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A Comprehensive Literature Review Examining the Efficacy of Autologous Intra-Ovarian Platelet-Rich Plasma in Women Diagnosed with Primary Ovarian Insufficiency (POI) and Diminished Ovarian Reserve (DOR) and its Impact on Assisted Reproductive Technology (ART) Outcomes

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Abstract

Background: *This extensive literature review examines the potency of autologous intra-ovarian platelet rich plasma (PRP) in women diagnosed with primary ovarian insufficiency (POR) and reduced ovarian reserve (DOR). Recent research has investigated PRP as a possible method to help improve ovarian function and improve fertility outcomes for these groups of patients.*

Methods: *A systematic search of medical databases was done in PubMed, Cochrane Library, Embase, and Web of Scopus done to identify relevant studies published from 2014 up to 2024. Inclusion criteria included observation studies, cohort studies and randomized controlled trials. Data extraction focused on changes in ovarian reserve parameters and ART outcomes like pregnancy rates, live birth rates and embryo quality. The studies were assessed for quality using the Newcastle-Ottawa Scale for observational studies and cohort studies and the Cochrane Risk of Bias Tools to assess the bias risk in randomized controlled trials.*

Results: *By using the MeSH terms related to "platelet-rich plasma," "intra-ovarian injection" and "Diminished Ovarian Reserve", several additional relevant keywords were identified. This led to an initial search that produced 297 articles. After applying the criteria for inclusion and exclusion to evaluate these articles for eligibility,10 studies were selected for review which included a total of 1516 women. The papers included 2 randomized controlled trails, 1 retrospective study and 7 prospective studies.*

Discussion: *Intraovarian PRP injections show potential in enhancing ovarian function and outcomes for women with POR and POI, with some studies reporting improvements in ovarian reserve markers and pregnancy rates. However, others indicate limited benefits, highlighting variability in methodologies and*

PRP preparation. Future research should standardize procedures and conduct larger trials to better understand PRP's mechanisms and its impact on long-term reproductive outcomes.

Conclusion: *Intra-ovarian PRP shows promise as a therapeutic option for women with POI and DOR, demonstrating improvements in ovarian reserve parameters and ART outcomes like the rates of clinical pregnancy and live births. However, further large-scale, randomized controlled trails are required to establish its extended duration of efficacy and safety. While encouraging, current evidence suggests that PRP should be considered an experimental treatment requiring additional research before widespread clinical application.*

Keywords: Autologous platelet-rich plasma; PRP; Intraovarian platelet-rich plasma; Primary Ovarian Insufficiency; POI; Diminished Ovarian Reserve; DOR; Artificial reproductive technology; ART.

Introduction

“Infertility is defined as the failure to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse”. In the UK, approximately 1 in 7 couples experience difficulty conceiving (1).

Ovary is referred to as the biological clock that regulates the process of aging of the ovaries in females which involves a gradual decline in both the quality and quantity of oocytes leading to decreased ovarian function (2,3).

In recent times, reproductive medicine has made significant advancements in addressing the difficulties faced by women with diminished ovarian reserve (DOR) and primary ovarian insufficiency (POI). Both these conditions can severely affect a woman’s ability to conceive, often leading to emotional stress and a sense of loss of reproductive potential (4).

POI, also referred to as premature ovarian failure, is characterized by the loss of function of the ovaries prior to the age of forty. It is marked by the absence of menstruation, increased levels of gonadotropins, and low estradiol levels (5). The incidence of POI is estimated to be 1% in women under 40 years of age and 0.1% in women under 30. The prevalence increases with age, impacting around 1 in 10,000 women by age 20, 1 in 1,000 by age 30, and 1 in 100 by age 40 (6). POI can have devastating consequences for women's reproductive potential and overall health, including increased risks of osteoporosis, cardiovascular disease, and cognitive decline (7).

DOR, on the other hand, refers to reduced quality and number of oocytes in women of childbearing age. While not as severe as POI, DOR significantly impacts fertility and ART outcomes. The estimated prevalence of DOR is around 10% in women seeking fertility treatment (8). However, the exact incidence is challenging to determine due to variations in the criteria for diagnosis and the gradual nature of ovarian reserve decline.

Women with these conditions often experience poor response to ovarian stimulation, reduced oocyte yield, lower quality embryos, and decreased pregnancy rates (9). Currently, the primary treatment choice for women with POI is oocyte donation (10).

Autologous intraovarian PRP has recently come up as a promising treatment for ovarian rejunuvation in women diagnosed with POI and DOR who desires to conceive with their own egg .PRP, which is obtained from the patient's own blood, is a concentrated source of platelets that includes various growth factors like fibroblast growth factor (FGF)platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF) and cytokines that help in tissue regeneration and neovascularization. PRP is being used in cases of ovarian insufficiency due to its potential to stimulate folliculogenesis, improve ovarian blood supply and activate the dormant follicles (11). A key characteristic feature of PRP is its potential ability to promote the repair of tissues without causing inflammatory responses due to the presence of anti-inflammatory substances like Hepatocyte growth factor (HGF) (12).

The idea of PRP originated in the field of haematology during the 1970s, initially being used as a transfusion solution for patients with thrombocytopenia. Over time, its use has been widened to include several medical specialties, such as skin regeneration, management of autoimmune disease and in hair loss therapy (13).The use of PRP to enhance ovarian function first started in Greece which was demonstrated with a study involving eight perimenopausal women who were investigated on the impact of autologous PRP treatment on ovarian rejunuvation. The findings showed that menstrual cycles were restored, oocytes retrievals were successful and potential activation of dormant primordial follicles which was due to the property of PRP in promoting angiogenesis and provide essential growth factors required for tissue regeneration and reactivation of folliculogenesis (14).

