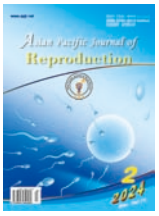

Meta-Analysis

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Efficacy of intraovarian autologous platelet-rich plasma administration in women with low ovarian reserve: A systematic review and meta-analysis

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ABSTRACT

Objective: To conduct a systematic examination and meta-analysis of the most reliable data from experimental studies evaluating the efficacy of autologous platelet-rich plasma (PRP) on low ovarian reserve.

Methods: A comprehensive search was performed utilizing pertinent search terms across electronic databases, including PubMed, Cochrane, and Google Scholar. We included studies that assigned infertile women with low ovarian reserve in experimental studies. Ovarian reserve parameters were measured before and after PRP injection into ovaries. The data of each study was retrieved and subsequently compiled.

Results: Of 301 articles collected and reviewed, six studies were finally included in the meta-analysis. Following PRP injection, infertile women showed a non-significant increase in anti-Mullerian hormone (AMH) level (MD=0.10; 95% *CI* -0.04, 0.23), a significant increase in antral follicular count (AFC) (MD=1.88; 95% *CI* 0.47, 3.29), and a non-significant reduction in follicle-stimulating hormone (FSH) level (MD=-0.22; 95% *CI* -8.32, 7.87).

Conclusions: Autologous PRP may increase AFC, but not AMH. Although it is found beneficial in enhancing ovarian reserve (AFC), further research with strong evidence is still required.

KEYWORDS: Platelet-rich plasma; Low ovarian reserve; Ovarian rejuvenation

1. Introduction

These days, ovarian insufficiency is linked to a significant number of infertility cases, which can result from a variety of causes, such as genetic predisposition, obstructive disorders, and environmental factors[1]. Approaches to repair and rejuvenate fertility in women with low ovarian reserve are being studied, including platelet-rich plasma (PRP) therapy, due to predisposition, obstructive disorders, and environmental factors[2–4]. PRP is considered to be one of the most promising autologous substances, and it has been widely researched and used in various medical fields due to its remarkable healing properties[5]. PRP was first implemented in sports medicine and has grown to encompass numerous medical specialties, including skin rejuvenation, cartilage repair, and autoimmune disorders[6]. Higher concentrations of autologous growth factors and secretory proteins in PRP improve the recruitment, differentiation, proliferation, angiogenesis, and chemotaxis of cells involved in tissue regeneration[7]. PRP therapy is used to promote and accelerate recovery from injuries, inflammation, and other conditions. It is considered a minimally invasive and relatively safe procedure, as it utilises the patient's own blood components[6,7]. PRP is expected to favor ovarian reserve, a portion of regeneration and repair processes in somatic tissues. It has been hypothesized that the use of PRP in infertility treatment can influence follicle maturation and potential improvements to the follicular milieu[2,9]. Growth factors influence ovarian stem cells throughout the postnatal oogenesis phase[4]. Growth factors secreted by platelets can restore a depleted follicle reservoir by stimulating germline stem cells to differentiate into primordial follicles[3]. Granulose cells contain growth factor receptors, indicating a connection between these cells and stimulating the primordial follicles[3].

Since definitive clinical evidence to confirm its efficacy has not yet been established, the use of ovarian PRP treatment is too new to be extensively implemented. In the context of ovarian PRP treatment, PRP is still considered experimental and investigational.

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It is primarily being explored as a potential option for women with certain reproductive issues. It is important to note that the efficacy and safety of ovarian PRP treatment have not been fully established, and more research is needed to determine its potential benefits and risks. There is currently little clinical research assessing the effects of PRP therapy on ovarian rejuvenation and fertility enhancement, and the majority of the evidence that is available is derived from small-scale observational studies. Currently, few clinical research assessing the effects of PRP therapy on ovarian rejuvenation and fertility enhancement, and the majority of the evidence that is available is derived from small-scale observational studies.

