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A meta-analysis of the effect of Autologous Platelet-Rich Plasma Treatment in IVF/ICSI on the endometrium and clinical pregnancy rate

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Abstract

Background: The thickness of the endometrium has been identified as a prognostic factor for improving the pregnancy rate in patients with female infertility.

Study Question: What are the effects of autologous platelet-rich plasma (PRP) treatment in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) on the endometrium and clinical pregnancy rate (CPR) as a prognostic factor for the pregnancy rate in patients with female infertility?

Objective, Study Design: This is a meta-analysis of published controlled studies. Searches were conducted from 2018 to 2022 on PubMed, Medline, EMBASE, and ISI Web of Science electronic databases to collect data using the following search terms: “Platelet-Rich Plasma”, “IVF/ICSI”, and “Endometrium”, and “pregnancy rate”.

Materials and Methods: A total of nine full-text articles were preselected from 139 references based on their titles and abstracts. Two independent reviewers performed data selection and extraction according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA). This review was conducted according to the PICO standard. Random-effect meta-analysis was performed on all data (overall analysis).

Results: Data from nine relevant articles were extracted and integrated into the meta-analysis. The nine studies reported CPR as an outcome in 712 patients; 360 of these patients were administered PRP, while the control comprised 352 patients who were not administered PRP. A similar CPR was observed in both groups (odds ratio, 0.12; 95% confidence limit, 0.02–0.22). Endometrial thickness was an outcome in 619 patients; 317 patients were administered PRP and 302 patients in the control group were not administered PRP and had similar outcomes of 1.16 (0.57–1.76). Sensitivity analysis led to similar results and conclusions.

Conclusions: Intrauterine instillation of autologous PRP does not improve the pregnancy rate or endometrial thickness in patients who underwent IVF embryo transfer. This meta-analysis included a randomized controlled trial (RCT). All practitioners who preferably use the PRP cycle should refrain from using this procedure till further large RCTs are performed to address whether PRP should be used.

Keywords: platelet-rich plasma, thin endometrium, pregnancy rate meta-analysis, systematic review.

Introduction

Infertility refers to the inability of couples to achieve pregnancy after 12 months or more of regular sexual intercourse. [1] Infertility affects a large number of individuals between the ages of 15 and 45 years worldwide and impacts their families and communities. [2] It is estimated that about 186 million individuals live with infertility globally. [3] It has also been estimated that infertility affects between 8% and 12% of reproductive-aged couples worldwide. [4]

Many factors prevent normal implantation and pregnancy, including the embryo and endometrial quality. [5] A thin endometrium is defined as an endometrium that is <7 mm on the day of ovulation, on the day of injection of human chorionic gonadotrophin (HCG) in fresh in vitro fertilization (IVF) cycles, or on the day progesterone is started in frozen-thaw embryo transfer cycles. [6]

Many studies have already proved that endometrial thickness affects pregnancy outcomes, and a thin endometrium is considered to be an independent adverse factor for achieving pregnancy in patients, irrespective of ovary stimulation. [7.8.9]

Endometrial thickness influences the pregnancy rate. [10] The incidence rate of a thin endometrium is 2.4%, and it has been associated with lower implantation and pregnancy rates. [11]

Treating a thin endometrium remains a challenge, and extensive research is required to further elucidate the management of patients with thin endometrium in the future. Some studies in the form of randomized controlled trials that used the application of platelet-rich plasma (PRP) in patients with a thin endometrium have reported the effectiveness of this therapy in improving endometrial growth and pregnancy outcomes. [12,13,14]

This meta-analysis aims to review and evaluate the efficacy of PRP for the treatment of patients with a thin endometrium compared to those who received no

treatment. The main out measures were endometrial thickness and pregnancy rate.

Materials and Methods for meta-analysis

Data source

Electronic search database and approach

This is a meta-analysis, and a systemic review of all the data was performed using published articles and studies; therefore, ethical approval was not required. The analysis was performed using randomized controlled clinical trials (RCTs) published between 2018 and 2022. PubMed, Medline, EMBASE, and the ISI Web of Science electronic database were used to collect data using the following search terms: “Platelet-Rich Plasma”, “IVF/ICSI”, “Endometrium”, and “pregnancy rate”. Complete studies published in peer-reviewed journals with good design and quality were considered for this review.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA) and PICO standards were used. (Table 1)

Other sources of search

Full texts were obtained through an electronic library or the internet. Data was also obtained from conference papers by contacting the author for details of the original research. Manual retrieval of references also assisted in identifying studies related to this review.