Autologous PRP is prepared by collecting a person's whole blood through a puncture in a peripheral vein, which is subsequently processed in a lab to separate the red blood cells from the plasma (15). The aim is to create a platelet sample that is highly concentrated, containing growth factors released by activated platelets at levels that are 5 to 10 times greater than normal. The standard procedure for preparing PRP involves several stages: initially collecting whole blood, followed by an initial centrifugation to separate and remove red blood cells. A subsequent centrifugation is then performed to further increase the platelet concentration. Finally, the PRP is activated by introducing a platelet agonist (16). Figure 1 shows the preparation and intra-ovarian injection of PRP.

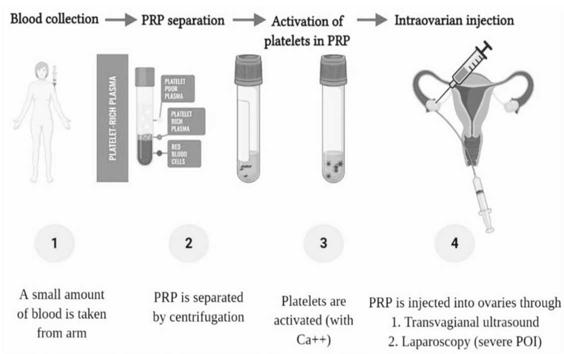

Figure 1: PRP preparation and intra-ovarian injection (Vo, Tanaka, and Kawamura, 2021)

There are several techniques for processing whole blood to extract PRP (17). The speed and duration of centrifugation, as well as the separation techniques, can vary. Once PRP is prepared, it is chemically activated, if necessary, to trigger the release of growth factors. When the soft tissue is injected with PRP, it activates naturally due to the collagen already present in the tissue (18). Additionally, the mechanical stress from centrifugation can also help activate the platelets. Chemical activation involves using agents like calcium chloride, calcium gluconate, or anticoagulants such as thrombin (19).

Some practitioners administer a single PRP injection directly into the ovarian cortex, while others prefer to give several injections in the same region. It is believed that PRP achieves its maximum effectiveness around three months after the injection, as this is the duration for pre- antral follicles to develop into antral follicles. Also, significant effects have been observed even before this three-month period, suggesting that PRP may also affect the antral follicles that are already present (20).

Multiple studies have investigated the effects of intra-ovarian PRP injections. on women diagnosed with POI and DOR. In a case series by Pantos et al. (2019), improvements in hormone levels and successful pregnancies were observed in women with POI following treatment with PRP (22). A larger study by Sfakianoudis et al. (2020), which involved 30 women with POI, showed significant increase in AMH levels and antral follicle counts following the administration of PRP injections (23).

In a study on DOR, Agarwal et al. (2023) found that poor responders undergoing IVF had improved ovarian responses and increased pregnancy rates after receiving PRP treatment (24). Similarly, Cakiroglu et al. (2022) noted that women with DOR showed higher AMH levels and greater oocyte yields after treatment with intra-ovarian PRP injections (25).

The purpose of this literature review was to collect all related clinical data regarding the impact of PRP treatment on ovaries and to present the findings. The research question being investigated is:

1. The efficacy of platelet rich plasma in women with diminished ovarian reserve or primary ovarian insufficiency.
2. How does PRP treated ovarian rejunuvation affect the ART procedure outcomes.

However, it is important to understand that most of the studies on PRP for ovarian rejunuvation are observational studies involving sample sizes that are small and short follow-up periods. The lack of randomized controlled trials (RCTs) and standardized protocols for preparation and administration of PRP makes it difficult to reach a conclusion regarding its effectiveness.

METHODS

Search Strategy:

The literature search was done in databases such as PubMed, Cochrane Library, Embase, and Scopus. The MeSH keywords used, included “Autologous Platelet-Rich Plasma,” “Platelet-Rich Plasma,” “Diminished Ovarian Reserve,” “DOR,” “Premature Ovarian Insufficiency,” “POI,” “Assisted Reproductive Technology,” “ART,” “Intracytoplasmic Sperm Injection,” “ICSI,” “In Vitro Fertilization,” “IVF.” Boolean operators (AND, OR) were used to improve the selection of articles.

Inclusion and Exclusion Criteria:

The review has included all research articles that investigated the outcomes of intraovarian PRP injection in women with diminished ovarian reserve (DOR) or primary ovarian insufficiency (POI), as well as any review articles relating to intraovarian platelet-rich plasma. Only studies published between 2014 and 2024 has been taken into account. On the other hand, the exclusion criteria have ruled out case series, case reports, and animal studies, along with any research that does not specifically address the use of autologous intraovarian PRP in relation to DOR or POI. Additionally, studies not published in English and those that required payment has also been excluded.

Study Selection:

An independent evaluation was done of the titles and abstracts of articles identified through the search method, following the established inclusion criteria. Since this review is part of an MCh Surgery dissertation, no other author was involved. Various database search was done through institutional access to retrieve the articles, although some studies were not available as full literature. Furthermore, due to the large volume of literature, time constraints, and the fact that it was authored by a single person, the timeframe for included studies was narrowed to only those published from 2014 to 2024.

Data Extraction:

The data collected included various details such as the name of the author, study settings, design, characteristics and number of participants, methods for preparing PRP, follow-up and the results. The outcome measures focused on parameters like basal FSH, basal E2, Serum levels of AMH, antral follicular count, the number of retrieved oocytes , the count of cleavage and high-quality embryos, rates of spontaneous pregnancy and rates of fertilization, cancellations, clinical pregnancies, chemical pregnancies, and live births.

RESULT

Literature search:

The initial electronic search using the MeSH and Boolean words resulted in 297 studies. After removing duplicates and irrelevant studies, 15 potentially eligible articles were identified. Upon reviewing the full texts of these 15 articles,5 articles were excluded. In the end, 10 studies were included in this literature review. Figure 2 presents the flow diagram detailing the literature search and the study selection process.