Therefore, the purpose of this study was to conduct a systematic review and meta-analysis of the most reliable data from experimental studies assessing the efficacy of autologous PRP in managing women with low ovarian reserve.

2. Materials and methods

2.1. Protocol

Systematic searches in electronic databases, including PubMed, Cochrane, and Google Scholar, use relevant search terms. We included studies that assigned infertile women with low ovarian reserve to experimental studies, and ovarian reserve parameters were measured before and after PRP injection into ovaries.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions recommendations. This research was registered under the CRD42023459530 registration number in the PROSPERO International Prospective Register of Systematic Reviews.

2.2. Eligibility criteria

We included studies in our review if they satisfied the subsequent criteria: i) experimental studies, including women with medically confirmed low ovarian reserve; ii) the intervention was PRP injected intraovarian; and iii) ovarian reserve as the primary outcome.

Exclusion criteria were as follows: (i) non-experimental studies (cross-sectional studies, case series, cohort studies, and case-control studies): (ii) women without infertility disorders: (iii) non-English language: and (iv) studies conducted in animals and cell culture studies.

Studies were excluded from our analysis too if we were unable to get their complete texts or sufficient information regarding their methodology or findings. Research studies were omitted from consideration if there were no available, extractable, recorded follow-up data, or if the authors failed to respond. An email was sent to the relevant author requesting clarification; in the absence of a response, the data sets were omitted.

2.3. Sources and search strategies

For this systematic review, the Population, Intervention, Comparison, and Outcome (PICO) parts were used as inclusion criteria: (i) Population: women with infertility, low ovarian reserve; (ii) Intervention: autologous PRP intra-ovarian injection; (iii) Comparison: before-after treatment; (iv) Primary outcomes: ovarian reserve. The primary search for identifying suitable studies was performed in the electronic databases Google Scholar, PubMed, and Cochrane, the year of publication was unrestricted, and using the following search strings: "ovarian reserve" OR "ovarium" OR "ovarii" OR "ovary" OR "ovaries" OR "low ovarian reserve" AND "plasma, platelet rich" OR "platelet-rich plasma" OR "trombosit rich plasma" OR "platelet-rich growth factor" OR "platelet rich fibrin" OR "platelet rich fibrin matrix" OR "platelet concentrate "OR "PRF" OR "PRP".

A manual search of the literature has also been conducted. The year of publication in the literature search, both electronic and manual, were limited to 30 November 2022.

2.4. Study selection process

Two reviewers completed the primary investigation independently. Consultation with an investigator resolved any discrepancies. All reviewers selected the sources or evidence included in this systematic review. Two authors assessed the titles and abstracts of the electronic searches following the qualifying criteria. Full articles were retrieved for further assessment and analysis if the reviewer considered the studies relevant. After evaluation, the study was discussed with the third reviewer if there were any questions about its inclusion.

2.5. Data synthesis and charting process

All eligible studies underwent an independent review by two researchers. The following data have been extracted and documented: (i) author, (ii) year of publication, (iii) country in which the study was conducted, (iv) study duration, (v) total number of participants, (vi) aetiology of infertility, (vii) dose and duration of autologous PRP intra-ovarian injection, (viii) type of comparison, and (ix) primary and secondary outcomes.

The complete articles were obtained for additional investigation if the reviewers deemed the study pertinent. The results were extracted from every eligible paper and verified by two reviewers. When there was any doubt concerning the study's inclusion, it was evaluated and discussed with the third reviewer. The extracted data were immediately abstracted on a standardized electronic abstraction form previously established.

