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REVIEW

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Effect of intra-ovarian injection of platelet-rich plasma on the patients with a poor ovarian response (POR) or premature ovarian insufficiency (POI): a systematic review and meta-analysis

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Abstract

Background POR or POI poses a significant challenge to fertility treatment with different ovarian stimulation strategies. Intra-ovarian injection of platelet-rich plasma (PRP) has been hypothesised to improve ovarian reserve and pregnancies in POI or POR. However, its effectiveness on pregnancy, embryology and ovarian reserve outcomes need to be established. Therefore, we systematically searched databases based on PRISMA guidelines that reported on the effects of intra-ovarian autologous PRP injections in sub-fertile women with POI and POR. The following outcome effects were analysed by random model and included in the meta-analysis in pre- and post-PRP injection groups of POI & POR: (a) pregnancy rates, rate of oocyte & embryo formation (b) ovarian reserve markers (Antral follicular count, Anti-Mullerian Hormone, Follicle Stimulating Hormone). A separate analysis of pregnancies, AFC and AMH was done in POI and POR groups and in age groups < 35 years and > 35 years. A total of 12 studies were included. The estimated overall effects size of the log odds ratio (log OR = 2.03; 95% CI = 0.13 to 3.92; $P = 0.04$; $I^2 = 0.42$) favoured post-PRP with a moderate level of evidence. There are no significant differences in POI/POR and those with < 35 years or > 35 years.

The pooled standard difference of means favoured the post-PRP injection group significantly with regards to rates of embryo formation (1.39; 95% CI = 0.56 to 2.21; $P = 0.02$; $I^2 = 46\%$.), Oocyte (0.84; 95% CI = -1.3 to 3.0; $P = 0.24$; I^2 93%), Antral follicle count (1.78; 95% CI = 0.73 to 2.84; $P = 0.01$. $I^2 = 97\%$) with a low level of evidence and Anti-Mullerian Hormone (1.11; 95% CI = 0.16 to 2.05; $P = 0.03$; $I^2 = 96\%$) with low level of evidence.

Conclusion Our study shows that intraovarian PRP injection was associated with no significant increase in the rates of pregnancy, in the rates of pregnancy, oocyte, embryo formation, Anti-Mullerian Hormone and antral follicle count. Live birth rates were not calculated. There was no statistical difference between POR/POI and those with < 35 years or > 35 years. Further randomized studies are warranted to confirm our findings.

Keywords Platelet-rich plasma, Ovarian rejuvenation, Premature ovarian insufficiency, Pregnancy, In-vitro fertilization (IVF), Intracytoplasmic sperm injection (ICSI)

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Introduction

Poor ovarian response (POR), Premature ovarian insufficiency (POI), and low ovarian reserve women pose clinical challenges to fertility treatment. They are (a) women with decreased ovarian response to controlled ovarian stimulation with conventional gonadotrophin dose [1] and (b) premature ovarian insufficiency (POI) [2]. Although they differ in their etiopathogenesis, they all pose similar clinical challenges to fertility treatment i.e., poor fertility outcomes.

Bologna criteria and POSEIDON criteria are the two methods of categorization of patients with POR. Bologna criteria are based on 1. Age 2. Ovarian reserve status. At least two of the following three features must be present. Advanced maternal age (≥ 40 years) or any other risk factor for poor ovarian response (POR); A previous POR (≤ 3 oocytes with a conventional stimulation); An abnormal or low ovarian reserve is AFC < 5–7 follicles or Anti Mullerian hormone (AMH) < 0.5–1.1 ng/ml) [3]. Both POI and low ovarian reserve result in POR.

The POSEIDON (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) criteria brought a change in the terminology from POR to low prognosis. This helps to stratify low-prognosis patients to undergo ovarian stimulation for IVF to address POR[4].

The age-related natural decline in ovarian reserve in women over 40 years is a well-known reason for the POR. On the other hand, in some women, the qualitative and quantitative reduction in oocytes occurring in the younger age group will result in POI and POR. The European Society of Reproductive Medicine (ESHRE) guidelines define POI as the presence of oligomenorrhea-amenorrhea for at least 4 months and serum follicle-stimulating hormone (FSH) levels of ≥ 25 IU/ml measured at least twice with a 4-week interval, with an onset before the age of 40 years [5]. The prevalence of POI has doubled in the last few decades [6, 7]. The available treatment options for POI or POR are either to maximize the ovarian response from the available limited follicular pool or oocyte donation.

Various stimulation strategies have been attempted to maximize the ovarian response in these subsets of patients, without much improvement [8, 9]. The option of oocyte donation results in better outcomes, but this may not be acceptable to infertile couples who desire to have their genetic child [10]. Recently plasma platelets (PRP) have been used in the regeneration of ovarian function by injecting concentrated autologous PRP into the ovaries [11]. It is hypothesized to improve pregnancies and other ovarian reserve markers in women with POI [12].

PRP injected into ovaries may help to restore proliferation, angiogenesis, and cell migration and reset the programmed cell death of remaining primordial follicles to respond better to ovarian stimulation [13] by releasing growth factors like vascular endothelial growth factors (VEGF) and platelet-derived growth factors AB (PDGF-AB) and TGF-b1[14].

However, this hypothesis is not fully understood. In this review, we would like to evaluate the effects of ovarian PRP injection on pregnancy outcomes and ovarian reserve markers in women with POI who underwent IVF/ICSI so that this intervention can be incorporated into the clinical practice more effectively.