Inclusion and excluded criteria

Study design

This review included only studies on human RCT. Other kinds of studies, such as observational studies, retrospective analyses, self-controlled trials, case reports, reviews, patient series, and animal experiments, were excluded.

Included population

The included population comprised infertile patients who required IVF/ICSI and whose endometrial thickness measured using B ultrasound scanning was <7 mm on the day of ovulation or HCG administration.

Excluded population

The criteria for inclusion/exclusion of studies were established before the literature search. A study was considered eligible only if the researchers studied autologous platelet-rich plasma treatment in IVF/ICSI and assessed its effect on the endometrium and implantation rate.

All references were identified and reviewed to determine any other new eligible studies. The analysis was performed using only publication in the English language. Two independent authors (AJ and HA) searched PubMed, Medline, EMBASE, and S.I. Web of Science electronic database for RCT studies whose participants fulfilled the inclusion criteria using the following keywords “Platelet-Rich Plasma”, “IVF/ICSI”, “endometrium”, and “pregnancy rate” in the title, abstract, or index term fields.

Data were extracted from eligible studies that were assessed by two independent authors (AJ and MG). Another author checked these according to the standard protocol.

The following variables were collected from the eligible studies: study name, publication year, study design, number of cycles, odds ratio, lower and upper 95% CL, and p-values (Table 2 and Table 3)

The weight of the study was calculated, and sensitivity analyses were implemented using a visual inspection of the forest plot.

The meta-analysis was rerun and the first step-by-step guide pooled effect sizes were considered statistically

significant at P < 0.05. Additionally, a chi-square test was used to calculate the statistical heterogeneity across the studies.

For dichotomous outcomes, the random-effect model estimated odds ratios (ORs) with two-sided 95% CI were used. We used the fixed and random-effect models for the analysis. However, we reported only the random-effect model because of underlying heterogeneity in the studies. [15]

Interventions

The treatment group consisted of patients with thin endometrium treated with PRP. The control group comprised patients who were not treated with PRP.

Outcomes

The primary outcome indicator was the endometrial thickness, which was defined and measured using ultrasound radiography. The clinical pregnancy rate was defined as the rate of detection of a gestational sac using ultrasonography with fetal heart activity at 4–5 weeks after embryo transfer.

Endometrial thickness and clinical pregnancy rate were extracted and assigned as dichotomous frequency data. afterward ORs with 95% confidence intervals were calculated from individual studies before pooling. The pooled ORs for investigated outcomes were calculated using the random-effects model, considering that the underlying effects varied across the studies included.

Data analysis and synthesis

We pooled all similar studies, which were identical without heterogeneity, and the meta-analysis was conducted using RevMan 5.3 software.

Dichotomous variables were compounded to risk ratios (RR) and 95% confidence intervals, while the continuous variable was merged to mean difference and 95% confidence intervals. The Cochran Q statistic and I2 statistic were used to calculate the indicators that reflected heterogeneity. For example, P < 0.10 indicated heterogeneity, and I2 > 50% indicated significant heterogeneity. A fixed-effect model (Mantel–Haenzel method for RR) was used when I2 was < 50%, while a random-effects model (D-L method) was used when heterogeneity was significant after sensitivity analysis. Statistical significance was set at P <.05 in the Z test.

The endometrial thickness and clinical pregnancy rate were extracted and assigned as dichotomous frequency data. Afterward, the ORs with 95% confidence intervals were calculated from individual studies before pooling. The pooled ORs for investigated outcomes were calculated using the random-effects model, considering that the underlying effects varied across the studies included.

Heterogeneity tests across the included studies were conducted using I-squared and Q statistics. P < 0.010 was regarded as significant heterogeneity. Sensitivity analyses were conducted to investigate outcomes and assess the effects of a single study from the overall analysis.

The inspection levels for the pooled results were two-sided, and P < 0.05 was considered statistically significant. SPSS version 22.0 (IBM Corp., Armonk, NY) was used for all statistical analyses conducted in this study.