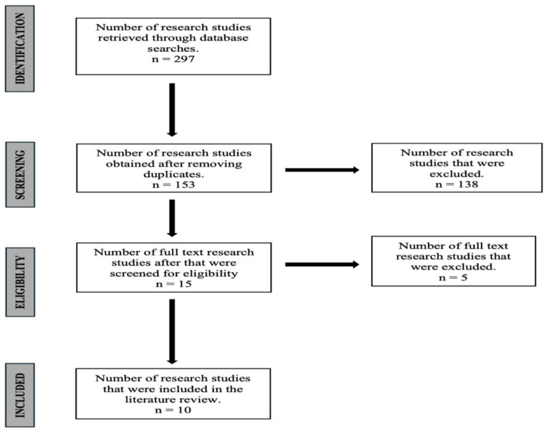

Figure 2: PRISMA flowchart of the selection of studies

Characteristics of the study:

The research papers included in this literature review consists of 2 randomized controlled trails, retrospective study and 7 prospective studies. Tabe 1 summarises the features of the studies included.

No.	Author	Title	Place	Study Design	Level of Evidence	Sample Size	Classification Criteria	PRP Preparation	Outcomes
1.	**Herlihy et al., 2024 [26]**	Effect of intraovarian platelet -rich plasma injection on IVF outcomes in women with poor ovarian response: the PROVA randomized controlled trial	USA, Turkey	Multicentre Randomized Controlled Trial	II	83	-	Blood was collected into two RegenKit -THT-3 tubes and centrifuged at 1500× g for 9 minutes. After mixing the platelets and leukocytes with the plasma, 8 ml of growth factor-rich PRP was obtained	No significant differences in mature oocyte retrieval per cycle, with the PRP group resulting in 2.8 ± 2.4 and the control 3.1 ± 3.3 (P = 0.9). Blastocyst numbers were also similar (PRP: 1.0 ± 1.3, control: 1.3 ± 2.1; P = 0.8), and no differences in AFC or AMH levels were noted

2.	**G Barrenetxea et al., 2024 [27]**	Intraovarian platelet-rich plasma injection and IVF outcomes in patients with poor ovarian response: a double-blind randomized controlled trial		A double-blind randomized controlled trial	II	60	POSEIDON	PRP was prepared during the follicular phase of ovarian stimulation right after blood was collected. A 15 ml blood sample with 0.5 ml anticoagulant was drawn and centrifuged at 200 g for 20 minutes, separating it into three layers. The upper and buffy layers were processed into pellets, mixed with plasma, and stored at 4°C for injection during oocyte retrieval.	Baseline demographics were similar; the treatment group had more retrieved mature oocytes (10.45±0.41 vs. 8.91±0.39; P=0.008), while the control group had a higher clinical pregnancy rate (60% vs. 27%; P=0.018)
3	**Cakiroglu et al., 2022 [28]**	Ovarian reserve parameters and IVF outcomes in 510 women with poor ovarian response (POR) treated with intraovarian injection of autologous platelet rich plasma (PRP)	Turkey	Prospective Observational Study		510	POSEIDON	Using a T-lab kit, PRP was prepared from 20 ml blood collected and centrifuged at 830 g for 8 minutes. 2-4 cc of PRP was drawn from the buffy coat and mixed gently for 30-60 seconds	PRP treatment improved AFC, serum AMH, and reduced FSH. 22 women (4.3%) conceived spontaneously, 20.5% achieved pregnancy with IVF, while 12.9% had sustained implantation/live birth after IVF attempts.
4.	**Barad et al., 2022 [29]**	Preliminary report of intraovarian injections of autologous platelet-rich plasma (PRP) in extremely poor prognosis patients with only oocyte donation as alternative: a prospective cohort study	USA	Prospective Cohort Study	III	80	POSEIDON	Using the Regen Lab PRP Kit, a 10 ml blood sample was obtained, mixed, and then centrifuged twice, producing 2.5–3.0 ml of PRP with over 80% platelet recovery and more than 99.7% red cell removal.	Intraovarian PRP showed no significant benefits; however, two 40-year-old patients with previous IVF failures conceived, resulting in a 4.7% continuing pregnancy rate among 42 patients who retrieved at least one oocyte.
5.	**(Tülek and Kahraman, 2022) [30]**	The effects of intraovarian autologous platelet rich plasma injection on IVF outcomes of poor responder women and women with premature ovarian insufficiency	Turkey	Prospective Interventional Study	III	71	Bologna	Two tubes with 20 mL of blood was taken for T-LAB PRP processing. After centrifugation at 1500 g for eight minutes, 4 mL of PRP solution is prepared for ovarian injection.	Post-PRP, poor responders produced more oocytes and embryos, but clinical pregnancy and live birth rates remained unchanged. In women with POI, 8 embryos were produced, but no clinical pregnancies occurred.