The quality of each study was evaluated using the "Cochrane's Collaboration technique for assessing the risk of bias". According to the Cochrane Handbook's advice, the methodological quality of trials was evaluated using the risk of bias 2 (RoB 2). These

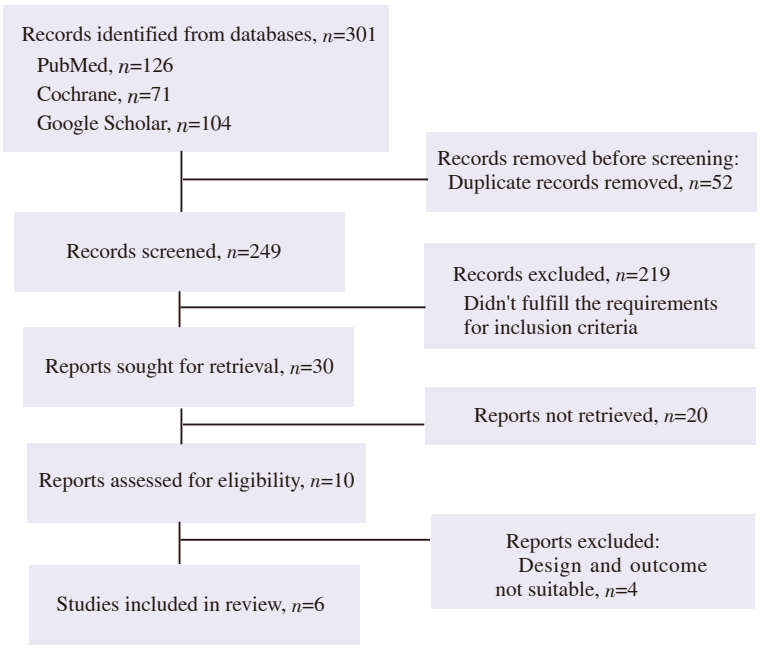


Figure 1. Flowchart of the literature search and selection of study.

involved assessments of the randomization procedure, departures from the intended intervention, incomplete or missing outcome data, measurement of the outcome, and selection of the reported result.

2.6. Statistical analysis

All analyses were done with the Rstudio version 2023.06.1 software. The heterogeneity of the studies was assessed with forest plots by Tau^2 and I^2 values. I^2 concentrations ranging from 30% to 60% were considered moderate, whereas values beyond 60% indicated highly significant heterogeneity.

The random effects model was used for data synthesis when I^2>30%[8]. Associations were reported as mean differences (MD) with 95% confidence intervals (*CI*s). A *P*-value of < 0.05 was considered statistically significant[8].

We extracted the included studies according to treatment strata for each endpoint in the PRP before and after intraovarian injection and computed the MD and standard deviation (SD) with the appropriate 95% *CI*. Analyses were conducted to determine how PRP performed compared to before and after interventions on ovarian reserve, such as anti-Mullerian hormone (AMH), follicle-stimulating hormone (FSH), and antral follicular count (AFC).

3. Results

3.1. Selection sources of evidence

Three hundred-one publications were discovered during the initial electronic literature search (71 from the Cochrane Central Register of Controlled Trials, 104 from Google Scholar, and 126 from PubMed). To identify the 52 duplications, every citation was entered into the reference manager Endnote. The titles and abstracts of these citations were examined to weed out unrelated works. Two hundred nineteen studies were eliminated, and 20 studies were reported but could not be retrieved. Four reports were excluded due to different designs and outcomes. Six studies of those studies were included in the review[2,9–13]. Figure 1 depicts the literature search and study selection process flow.

3.2. Study characteristics and data extraction of the included studies

Six studies were included in this systematic review. The primary features of the included studies are described in Table 1. The research was done between 2019 and 2022. The research was done in Iran twice[11,12], Iraq once[9], Turkey once[2], the USA once[13], and Bangladesh once[10]. Every study was an experimental study (clinical trials[2,9,11–13] and quasi-experimental[10]). Women with low/poor ovarian reserve, poor ovarian response (POR), poor ovarian insufficiency (POI), and menopause are the populations of this research. Studies by Aflatoonian *et al* are divided into subgroups: POR and POI[11]. The number of participants in the sample ranges from 20 to 140. In four of these investigations, PRP was injected into unilateral/bilateral ovaries transvaginally (1-3 mL)[2,9,12,13]. In two studies, PRP was injected into unilateral/bilateral ovaries (2–5 mL)[10,11].