Of the 139 potentially relevant studies screened by electronic databases, 24 were excluded owing to irrelevant and duplicate topics. The full-text articles for the remaining 66 studies were evaluated, and nine articles met the inclusion criteria and were included in this study (Figure 1)

Protocol

This protocol was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement. The systematic review was reported using the PRISMA statement. [16]

Figure 1: The PRISMA literature screening flow chart.

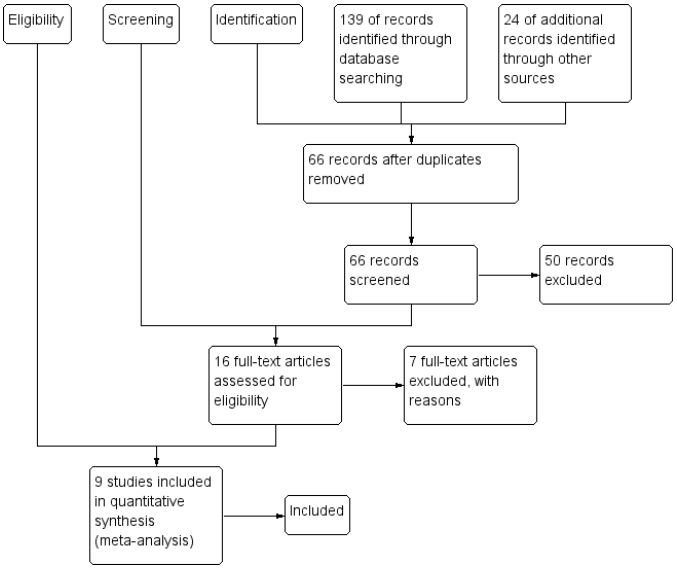

Figure 1: PRISMA (Preferred reporting items for systematic reviews and meta-analyses)

Table 1: PICO

P	Patients with thin endometrium who underwent IVF/ICSI
I	Autologous platelet-rich plasma
C	Patients who did not undergo treatment with platelet-rich plasma
O	Endometrial thickness, pregnancy

This flow diagram depicts the flow of information through the different phases of a systematic review or meta-analysis. Figure 1 shows the number of identified, included, and excluded studies and the reasons for exclusions. Meta-analyses results are presented in a forest plot, where each study is shown with its effect size and the corresponding 95% confidence interval.

Results (meta-analysis)

Data from nine relevant articles were extracted and integrated into the meta-analysis that reported patients' age, BMI, the thickness of the endometrium, and clinical pregnancy rate.

Risk of bias assessment

Biases consist of five types

1. Selection bias
2. Performance bias
3. Detection bias
4. Attrition bias
5. Reporting bias

As reported by the Cochrane Collaboration Network Risk Assessment Tool, each of the reviewers evaluated the risk of bias. A discussion was carried out with a third author if the bias was unclear. The risk of bias assessment chart of the included studies was created using RevMan 5.3 (Figures 1, 2.3).

Figure 2 Risk of bias graph:

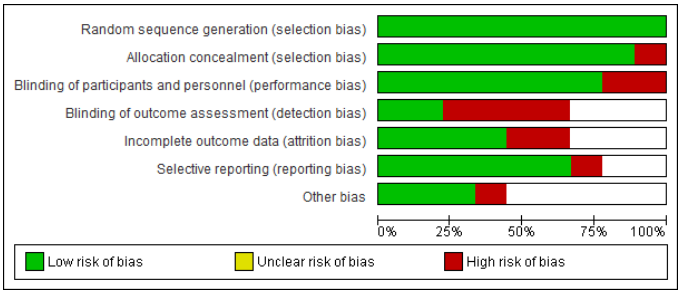

Figure 2: Risk of bias graph: this is a review of authors' judgments of the risk of bias item presented as (percentages)