6.	**Farimani et al., 2021 [31]**	Evaluation of intra-ovarian platelet-rich plasma administration on oocytes- dependent variables in patients with poor ovarian response: A retrospective study according to the POSEIDON criteria.	Iran	Retro-spective study	III	96	POSEIDON	Not mentioned	According to POSEIDON criteria, group 4 (Age ≥ 35, AMH < 1.2 ng/mL) had the highest prevalence at 58.3%. PRP treatment significantly increased total oocyte counts and clinical pregnancies in 14.6% of cases.
7.	**Sills et al., 2020 [32]**	Regenerative Effect of Intraovarian Injection of Activated Autologous Platelet Rich Plasma: Serum Anti- Mullerian Hormone Levels Measured Among Poor-Prognosis In Vitro Fertilization Patients	USA	Pro-spective Clinical Trial	III	182	-	Around 8-10 mL of whole blood was drawn, processed, and centrifuged, separating erythrocytes from a platelet-poor plasma fraction, which was then aspirated and resuspended as instructed.	The average patient age was 45.4±6.1 years. After treatment, 28% of patients showed improved serum AMH, with a median increase of 167% (95% CI 91; 280), peaking at 4 weeks. Significant improvements were noted in both age groups (<42 and ≥42 years, p=0.03 and p=0.009). Responders had a higher mean basal PLT count (274K) compared to non-responders (250K); p<0.001
8.	**Melo et al., 2020 [20]**	The use of autologous platelet- rich plasma (PRP) versus no intervention in women with low ovarian reserve undergoing fertility treatment: a non- randomized interventional study	Venezuela	Non-Randomized Interventional Study	III	83	-	Platelet-rich plasma was derived from whole blood drawn on the injection day. Five blood tubes, each containing 4.5 mL of 3.8% sodium citrate, were centrifuged at 270 g for 10 minutes. From four tubes, 100 µL of the platelet-rich	83 women participated, with 46 receiving PRP treatment. At three months, PRP significantly improved FSH, AMH, and AFC. Biochemical pregnancy rates were 26.1% vs. 5.4% (P=0.02), and clinical rates
9.	**Cakiroglu et al., 2020 [25]**	Effects of intraovarian injection of autologous platelet rich plasma on ovarian reserve and IVF outcome parameters in women with primary ovarian insufficiency	Turkey	Non-Randomized Clinical Trial	III	311	Bologna	20 ml blood sample was collected and centrifuged using a T-lab kit from T- Biotechnology Laboratory. The tubes were rotated at 830 g for 8 minutes, and PRP was collected from the buffy coat layer. 4-8 cc PRP in total was obtained and gently re-suspended	PRP treatment led to increased antral follicle count (AFC) and serum AMH, with no significant change in serum FSH. Among 311 women treated, 23 (7.4%) conceived spontaneously, 201 (64.8%) attempted IVF, producing 82 embryos. Ultimately, 25 women achieved live births or sustained implantation, and another 25 cryopreserved embryos.

10.	**Stojkovska et al., 2019 [33]**	Live Birth Rates in Poor Responders' Group after Previous Treatment with Autologous Platelet-Rich Plasma and Low Dose Ovarian Stimulation Compared with Poor Responders Used Only Low Dose Ovarian Stimulation Before In vitro Fertilization	Turkey	Prospective Pilot Study	III	40	Bologna	Regen PRP was prepared under strict aseptic conditions at 21-24°C, following the manufacturer's guidelines. The layer of fluid above the erythrocytes was collected and an activator, calcium gluconate was added.	No statistical significance was found in clinical pregnancies or live birth rates between groups. The PRP group had rates of 33.33 ± 44.99 and 40.00 ± 50.71, while the control group had 10.71 ± 28.95 and 14.29 ± 36.31, respectively.

Table 1: Summary of the studies reviewed

Risk Of Bias Assessment:

The quality of the studies was evaluated using the Newcastle-Ottawa Scale for observational studies and cohort studies and the Cochrane Risk of Bias Tools to assess the bias risk in randomized controlled trials.

Results:

The study by Herlihy et al. (2024) aimed to evaluate the effect of intraovarian platelet-rich plasma (PRP) injections on IVF results for young women diagnosed as poor ovarian response (POR) (26). This was a multicentre study between January 2020 and November 2022, the study focused on participants under 38 years old who had previously shown inadequate ovarian response in IVF cycles. The trial randomly assigned eligible participants to receive intra-ovarian platelet rich plasma or no injection. Eight millilitres of blood was drawn into two tubes to prepare PRP, centrifuged at 1500 x g for nine minutes and plasma containing platelet was collected. This PRP was then injected by ultrasound guidance into both the ovaries. Participants then underwent a controlled ovarian stimulation regimen with an estrogen and progesterone overlap. Oocyte collection was carried out 36 hours after trigger followed by ART procedures, including intra-cytoplasmic sperm injection (ICSI) and preimplantation genetic testing (PGT) with transferring euploid embryos in a later cycle .

After 224 women were screened, 112 were potentially considered eligible; of which only 83 women consented to enrol and were randomized into the trial: 41 to PRP and 42 to control group. The main outcome measure, which was the mean of mature oocytes collected, no significant difference was seen between PRP group: 3.1 and control group: 2.8 (p=0.94). The baseline characteristics of the donors, e.g. age, body mass index and ovarian reserve tests were similar.

The secondary outcomes showed that both groups had increased antral follicle count (AFC) and anti-Müllerian hormone (AMH), but there was no significant difference between them. No significant differences were seen in the total number of blastocysts or viable clinical pregnancy outcomes: implantation rate for PRP was 29% (18/62) and control was 31%, P=0.87. Adverse events were low, with only mild post injection discomfort reported but no serious adverse effects. The study overall concluded that PRP injections made no clinically significant difference in IVF outcomes compared to the control group, although there were some positive changes noted regarding ovarian reserve parameters.

G Barrenetxea et al. (2024) conducted a randomized controlled trial that was double-blinded which examined the efficiency of intraovarian platelet-rich plasma (PRP) injections in enhancing ovarian response in 60 women with poor ovarian reserve (POR) as defined by the POSEIDON criteria (27). Conducted from January to December 2021, participants underwent three ovarian stimulation cycles and egg retrievals, with either PRP or a placebo administered during the first retrieval. PRP preparation involved drawing 15 mL of blood into tubes with anticoagulant, followed by centrifugation to separate components. The top layer and buffy coat were separated, underwent a second time centrifugation to produce a pellet of PRP that was activated with Calcium chloride before injection. During oocyte retrieval, 4 mL of saline was injected into control group participants to maintain blinding. The main outcome was the number of mature oocytes collected and secondary outcomes included blastocyst development, clinical pregnancies, and live birth rates .

