was reported in 18% of the patients with p=0.05.[20] Mehrafza et al. (2018) conducted a retrospective cohort study on 123 patients with a history of failed embryo transfer. In this study, the PRP group of 67 patients showed chemical pregnancy in 43.3% of patients while the control group (n=56) reported chemical pregnancy in 26.8% of patients (p=0.057).[26]

Ongoing pregnancy

As per the present meta-analysis, the statistical analysis for ongoing pregnancy rate showed statistically significant outcomes and these outcomes showed clinically significant improvement in improving the ongoing pregnancy rates. Zamaniyan et al. conducted a blind randomized clinical trial in 2020 on 120 patients who suffered from RIF. Ongoing pregnancy rates in the group that received intrauterine PRP perfusion (n=60) during IVF showed higher and statistically significant ongoing pregnancy rates than the control group (n=60) (46.7% and 11.7% respectively, p<0.05).[27] In the RCT conducted by Eftekhar et al. (2018), ongoing pregnancy rates were found to be improved in the study group when compared to the control group (27% and 14% respectively, p>0.05).[20]

Multiple pregnancies

The present study's statistical analysis suggested a clinically significant improvement in the multiple pregnancy rates in the study group undergoing IVF with PRP as an adjuvant. Zamaniyan et al. (2020) also reported similar results where the improvement in the PRP group was higher than the control group. However, the difference was not statistically significant.[27] In an RCT conducted by Nazari et al. (2022) similar results were found. The PRP group showed multiple pregnancies of 3.06% (n=196) while the control group had a multiple pregnancy rate of 1.01% (n=197) with p>0.05.[25]

Miscarriage rates

The pooled analysis of the present study after statistical analysis suggested that the miscarriage rates can be reduced with the use of PRP during the IVF treatment. However, the difference between the miscarriage rate of the PRP group and the control group. In 2019, Chang et al. conducted a study on women experiencing RIF. In this study, after intrauterine perfusion of PRP during the IVF there were no cases of miscarriage rates (n=34). However, in the control group (n=30) 16.7 % of patients experienced miscarriage (p>0.05).[19] Similar outcomes were obtained by Nazari et al. in 2016, where a pilot study was conducted on 20 women undergoing IVF with a history of RIF. The outcomes of the study showed that only one patient experienced a miscarriage and 18 patients experienced improvements in pregnancy outcomes.[28]

Abortion rates

Eftekhar et al. (2018) conducted an RCT to study the outcomes of PRP in 83 women undergoing IVF. The abortion rate results of this study suggested that the chances of abortion may not be minimized with PRP infusion during the IVF treatment. The abortion rate in the study group was 9% (n=4) and 6% in the control group (6%). However, the results were statistically insignificant (p>0.05) and more such studies are needed to get a definitive conclusion.[20] However, the outcomes of the present meta-analysis showed contradicting results with decreased abortion rates after PRP infusion during IVF treatment when compared to routine care. The clinical outcomes of the study conducted by Coksuer et al. (2019) were similar to the current study, where the PRP group of 34 women undergoing IVF treatment had an abortion rate of 8.8% while the control group of 36 women undergoing IVF treatment with routine care reported abortion rates of 16.7% (p>0.05).[21]

The present meta-analysis revealed that PRP had a clinically significant impact in enhancing pregnancy outcomes in women undergoing IVF treatment when compared with routine care outcomes. The pooled analyses showed statistically significant improvements in the PRP group for parameters like clinical pregnancy, chemical pregnancy, and ongoing pregnancy. Statistical analyses for other parameters like total implantation, live birth, multiple pregnancies, miscarriage, and abortion were insignificant. However, clinically significant results were observed for all the parameters. Additional high-quality RCTs with a larger sample size are necessary to confirm the findings reported in the present meta-analysis.

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