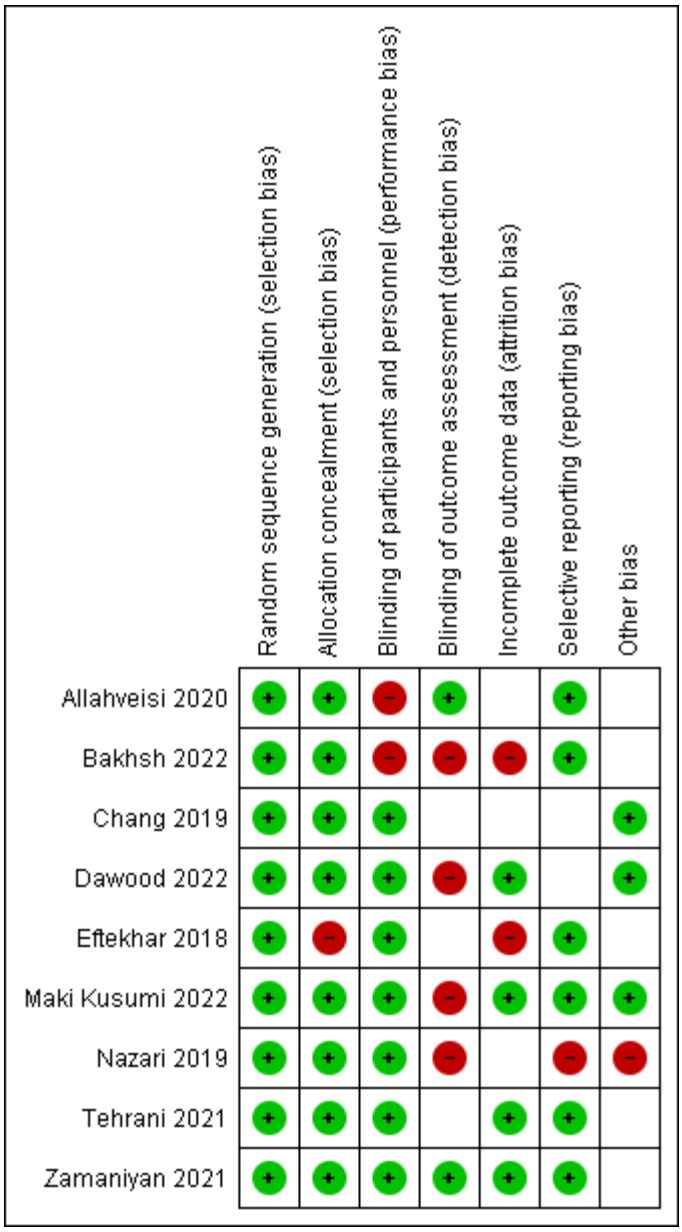

Figure 3: This show the risk of bias summary

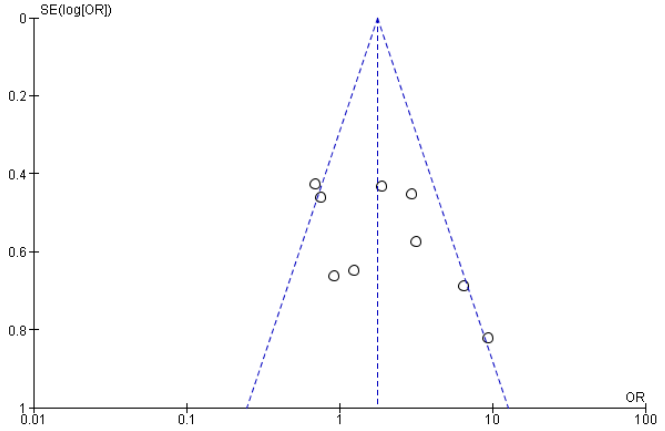

Figure 4: Funnel plot of comparison: PRP X NONE, outcome (pregnant)

Table 2: Age comparison of the mean SD age of Patients treated with PRP and control

Study/Year	Mean	SD	PRP	Mean	SD	Control	95% CI	Sig. level
1. Allahveisi 2020	33.8	0.54	25	33.0	0.9	25	-1.2221 to -0.3779	P = 0.0004*
2. Chang 2019	34.7	0.75	34	32.6	1.76	30	-2.7621 to -1.4379	P=<0.0001*
3 Dawood 2022	30.52	3.381	52	29.6	2.99	52	-2.1615 to 0.3215	P = 0.1447
4. Eftekhar 2018	31.9	2.26	40	32.4	2.63	43	-0.5747 to 1.5747	P = 0.3574
5. Maki Kusumi 2022	39.7	3.0	39	39.7	3.2	36	1.4268 to 1.4268	P = 1.0000
6. Nazari 2019	33.9	2.76	30	32.3	0.973	30	-2.6695 to -0.5305	P=0.004 *
7 Tehrani 2021	32.9	3.0	42	33.5	2.5	43	0.5902 to 1.7902	P = 0.3189
8. Zamaniyan 2021	33.88	6.323	55	33.31	5.0	43	-2.8836 to 1.7436	P = 0.6259
Total			317			302		

In the analysis of all the above studies, (13,14,17,18,19,20,21.22. and 23) ,.the number of patients included was 619; 317 were treated with PRP, and 302 were the control. When comparing the mean of age ± stander deviation only in three studies, showed difference which was statistically significant (1, 2, and 6)

*Statistically significant.