The trial included 60 patients, with 30 in the PRP group and 29 in the control group but one control participant discontinued. The baseline characteristics had no differences, with an overall mean age of 37.59 years; a Body Mass Index (BMI) of 22.91 kg/m²; and AMH levels around 0.70 ng/ml. A total of 169 egg retrievals were conducted with significant increase in cumulative mature oocytes retrieved for the PRP group versus control (10.45 vs 8.91; P =0.008). Mature oocytes were higher in all the following retrievals, with significant differences noted at third cycle (5.27 ±2.9 vs 4.15±1; p=0.029). The rate of fertilization for fresh and cryopreserved oocytes were equivalent, 76% (fresh) versus 72%, respectively but outcomes improved in the control group leading to an increased mean number of developed and biopsied blastocysts (2.43) compared to the PRP group (1.90; p = 0.449). There was no statistical difference between groups in the euploid blastocyst rates; 53% for control and 43% for PRP (P=0.606). The rates of clinical pregnancy were significantly higher in the control group (60%) compared to PRP (27%; p=0.018), with no differences in miscarriage rates or full-term pregnancies between groups. Among the patients who underwent embryo transfer, pregnancy was achieved in 21 controls and 20 PRP subjects, with no significant differences found for type of delivery or sex ratios of the newborns. The total pregnancy rate per intention to treat was 43%. These results suggest that while PRP may improve the number of retrieved oocytes, it does not enhance the quality of blastocysts or improve pregnancy outcomes. The possible mechanism of PRP's effect on follicular reactivation might be due to the mechanical influence of the injection. The study concludes that PRP may activate follicles but does not completely help in ovarian rejuvenation, emphasizing the need for cautious interpretation and additional investigation.

In a prospective observational study by Cakiroglu et al. (2022), the researchers looked at how intraovarian injections of autologous platelet-rich plasma (PRP) affect ovarian health and IVF results in women diagnosed with poor ovarian response (POR) in Istanbul, between January and December 2020 (28). This study included women aged 30 to 45 years diagnosed with POR, as per the POSEIDON criteria and excluded those women having malignancies; undergoing major surgeries, those on anticoagulant treatment or with a medical history of IgA deficiency. PRP was prepared by collecting 20 mL of blood, centrifuging it at 830 g for eight minutes, and extracting the PRP from the buffy coat layer. Intra-ovarian injection was done under ultrasound guidance within 2 hours of PRP preparation. Patients were monitored for up to 6 weeks for either spontaneous pregnancy or menses. Hormonal assessments, including serum AMH and FSH levels were done before and after the PRP procedure. Controlled Ovarian Stimulation (COH) was started on cycle days 2 and 3 using FSH and hMG (300 IU) followed by administration of rHCG for final maturation. Intracytoplasmic Sperm Injection (ICSI) was done at 34 hours after oocyte retrieval. Embryos were transferred or biopsied for genetic testing, and pregnancy outcomes were confirmed by serum Beta-HCG levels .

The study included 510 women diagnosed with poor ovarian reserve (mean age 40.3 ± 4.0). Following PRP treatment, 22 women achieved spontaneous pregnancies (4.3%, mean age 39.1 ± 4.4), with 12 resulting in sustained implantation or live births (2.3% of the total participants).

Assessment of ovarian reserve parameters showed significant improvements, such as an increase in antral follicle count (AFC) from 2.6 ± 1.3 to 4.2 ± 2.4 ($p<0.001$) and serum AMH levels rising from 0.35 ± 0.32 to 0.53 ± 0.39 ($p<0.001$), along with a fall in serum FSH from 20.6 ± 18.3 to 16.4 ± 14.0 ($p<0.001$). After excluding 22 spontaneous pregnancies and 14 participants who could not be followed-up, 474 women underwent IVF. Oocyte retrieval was successful in 424 women (89.5%), with 367 (86.6%) obtaining at least one mature oocyte. The average number of retrieved oocytes increased from 2.2 ± 1.9 to 3.4 ± 2.7 ($p<0.001$), and the number of blastocysts increased from 0.6 ± 0.9 to 2.3 ± 1.6 ($p<0.001$). Among the 312 women who produced embryos, 83 (26.6%) became pregnant, and 54 (17.3%) had sustained implantation or live births. The total cumulative pregnancy rate was 21.2% (105 out of 496), with a sustained implantation/live birth rate of 13.3% (66 out of 496). Age had a significant impact on outcomes, with younger women (under 38) showing higher pregnancy rates compared to older groups. Factors predictive of embryo production included lower FSH, higher AMH, and higher AFC levels. The researchers concluded that intraovarian PRP injections may be helpful as a treatment alternative for women with POR, improving their ovarian response and IVF outcomes.

Barad et al. (2022) conducted a study looking at how intraovarian platelet-rich plasma (PRP) injections affected ovarian function in 80 women aged 28-54 with very low functional ovarian reserve (LFOR), who otherwise would need oocyte donation (29). PRP was offered as an alternative treatment for patients with FSH levels above 12 mIU/mL or AMH levels below 1.2 ng/mL, excluding those over 54, with autoimmune diseases, or on anticoagulants. Using the Regen Lab PRP Kit, 10 mL of blood was obtained and centrifuged to separate the platelets and plasma, yielding 2.5 to 3.0 mL of PRP. Under conscious sedation, 0.1 mL of PRP injections were done into each ovary several times. Patients were monitored for hormonal changes, and IVF cycles used 300 to 450 IU of FSH and 150 IU of hMG.The purpose of the study was to assess the increase in number of oocytes collected and antral follicle count post-treatment. Good quality embryos were defined as Day 3 embryos with at least 6 cells and less than 10% fragmentation.