Table 1. Studies include women with infertility and low/poor ovarian reserve.

Author/Publication year	Country	Study design	Study population	Sample size (*n*)	Intervention	Duration (months)	Outcome measures
Navali *et al*, 2022[12]	Iran	Clinical trials	Poor ovarian responders (POR)	35	2 mL PRP injected into the cortex both ovaries, transvaginal	2	AMH, FSH, AFC, FSH/LH ratio, estradiol, MII oocytes, embryos, spontaneous pregnancy
Sills *et al*, 2020[13]	USA	Clinical trials	Low ovarian reserve, 1 failed IVF	134	1 mL of activated PRP injected into unilateral/bilateral ovaries, transvaginal	3	AMH, platelet count, FSH, estradiol
Abdullah *et al*, 2019[9]	Iraq	Clinical trials	Poor ovarian reserve: Poor ovarian insufficiency (POI), poor ovarian response (POR), menopause	30	2.5 mL PRP injected into both ovaries, transvaginal	1	AMH, FSH, AFC, ovarian volume
Aflatoonian *et al*, 2021[11]	Iran	Clinical trials	Poor ovarian insufficiency (POI, *n*=9), poor ovarian response (POR, *n*=17)	26	1.5 mL (1st month) and 3 mL (2nd, 3rd month) of activated PRP injected into both ovaries, transvaginal	3	AMH, FSH, LH, Estradiol, menstrual cycle, miscarriage rate, pregnancy rate
Gürkan *et al*, 2022[2]	Turkey	Clinical trials	Poor ovarian reserve	40	2 mL PRP injected into unilateral/ bilateral ovaries	2	AMH, FSH, AFC
Uddin *et al*, 2022[10]	Bangladesh	Quasi-experimental	Poor ovarian reserve	23	5 mL PRP injected into both ovaries per laparoscopy	3	AMH, AFC

PRP: platelet-rich plasma.

3.3. Risk of bias assessment

Figure 2 displays a summary of the risk of bias evaluations. According to the assessment, the studies have minimal risk of bias. Two studies were evaluated with minimal risk of bias, whereas four studies were evaluated with low risk of bias. The risk of bias for missing outcome data was rated as minimal for each study.

3.4. Synthesis of results

3.4.1. FSH level

Results from 5 studies, which compared FSH levels before and after PRP infusion, including 268 participants, showed there was a non-significant reduction in FSH level (MD=-0.22; 95% *CI* -8.32, 7.87; I^2=99%, *P*<0.01) (Figure 3).

3.4.2. AMH

Results from 6 studies, which compared AMH levels before and after PRP infusion, including 291 participants, showed there was no significant increase in AMH level (MD=0.10; 95% *CI* -0.04, 0.23; I^2=98%, *P*<0.01). Forest plot of the AMH level before and after autologous platelet-rich plasma administration (Figure 4).

3.4.3. AFC

Results from 3 studies, which compared AFC levels before and after PRP infusion, including 93 participants, showed there was a significant increase in AFC (MD=1.88, 95% *CI* 0.47, 3.29; I^2=94%, *P*<0.01) (Figure 5).

3.5. Publication bias

Funnel plots were used to examine the potential presence of publication bias. All the funnel plots in this meta-analysis were asymmetrical, indicating the potential publication bias in the included studies could not be excluded.

As shown in Figure 6A, the funnel plot for the FSH before and after PRP administration was asymmetric. The funnel plot for the AMH before and after PRP administration was asymmetric, as each point was scattered in Figure 6B. The funnel plot for the AFC before and after PRP administration was asymmetric., as shown in Figure 6C.