Table 3: BMI comparison of the mean SD age of Patients treated with PRP and control

Study/Year	Mean	SD	PRP	Mean	SD	Control	95% CI	Sig. level
1. Allahveisi 2020	25.76	0.76	25	25.96	0.54	25	-0.1749 to 0.5749	P = 0.2888
2. Bakhsh 2022	25.3	0.4	50	25.9	0.6	50	0.3976 to 0.8024	P < 0.0001*
3. Chang 2019	22.42	0.42	34	22.39	0.8	30	-0.3440 to 0.2840	P = 0.8492
4. Dawood 2022	25.2	3.2	52	27.65	3.5	52	-1.1456 to 3.7544	P = 0.0003*
5. Maki Kusumi 2022	21.24	2.11	39	21.19	1,90	36	-0.9768 to 0.8768	P = 0.9147
6. Nazari 2019	24.3	2.8	30	25.46	2.68	30	-0.2565 to 2.5765	P = 0.1066
7. Tehrani 2021	26.2	2.8	42	26.3	3.3	43	-1.2218 to 1.4218	P = 0.8808
8..Zamaniyan 2021	26.49	4.43	55	25.03	3.66	43	-3.1211 to 0.2011	P = 0.0842
Total			327			287		

In the analysis of all the above studies, the number of patients included was 617; 327 were treated with PRP, and 287 were the control. When comparing the mean of age ± stander deviation only in three studies, showed difference which was statistically significant (1, 2, and 6)

*Statistically significant.

Forest plots (Figure 5)

All studies: Number of Pregnancy

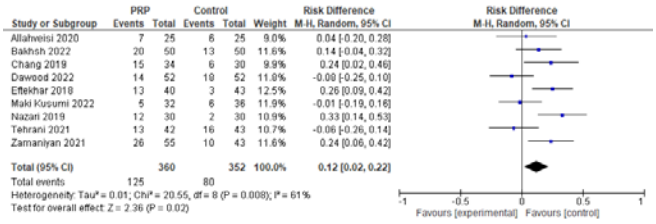

Table 4: Shows the Study/ Year PRP and Control (OR-M-H Random 95% CI)

Study/ Year	Event	PRP	Event	Control	Weight	OR-M-H Random 95% CI
1. Allahveisi 2020	7	25	6	25	9.0%	0.04 [-0.20, 0.28]
2. Bakhsh 2022	20	50	13	50	11.6%	0.14 [-0.04, 0.32]
3. Chang 2019	15	34	6	30	9.9%	0.24 [0.02, 0.46]
4. Dawood 2022	14	52	18	52	11.8%	-0.08 [-0.25, 0.10]
5. Eftekhar 2018	13	40	3	43	12.5%	0.26 [0.09, 0.42]
6. Maki Kusumi 2022	5	32	6	36	11.9%	-0.01 [-0.19, 0.16]
7. Nazari 2019	12	30	2	30	10.9%	0.33 [0.14, 0.53]
8. Tehrani 2021	13	42	16	43	10.7%	-0.06 [-0.26, 0.14]
9. Zamaniyan 2021	26	55	10	43	11.6%	0.24 [0.06, 0.42]
Total (95% CI)		360		352	100.0%	0.12 [0.02, 0.22]
Total events	125		80			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 20.55$, df = 8 (P = 0.008); $I^2 = 61\%$

Test for overall effect: Z = 2.36 (P = 0.02)

Forest plots of the nine studies

The meta-analysis addressed the use of PRP compared with no treatment in infertility (IVF/ICSI). The outcome was the endometrial thickness and pregnancy rate in the studies that were included in the meta-analysis (Figure 4; Table 4).

RR <1 favour positive discrimination use of PRP, whereas RR > 1 suggest that no treatment is better. Left panel, Studies/year of publication. Each study is represented along with the corresponding 95% confidence interval.