The study investigated 80 women experiencing diminished ovarian reserve from October 2018 to

December 2021, dividing them into two groups: 54 who had regular menstrual cycles (Group 1) and 26 who had oligo-amenorrhea or irregular cycles (Group 2), with an average age of 44.2 years. Majority of women in Group 2 had an AMH level of ≤0.03, indicating they were likely in early menopause. After PRP treatment, 67 women began at least one IVF cycle, but 38 did not produce any oocytes. Although no significant changes were observed in maximum lead follicle size or hormone levels before and after PRP treatment in either group, Group 2 exhibited a significant rise in antral follicle count from 1.9 ± 2.1 to 3.5 ± 3.2 (p=0.002). Despite these changes, the number of good-quality embryos showed no significant improvement. Only six women achieved positive pregnancy test post-IVF after PRP, with two having ongoing pregnancies. The authors conclude that the improvements might just be due to chance occurrence and stress that PRP should still be considered experimental until more is known regarding its advantages and potential risks. This preliminary report adds to ongoing research but does not support PRP as a regular therapeutic option for women with poor ovarian reserve.

Tulek et al. (2022) carried out a study investigating the impacts of intra-ovarian autologous platelet-rich plasma (PRP) injections on IVF outcomes in women with poor response and those with premature ovarian insufficiency (POI) (30). The research, carried out at a tertiary centre in Istanbul, Turkey, from 2018 to 2021, retrospectively reviewed the medical records of 71 women—21 diagnosed with POI and 50 identified as poor responders according to the Bologna criteria. Poor responders were identified based on Bologna criteria. To prepare the PRP, 20 mL of blood was drawn from each patient and processed using a T-LAB PRP kit, resulting in 4 mL of plasma that was injected into each ovary under ultrasound guidance with sedation. Patients were monitored every month for their menstrual status and hormone levels for a minimum of six months after the PRP procedure. Eligible patients received controlled ovarian stimulation with various gonadotropins, followed by oocyte retrieval and transfer of embryo. The study aimed to evaluate live birth rates as the primary outcome, with secondary outcomes including oocyte retrieval and fertilization rates.

A study examined 71 women who underwent ovarian PRP injections, with 50 treated for poor ovarian response and 21 for primary ovarian insufficiency (POI). Two POI patients were excluded due to lost follow-ups. The average age and BMI for the POI group were 37.9±1.9 years and 24.9±3.1 kg/m², while the poor responders had an average age of 38.1±4.4 years and a BMI of 25±3.4 kg/m². Menstrual cycles resumed in 10 out of 19 POI cases (52.6%) after an average of 3.1 months. Sixteen stimulation cycles were attempted, but eight embryo transfers were cancelled for various reasons, resulting in only eight embryos transferred, none leading to pregnancy. In the poor responders, 84 controlled ovarian stimulation cycles were conducted post- PRP, revealing significant decreases in both gonadotropin doses and stimulation days (p=0.006 and p=0.002). The numbers of retrieved oocytes, M2 oocytes, and high-quality embryos improved significantly after PRP (p=0.026, p=0.02, p=0.001). After PRP, there were four live births and seven clinical pregnancies, three of which ended in miscarriage. The authors highlight the necessity for further research to standardize PRP preparation techniques and to better understand the mechanisms involved in folliculogenesis. Despite an increase in oocyte and embryo numbers, current

PRP methods available do not significantly enhance live birth outcomes for these patients.

A retrospective study conducted by Farimani et al. (2021) looked at how administration of intra- ovarian platelet-rich plasma (PRP) affects women who have a poor ovarian response (POR), who were classified according to the POSEIDON criteria (31). The study was carried out in Iran between April 2018 and April 2020, involving 96 women who received PRP injections. The criteria for exclusion included lack of follow-ups, laboratory results that were incomplete and conditions that affected fertility. PRP was prepared according to specific standards, requiring platelet counts to be over 106/mL and haemoglobin levels above 10 mg/dL. Ovarian stimulation was done using the Shanghai Protocol, and following the initial puncture into the follicle, 2 mL of intra-ovarian PRP was injected under ultrasound guidance. Hormonal levels, including FSH, LH, AMH, and estradiol, were assessed in the beginning and again after two menstrual cycles. Data on patients' ages and hormonal profiles were gathered, with participants classified into four groups according to the POSEIDON criteria. The total number and types of oocytes were evaluated using ultrasound and assessed by a qualified embryologist.

In this study, 383 patients were assessed, with 96 enrolled and 287 excluded based on above stated criteria. The mean age of participants was 38.30 ± 4.53 years, with 71.9% identified as poor responders. While PRP treatment did not significantly enhance hormonal levels, it resulted in a significant increase in both total oocyte count and MII oocyte count ($P < 0.001$). Pregnancy was achieved in 14.6% of treated patients, and 9.75% of excluded cases became pregnant afterward. Participants were categorized into four POSEIDON groups, revealing significant differences in age, AMH levels, and fertility outcomes among the groups ($P < 0.001$). The study suggests that PRP injections can improve the number of eggs in women with POR who do not respond well to traditional treatments of ovulation induction.

The prospective clinical trial by Sills et al. (2020) aimed to evaluate how activated autologous platelet -rich plasma (PRP) injections affect serum anti-Müllerian hormone (AMH) levels in women with low ovarian reserve who have had unsuccessful in vitro fertilization (IVF) attempts (32). After obtaining informed consent, 8-10 mL of whole blood was taken from patient, which was then processed to extract platelet-rich plasma (PRP). The collected blood underwent centrifugation to separate the plasma, which was subsequently activated with calcium gluconate. This activated PRP was divided into two portions and injected into the ovarian stroma under the guidance of transvaginal ultrasound with a 19G needle. Serum levels of AMH, estradiol, and FSH were measured at two-week intervals to assess the ovarian response, which was categorized as either an increase or no change or decrease from the baseline levels.