4. Discussion

One prominent factor contributing to female infertility is inadequate/low ovarian reserve. Despite undergoing *in vitro* fertilization (IVF) and other infertility treatments, some women continue to experience suboptimal rates of pregnancy success and recurrent miscarriages. Women going through perimenopause or postmenopause, diminished

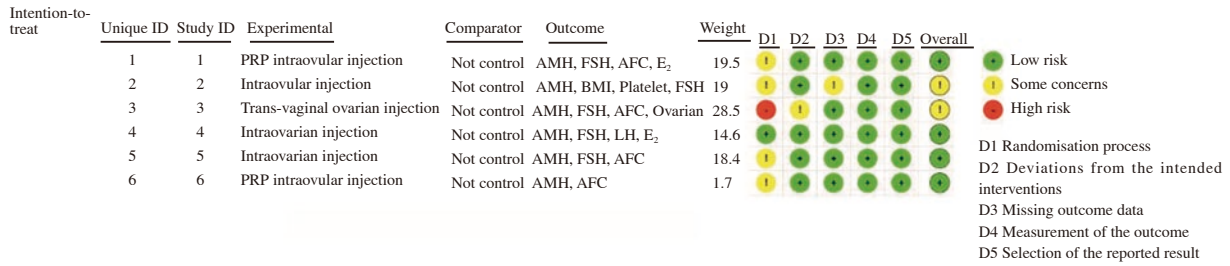
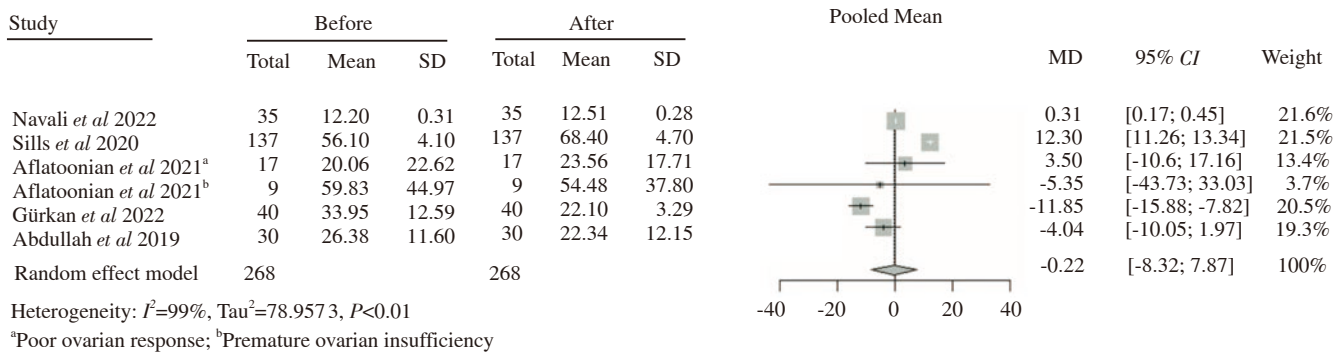


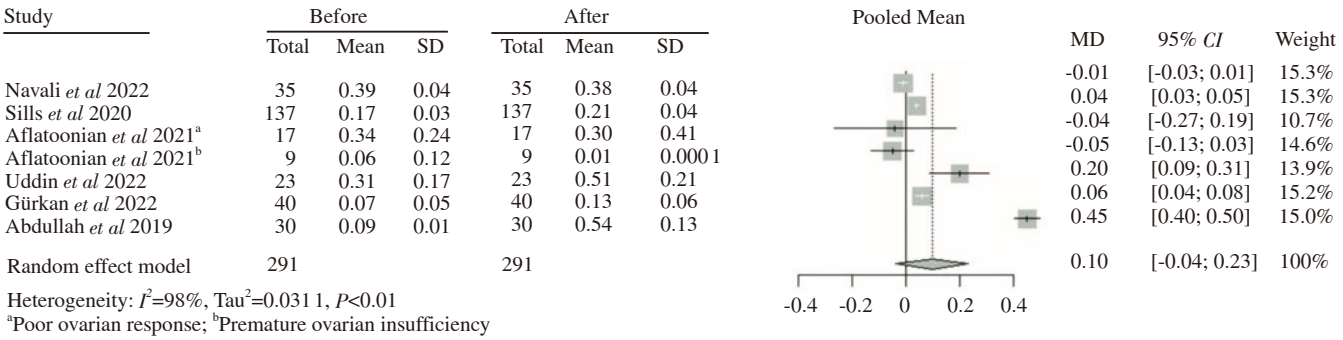
Figure 2. Risk of bias assessment.