Right panel, Cumulative meta-analysis of same studies with the random-effects model, where the summary risk ratio is re-estimated each time a study is added over time. Pooled results from all studies are shown at the bottom with the random-effect model 0.12 (0.02–0.22). All nine studies intersect the vertical line of unity (RR=1), and six indicate no difference between the PRP group and the control group.

Such cumulative meta-analysis can retrospectively identify the point when a treatment effect first reaches conventional levels of significance.

A cumulative meta-analysis is a compelling way to examine trends in the summary-effect size evolution and to assess the impact of a specific study on the overall conclusions.

The figure shows that nine studies were performed long after cumulative meta-analysis would have shown no significant beneficial effect of PRP on pregnancy rate.

Forest plots (Figure 6)

All studies: Endometrial Thickness

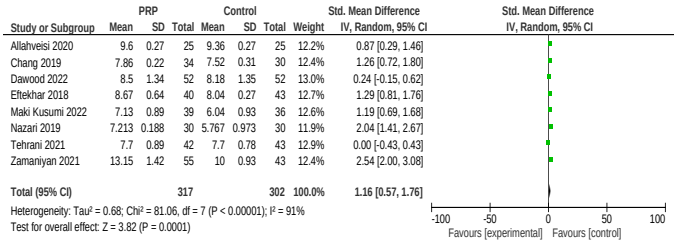

Table 5: Shows the Study/ Year PRP and Control (Std Mean Difference IV, Random 95% CI)

Study/Year	Mean	SD	PRP	Mean	SD	Control	Weight	Std Mean Difference IV, Random 95% CI
1. Allahveisi 2020	9.6	0.27	25	9.36	0.27	25	12.2%	0.87 [0.29, 1.46]
2. Chang 2019	7.86	0.22	34	7.52	0.31	30	12.4%	1.26 [0.72, 1.80]
3. Dawood 2022	8.5	1.34	52	8.18	1.35	52	13.0%	0.24 [-0.15, 0.62]
4. Eftekhar 2018	8.67	0.64	40	8.04	0.27	43	12.7%	1.29 [0.81, 1.76]
5. Maki Kusumi 2022	7.13	0.89	39	6.04	0.93	36	12.6%	1.19 [0.69, 1.68]
6. Nazari 2019	7.213	0.188	30	5.767	0.973	30	11.9%	2.04 [1.41, 2.67]
7. Tehrani 2021	7.7	0.89	42	7.7	0.78	43	12.9%	0.00 [-0.43, 0.43]
8. Zamaniyan 2021	13.15	1.42	55	10.0	0.93	43	12.4%	2.54 [2.00, 3.08]
Total (95% CI)			317			302	100.0%	1.16 [0.57, 1.76]

Heterogeneity: $Tau^2 = 0.68$; $Chi^2 = 81.06$, df = 7 ($P < 0.00001$); $I^2 = 91\%$

Test for overall effect: Z = 3.82 (P = 0.0001)

Right panel, Cumulative meta-analysis of the same analyses with the random-effects model, where the summary risk ratio is re-estimated each time a study is added over time. Pooled results from all studies are shown at the bottom with the random-effect model 1.16 (0.57 - 1.76). All studies intersect the vertical line of unity (RR=1), and nine indicate no difference between the PRP and control groups (Figure 5; Table 5).

The figure shows that nine studies were performed long after cumulative meta-analysis would have shown no significant beneficial effect of endometrial thickness.

Limitations and implications

The number and the quality of published studies available reflect the validity of the results of a meta-analysis. Only RCTs were included in this study. Future large RCTs need to focus on the endometrial thickness and pregnancy rate.

Contributors

A.J and H.H designed the study protocol and performed the search and data extraction. AJ and HH were critical independent reviewers who also contributed to statistical analysis and interpretation of data. N.R and G.K. drafted the manuscript, while H.H critically revised the manuscript.