The study included 182 patients who received ovarian PRP treatment, with a mean age of 45.4 ± 6.1 years and a pre-PRP body mass index (BMI) of 24.5 ± 0.34 kg/m². Pre-treatment serum AMH levels were not greater than 1.0 ng/mL. Following the treatment, 51 patients (28%) had an increase in serum AMH levels (classified as Category A), while 131 patients (72%) showed no change or a decrease (Category B). Those in Category A had a significantly higher average platelet count (274K compared to 250K, $p < 0.001$). Both age groups (<42 and ≥42 years) demonstrated significant improvements in serum AMH levels, with p-values of 0.03 and 0.009, respectively. The study highlighted the need for more research to understand how this works and to look at long-term fertility outcomes after PRP treatment. Overall, this research marks a major step in investigating the potential ability of PRP to help improve fertility in women facing difficulties due to aging.

A non- randomized interventional study by Melo et al. (2020) investigated the effects of autologous platelet-rich plasma (PRP) injections on markers of ovarian reserve in women with low ovarian reserve who were being prepared for assisted reproductive technology (ART) (20). This research took place at a fertility clinic in Venezuela and involved 83 women who were separated into two groups: 46 received monthly PRP injections for three months, while 37 did not receive any treatment. To create the PRP, 22.5 mL of whole blood was collected into sodium citrate tubes, then centrifuged at 270g for 10 minutes, with the platelet-rich supernatant combined with calcium chloride. Each woman received a 200 µL injection of PRP into the ovarian cortex under ultrasound guidance during the first three menstrual cycles. Measurements of baseline antral follicle count (AFC), FSH, and AMH levels were taken prior to the treatment and reassessed after the third cycle. After receiving PRP, participants were advised to consider fertility treatments like IVF/ICSI or IUI. The primary outcome was changes in AFC, FSH, and AMH, while secondary outcomes included number of oocyte collection, fertilization rates, and pregnancy results, evaluating PRP's potential to enhance ovarian reserve and improve ART outcomes.

The findings indicated that women in the PRP group had significant improvements in ovarian reserve markers, with a 63% rise in anti-Müllerian hormone (AMH) levels and a 33% decrease in the levels of follicle-stimulating hormone (FSH), compared to no changes in the control group.

The PRP group also had higher biochemical pregnancy rates (26.1% compared to 5.4%) and clinical pregnancy rates (23.9% compared to 5.4%). However, the two groups did not show any significant changes in fertilization rates, miscarriage rates, or live births. The study concluded that PRP injections are a safe and effective way to enhance ovarian reserve markers in women who have low ovarian reserve before ART, but more research is needed to see how PRP affects long-term pregnancy outcomes. Overall, this study adds to the understanding of PRP as a possible treatment option in reproductive health.

A study by Cakiroglu et al. (2020) looked at how injecting autologous platelet-rich plasma (PRP) into the ovaries affects ovarian health and affect IVF results in women with primary ovarian insufficiency (POI) according to ESHRE criteria (25). A total of 311 women aged 24 to 40 received PRP injections. PRP was prepared by drawing approximately 20 mL of blood, which was then centrifuged to separate the plasma. A 16 G needle was utilized to extract 2-4 cc of PRP from the buffy coat layer. The injection was done transvaginally under ultrasound guidance within two hours of preparation. After the injection, participants were observed for six weeks to check for spontaneous pregnancies or the return of menstrual cycles. Baseline assessments of ovarian reserve were conducted, and those who showed improvements in antral follicle count or serum AMH levels were initiated on controlled ovarian hyperstimulation

(COH). The COH process included gonadotropin stimulation and monitoring, leading to oocyte retrieval and embryo transfer, with pregnancy outcomes assessed via serum β-HCG levels.

After the treatment, 23 women (7.4%) became pregnant naturally, and 201 (64.8%) developed antral follicles and proceeded with IVF. Out of those who tried IVF, 82 (26.4%) created embryos, and 57 had embryo transfers, resulting in 13 pregnancies (22.8% success rate per transfer). Overall, 25 women (8.0%) had live births or ongoing pregnancies, and another 25 stored embryos for later use. The authors based on the results suggest that PRP injections could help improve ovarian function and might be a possible experimental option for women with POI wanting to use their own eggs. They have also concluded that although the results are promising, using PRP for women with POI should be approached with caution and not yet considered standard practice without proper Randomised control trails.

Stojkovska et al. (2019) conducted a prospective pilot study assessing the efficacy of transvaginal intraovarian injection of autologous platelet-rich plasma (PRP) in poor ovarian responders (PORs) before undergoing low-dose ovarian stimulation for in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (33). The research periods were between June 2017 and December 2018, involving 40 women separated into two groups: 20 patients received PRP treatment, while the control group did not. Both the groups were balanced for basic characteristics, including age, BMI, hormonal status, and infertility duration. The PRP was prepared using Regen PRP under strict aseptic conditions, with 3-5 mL injected transvaginally under ultrasound guidance. Hormonal levels, including FSH, estradiol, and AMH, were monitored before and after the PRP treatment, along with the number of antral follicles. A mild ovarian stimulation protocol was implemented, using clomiphene citrate and low-dose gonadotropins, followed by hCG to induce oocyte maturation. Oocyte collection was conducted via transvaginal ultrasound, and ICSI was performed, with embryo transfers taking place 3 to 5 days later, supported by intravaginal progesterone. Pregnancy was confirmed through serum hCG levels.

The study found no statistical significance in clinical pregnancy and live birth rates (LBRs) between the groups. However, there was a tendency towards increased implantation rates and LBRs in the PRP group, with clinical pregnancy and LBRs of 33.33% and 40.00%, respectively, compared to 10.71% and 14.29% in the control group. The PRP treatment showed potential benefits in improving ovarian regeneration, angiogenesis, and follicular vascularization, although the exact mechanisms were unclear. The study concludes that while intraovarian PRP injections offer a promising alternative to improve IVF outcomes in PORs, the results should be interpreted cautiously due to the sample size being small.