Heterogeneity: I^2=99%, Tau^2=78.957 3, P<0.01

[a]Poor ovarian response; [b]Premature ovarian insufficiency

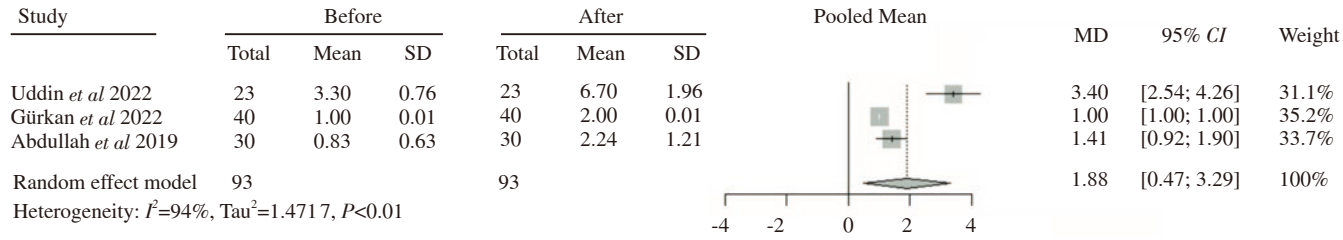
Figure 3. Forest plot of follicle-stimulating hormone (FSH) level before and after autologous platelet-rich plasma administration.



Heterogeneity: I^2=98%, Tau^2=0.031 1, P<0.01

[a]Poor ovarian response; [b]Premature ovarian insufficiency

Figure 4. Forest plot of anti-Mullerian hormone (AMH) level before and after autologous platelet-rich plasma administration.



Heterogeneity: I^2=94%, Tau^2=1.471 7, P<0.01

Figure 5. Forest plot of antral follicle count (AFC) before and after autologous platelet-rich plasma administration.

ovarian reserve, poor ovarian insufficiency, and poor responders to assisted reproduction treatment (ART) have become a focus of scientific investigation. To identify the factors that can enhance the ovarian reserve toward women's infertility, various attempts have been conducted. PRP, which has garnered interest in reproductive medicine, specifically in the treatment of infertility, is one such treatment that has demonstrated considerable promise and has been implemented across various medical specialties.

Numerous studies have confirmed the usage of PRP; there are pros and cons regarding the use of PRP. While the exact mechanisms through which PRP induced this enhancement remain elusive, prior experimental inquiries have shown that the elevated concentration of