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Abbreviation

PRP = platelet-rich plasma

IVF/ICSI = In vitro fertilization/intracytoplasmic sperm injection

CPR = clinical pregnancy rate

BMI = body mass index

RCT = Randomized control trail

Discussion

The human endometrium has a crucial role in the embryo implantation process. The measurement of the endometrial thickness is the most commonly used in clinical practice. Managing patients with a thin endometrium still represents a significant challenge for clinicians. 24 Oestrogen, granulocyte colony-stimulating factor, gonadotropins, Clomid, letrozole, sildenafil citrate, pentoxifylline, tocopherol, tamoxifen, and many other medications can be used to treat a thin endometrium. 25 According to the 2019 guidelines of the Canadian Fertility Society, PRP can be used to treat a thin endometrium; however, these guidelines had a weak level of evidence. 26 After the publishing of the guidelines, some RCTs have not been able to prove the effectiveness of PRP, while others have shown no effect. 27 Therefore, a systematic review of PRP for the treatment of a thin endometrium is necessary to study its efficacy and safety. 27 A limitation of this meta-analysis is that the reviewer focused only on articles and research

in the English language. PRP is still a novel procedure in gynaecology and reproductive medicine for treating patients with a thin endometrium. 28

Our meta-analysis review fully describes our search strategy, study selection, data summary, and analysis, exhibiting the sensitivity of all aspects of our approach. We have included every study that, to our knowledge, satisfies our inclusion and exclusion criteria, and used techniques that allow the integration of studies with high heterogeneity. Random-effects models were recommended as they produce study weights that primarily reflect the results.

Several studies support that PRP helps in improving endometrial thickness and pregnancy rate. Our meta-analysis shows that PRP has been utilised to improve endometrial thickness and pregnancy rate in patients with a thin endometrium undergoing IVF/ICSI. Although it is designed for management out lock, which concluded that it is reliable and valid to treat our IVF/ICSI populations with endometrium thickness less than 7.

The study showed that the endometrial thickness and pregnancy OR-M-H random 95% CI was 1.16 [0.57, 1.76] and 0.12 [0.02, 0.22], respectively. We found no differences in endometrial thickness and pregnancy rate in our meta-analysis.

The paper we miss has a critical concern. It is always challenging to obtain all studies that meet the inclusion criteria. This potential loss is concerning because studies with significant, positive results (positive studies) are more likely to be published than those with non-significant or "negative" effects (negative studies). Large studies with positive results are more likely to have been published, while there is usually some reluctance to publish small studies with non-significant results.

Further, publication bias is not solely the responsibility of editorial policies as there is reluctance among researchers to publish results that are either uninteresting or not randomised. However, there are problems with simply including all studies that have failed to meet peer-review standards.

It is vital to examine the results of each meta-analysis for evidence of publication bias. An estimation of the likely size of the publication bias in the review and an approach to dealing with such bias is inherent to the conduct of many meta-analyses. The most commonly used method for assessing bias is the funnel plot. The funnel plot provides a graphical evaluation of the potential for bias. 29

A funnel plot is a graph of the treatment effect against study size. If publication bias is not present, the plot is expected to have an asymmetric inverted funnel shape.

In a study with no publication bias, larger studies cluster close to the point estimate. There is evidence of the possibility that studies with smaller numbers of subjects and those that show a decrease in effect size (lower odds ratio) were not published. Asymmetry of funnel plots may result from clinical heterogeneity among studies.

Differences in control or exposure of subjects can lead to heterogeneity in the effects of modifiers or methodological heterogeneity between studies, such as a failure to conceal treatment allocation.

There are several statistical tests for detecting funnel plot asymmetry, such as the Eggers linear regression test and Begg's rank correlation test, but these are rarely used and do not have considerable power. 30, 31 However, the funnel plot is not without problems. Depending on the scale of the y axis, the appearance of the funnel plot can be different.

Other types of biases in meta-analysis include the time lag bias, selective reporting bias, and language bias. The time lag bias arises when studies with striking results are published earlier than those with non-significant findings.

Moreover, it has been shown that positive studies with high early accrual of patients are published sooner than negative trials with low early accrual. However, either due to publication bias or time lag bias, missing studies may increasingly be identified from trial registries. Selective reporting bias exists when published articles have incomplete or inadequate reports. Empirical studies have shown that this bias is widespread and essential when published studies compare their study protocols.

Furthermore, recent evidence suggests that selective reporting may be an issue in safety outcomes, and the reporting of harm in clinical trials is still suboptimal. Therefore, it might not be possible to use quantitative objective evidence for harm in performing meta-analyses and making therapeutic decisions.

Conclusions

Intrauterine instillation of autologous platelet-rich plasma does not improve pregnancy rate or endometrial thickness in patients who underwent IVF embryo transfer. This meta-analysis included a RCT. All practitioners who prefer to use the PRP cycle should discontinue this practice until further large RCTs are performed to address whether PRP should be used.

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