Discussion

Intraovarian platelet-rich plasma (PRP) injections have been investigated as a possible therapeutic option to enhance ovarian function and outcomes for women experiencing poor ovarian response (POR) and premature ovarian insufficiency (POI). The studies reviewed offer a varied perspective on the efficacy of PRP, with some reporting encouraging results while others suggest only limited benefits.

Several studies have shown enhancements in ovarian reserve markers and oocyte yield after PRP treatment. Stojkovska et al. (2019) noted a trend indicating a rise in the implantation and live birth rates in the PRP group, although these differences did not have a statistical significance (33).

Similarly, Melo et al. (2020) reported substantial increases in AMH levels and reductions in FSH levels, along with higher biochemical and clinical pregnancy rates in those receiving PRP compared to the control group (20). Additionally, Cakiroglu et al. (2020) found increase in antral follicle count and AMH levels, with some participants experiencing spontaneous pregnancies and successful embryo development [25].

The findings from these studies indicate that PRP injections might improve ovarian regeneration, promote angiogenesis, and enhance vascularization of follicles, which could result in a better ovarian response and improved IVF outcomes. Proposed mechanisms include the release of growth factors that encourage neo angiogenesis and the maturation of pre-antral follicles, as well as the activation of ovarian stem cells (34).

Despite these positive outcomes, some studies have reported limited or no significant benefits from PRP treatment. Barad et al. (2022) reported no significant improvements in ovarian function or IVF outcomes among women with severely diminished functional ovarian reserve (29). Similarly, Tulek et al. (2022) noted a rise in the number of oocytes and embryos but found no enhancement in clinical pregnancy or live birth rates (30). Barrenetxea et al. (2024) conducted a double-blind, randomized controlled trial that showed while PRP led to a higher number of mature oocytes collected, it did not improve the quality of blastocysts or enhance pregnancy outcomes (27).

The reviewed studies exhibit both methodological strengths and weaknesses that affect how their findings are interpreted. For instance, studies like those by Stojkovska et al. (2019) and Melo et al. (2020) utilized prospective designs and closely monitored participants, which limits the reliability of their results (33,20). However, the small sample sizes and the absence of randomization in some of these studies restrict the broader applicability of their conclusions.

The variability in PRP preparation methods and the lack of standardization across studies further complicate the comparison of results. Tulek et al. (2022) noted that the variations in PRP preparation techniques hinder the ability to reach definitive conclusions regarding its efficacy (30).

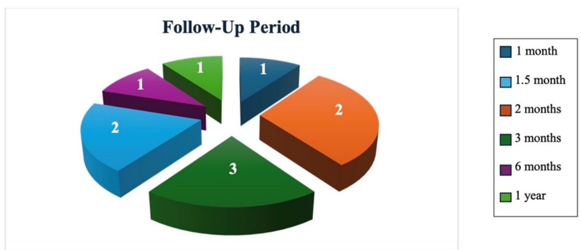

Figure 3: Summary of the timings of the outcome measurements following PRP treatment in the collected studies

The follow-up periods for outcome measurements after PRP treatment varies significantly among studies, ranging from 6 weeks to 1 year; as shown in Figure 3. This variation helps for both immediate evaluations of effectiveness and long-term assessments of treatment sustainability. However, the lack of standardized follow-up durations gives the difficulties in summarising results and may result in incomplete assessment of PRP's efficacy, and varying outcome measures can hinder comparisons. To enhance the understanding of PRP treatment's efficacy and safety, future studies should aim to standardize both follow-up durations and evaluation criteria.

This literature review has several limitations. As stated in the methods and results sections, the review only included research studies from Embase, PubMed, Web of Science, and Cochrane. This restriction has resulted in a limited number of articles being reviewed, which hinders the ability to provide a detailed overview of the existing research articles. Since this literature review is part of the author's dissertation for the MCh module, it needed to be completed within a tight timeframe. Consequently, the search was narrowed to include only articles published between 2014 and 2024. A longer timeframe would have allowed for a more extensive search strategy.

Moreover, while the author utilized the institution's access to retrieve several articles, some were not accessible and had to be excluded from the search. If more authors had been involved and the timeframe had been extended, a more detailed and robust review could have been conducted, as a systematic review or meta-analysis. Additionally, many of the selected articles are retrospective, which means that important clinical data that could have contributed to the overall findings may not have been collected.

The exact mechanisms through which PRP may enhance ovarian function are still not fully understood. Some studies suggest that the mechanical impact of the injection itself, rather than the biological properties of PRP, could be responsible for the benefits observed. Barrenetxea et al. (2024) suggested that the mechanical effect of the injection might contribute to the reactivation of follicles (27).

Future studies should aim to fully understand the mechanisms behind PRP's effects on ovarian function (35). Standardization of PRP preparation and PRP administration are important to ensure consistency and comparability across studies (36).

Additionally, larger randomized controlled trials with prolonged follow-up are required to confirm the efficacy and safety of PRP treatment and to determine its impact on live birth rates and other long-term reproductive outcomes (37).

Conclusion

The existing literature on intraovarian PRP injections for women with POR or POI offers a mixed assessment of its effectiveness. Some studies indicate encouraging results in enhancing ovarian reserve markers and increasing oocyte yield (28,38), while others found minimal benefits and no significant improvements in pregnancy outcomes (26). This inconsistency in findings can be attributed to differences in patient populations, study designs and methods of PRP preparation.

Although some studies suggest potential benefits, the overall evidence does not support suggesting PRP as a standard treatment for improving IVF outcomes in women with POR or POI. It is important for patients considering about PRP treatment to be informed about its experimental status and the lack of definitive evidence regarding its efficacy. Additional research, especially large-scale randomized controlled trials with standardized protocols and long-term follow-up, is necessary to determine the true efficacy and safety of PRP for these patients (37).

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