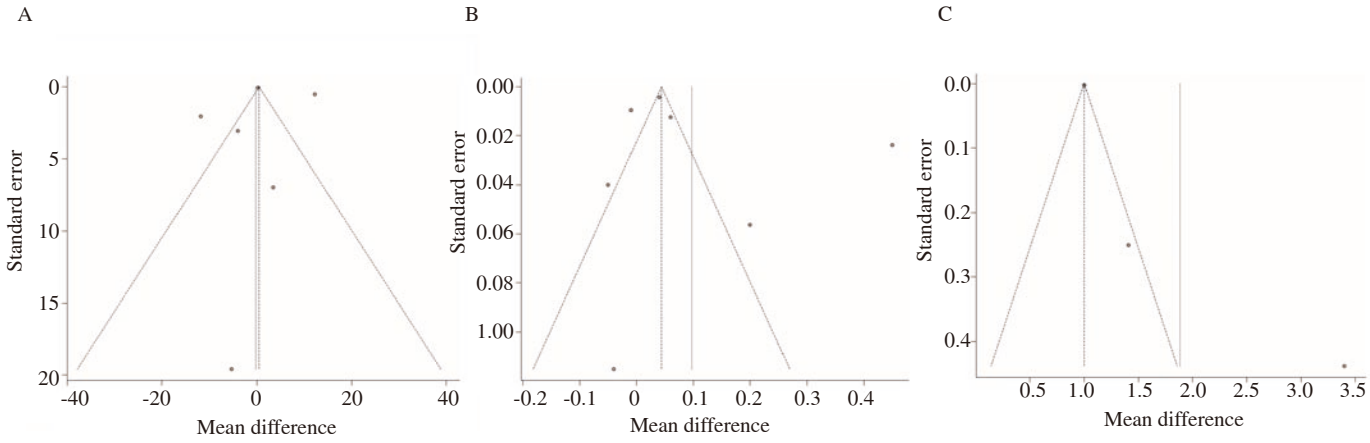


Figure 6. Funnel plot of FSH (A), AMH (B), AFC (C) before and after autologous platelet rich plasma administration.

growth-promoting elements in PRP might inhibit inflammation and infection, promote osteogenesis, surgical blood loss, and expedite the healing process[5,16]. PRP derives its healing and regenerative properties from the high amounts of growth factors discovered in platelet granules, including epidermal growth factor (EGF), insulin-like growth factors (IGF-1 and IGF-2), fibroblast growth factor (FGF), transforming growth factor (TGF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF)[17]. By initiating the ensuing phases of resolution, chemotaxis, cell regeneration, migration, and proliferation of cells; extracellular matrix formation, remodelling, epithelialization, and angiogenesis —growth factors facilitate the healing of wounds[9].

Growth differentiation factor 9 (GDF-9), an important PRP factor generated from oocytes, is associated with an increase in the quantity of primary and preantral follicles and is crucial for oocyte maturation. Additionally, the *GDF-9* gene mutation causes early ovarian failure[18]. Conversely, postmenopausal women's ovaries can produce new primordial follicles when PRP is injected into the ovary and activates and stimulates GnRH receptors[12].

AMH and transvaginal sonographic assessment of AFC are ovarian reserve indicators that are largely established. The granulosa cells of the preantral and small antral follicles release AMH[10]. Examining how PRP injection affects ovarian reserve has been the subject of several investigations. Navali *et al* reported that a single PRP injection is effective in patients with POR to conceive with their oocytes (two months of follow-up). The research findings indicated a statistically significant increase in both the quantity of oocytes (3.68±0.24, *P*=0.004 3) and embryos (3.17±0.14, *P*=0.000 1), in addition to estradiol concentrations (404.1±16.76 *vs.* 237.7±13.14, *P*=0.000 3)[12]. Meanwhile, Sills *et al* performed PRP injection into ovarian tissue measured at 4-week intervals for up to three months. After treatment, significant AMH improvements were seen in stratified age groups (*P*=0.03 and 0.009, respectively)[13].

Stojkovska *et al* found that after one month of 3-5 mL PRP intracortical ovarian injection, the ovarian reserve of women with POR improved significantly. The serum concentration of AMH was significantly elevated, and the number of AFC after applying PRP significantly increased. In a prior study, Melo *et al* discovered that women who received PRP treatment exhibited a noteworthy enhancement in FSH, AMH, and AFC at the three-month follow-up. Additionally, total rates of biochemical pregnancy (26.1% *versus* 5.4%, *P*=0.02) and clinical pregnancy (23.9% *versus* 5.4%, *P*=0.03) were higher in the PRP group. However, the frequencies of live births and miscarriages in the first trimester did not differ between the groups[19].

On the contrary, Aflatoonian *et al* reported that AMH and estradiol (E_2) concentrations and FSH and luteinizing hormone (LH) levels did not alter significantly in the POI and POR groups for two consecutive months following PRP injection[11]. Menstruation recovery was observed in 22.2% of women with POI after the second PRP injection; however, no cases of pregnancy were reported[11].

We conducted this meta-analysis to comprehensively examine the most reliable evidence from experimental studies (including clinical trials and quasi-experimental studies) that assess the effects of autologous PRP on ovarian reserve that is low or nonexistent. The findings demonstrated that PRP enhanced ovarian reserve (a significant increase in AFC). PRP injection did not result in a statistically significant elevation in AMH or a decreased FSH.

This meta-analysis demonstrates that following an intraovarian PRP administration, the AFC significantly increased to 1.88, nearly twice as high as before. Basic fibroblast growth factor (bFGF), insulin-like growth factors (IGF 1 and 2), transforming growth factor-beta (TGF-β) and epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) are specific cytokines and growth factors in PRP. These factors stimulated the ovaries and increased vascularity and angiogenesis[9]. One plausible hypothesis to account for some of the beneficial outcomes associated with PRP injection is that the VEGF contains induced neoangiogenic processes and vascular stimulation in the ovaries. To control angiogenesis and tissue perfusion, mediators must be used. The compounds found in PRP can tell

uncommitted ovarian stem cells how to develop into *de novo* oocytes or stimulate dormant oocytes[20]. The proliferation of mesenchymal and progenitor stem cells is notably impacted by growth factors (GFs) present in PRP, including bone morphogenetic protein (BMP-2, BMP-4) and growth differentiation factors (GDF)-5[18]. GFs that are mitogenic, such as bFGF and VEGF, help vascularize the granulosa and enable the early corpus luteum to function[21]. It has been proposed that stem cells help enhance the ovarian milieu and stimulate the ovarian reserve. PRP will probably encourage pre-existing follicles to grow or prevent them from atrophying[22].

Despite the promising prospects this innovative strategy has for reproductive health, this therapeutic decision should be tailored to the specific needs of subgroups of infertile women who differ in age, hormonal composition, and hormonal profile.

The strength of this meta-analysis is that the efficacy of intra-ovarian administration of autologous PRP in women with low ovarian reserve is evaluated in systematic study. There are some limitations in this study. The heterogeneity in the analyses between studies was observed to be high. There are a small number of samples and differences in protocols for the dosage and time interval of PRP's administration. This might have affected the accuracy and dependability of our findings. Clinical pregnancy rate, miscarriage rate, chemical pregnancy rate, and live birth rate are pregnancy parameters that have not been assessed in most studies. No randomized controlled trial (RCT) was included in the analyses.

In conclusion, AFC may be increased by autologous PRP, but not AMH, and no FSH reduction was observed. Even though it was discovered to be beneficial in boosting ovarian reserve and helpful for rejuvenation, more conclusive study is still needed.

To ensure consistent and accurate outcomes and the most significant potential benefit in the future, it is necessary to determine the ideal dosage and time interval (standardized protocol) for autologous PRP administration into ovaries. Furthermore, our study's promising outcome has established a foundation for implementing future systematic, randomized controlled trials.

As a result, more exhaustive systematic review and meta-analysis of this association were required. Autologous PRP use should be considered experimental until conclusive major RCTs are available.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

Yasmin Sabina Sa'diah and Agung Dewanto designed the study and guided the methodology. Yasmin Sabina Sa'diah and Lukman A Chandra were responsible for searching, selecting, and extracting data and wrote the first draft. Yasmin Sabina Sa'diah, Agung Dewanto and Lukman A Chandra reviewed and discussed the manuscript. All authors approve and are responsible for publication.

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