Materials and methods

This study was registered in Prospero (PROSPERO 2021 CRD42021245753).

This review is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Literature search

A systematic literature search of MEDLINE, EMBASE, CINAHL, Google Scholar, Scopus, Web of Science databases, the Cochrane Library, and SciSearch was conducted on studies that reported on the effects of intra-ovarian injections of autologous platelet-rich plasma in sub-fertile women with decreased/low ovarian reserve or premature ovarian insufficiency/failure from the inception of database to March 2022.

To improve our search yield, we adapted the Medical Subjects Headings (MeSH) search strategy to generate two subsets of citations. One subset included the search terms and words related to decreased ovarian reserve (DOR) or low ovarian reserve (LOR) or poor ovarian reserve (POR) or premature ovarian insufficiency (POI) or premature ovarian failure (POF).

The other subset included the search terms and words related to "assisted reproduction techniques (ART) or "in-vitro-fertilization (IVF)," "intracytoplasmic sperm injection (ICSI)," and "Platelet-rich plasma (PRP)", autologous platelet-rich plasma.

Both subsets were combined and searched again to capture all the relevant articles or citations for our study. The search was restricted to clinical studies in human subjects and published in English language were included in our review.

Data extraction was done by selecting the titles and abstracts, and full manuscripts of the studies that fulfilled our selection criteria were retrieved. They were independently reviewed by two reviewers (SV & PKA) and conflicts regarding inclusion and exclusion of studies were resolved by group consensus and with the third reviewer (NM). We also manually reviewed the bibliographies of retrieved original papers, review papers and relevant

studies for additional articles. In this way, missing data from our search criteria were identified and included.

Authors were contacted whenever possible if the full manuscript was not available.

Treatment effect

The log odds ratio was calculated for clinical pregnancy rates and Cohen's d mean differences were calculated for other outcomes with 95% confidence intervals, estimated overall effect sizes were presented with forest plots. An increase in the outcome values (post-PRP) from the baseline (pre-PRP) of the intervention is graphically displayed to the right of the central line in the meta-analysis favouring intraovarian PRP injection. A p-value of < 0.05 is considered as significant.

Statistical analysis:

- The characteristics (clinical & methodical) of all included studies were examined.
- In cases of overlapping data, the studies with the largest number of observations were included.
- We performed one group (pre-post) treatment summary size effect meta-analysis to look at the estimated overall effect size of intra-ovarian PRP intervention.
- We performed separate post-PRP analyses between POI and POR for pregnancies, antral follicle count and AMH (key outcomes) to find out any difference between POI and POR.
- We have done separate post-PRP analyses for those under 35 years and above 35 years to find out whether age impacts the post-PRP reproductive outcomes on pregnancies, antral follicle count and AMH.
- We used the random effect models for meta-analysis to calculate an overall OR and summary effects size and their 95% confidence intervals (CI) with the forest plots.
- The missing data on the changes of standard deviations from the included studies were imputed by the Pre/Post correlation value of 0.5 after reasoned argument and doing sensitive analysis.
- We used IBM SPSS Version 29.0. Armonk, NY: IBM Corp to perform these meta-analyses.

Assessment of heterogeneity

- The presence of heterogeneity was assessed by the I^2 statistic. An $I^2 > 50\%$ was taken to indicate substantial heterogeneity.
- The random-effects model was used as the I^2 statistic was greater than 50%. Exploration of the causes of heterogeneity was planned using variations in features of the population, exposure, and study quality. Sensitivity analyses were used where possible and appropriate to address the clinical and methodological variations.

Inclusion criteria based on outcomes:

We have included the studies that reported on the fertility outcomes and ovarian reserve markers before (pre) and after (post) intraovarian PRP injection in women with POI or POR.

POI / POR is defined based on the following criteria or in combination.

- POI: Any of the following
  - primary or secondary amenorrhea of > 4 months or oligomenorrhea of > 4 months before the age of 40 years; with FSH elevation > 25 IU/L on 2 assays at > 4 weeks' intervals, with low estradiol (ESHRE 2016 Guideline).
  - Bologna criteria of low ovarian reserve
  - Anti-Müllerian hormone < 1.1 ng/ml
  - Antral follicle count < 5
- POR: Any of the following
  - ≤ 3 oocytes retrieved with a standard gonadotrophin stimulation (based on Age/BMI/ovarian reserve markers)
  - POSEIDON criteria 3 or 4 with low prognosis ART outcome
- Age above 40 years or any age with any combination of the above

Objectives

Fertility outcomes & ovarian reserve markers:

1. Fertility outcomes are clinical pregnancies or live births either conceived spontaneously or after IVF/ICSI, number of oocytes and embryos after one month of intraovarian PRP administration. Pregnancies reported within one month of intraovarian PRP administration are considered pre-PRP pregnancies.
2. Ovarian reserve markers: AFC and serum AMH, FSH levels after intraovarian PRP administration.

Exclusion criteria:

- Studies that have not clearly defined POI or POR.
- Studies that did not report Pre and Post PRP values of the outcomes (reported only either pre or post-PRP values of the outcomes).
- Studies were excluded if they had no data available for retrieval or overlapping or duplication of the data.

Data extraction and management

The following information and data were extracted.

Trial methods

Prospective non-randomized studies with pre and post-PRP intervention for comparison. None of the studies were randomized controlled trials.

Participants

Data on the participants included infertile couples with POI/POR as defined above conceived either spontaneously or IVF / ICSI.

Intervention

Information on intraovarian injection of PRP with regards to the type of preparation, route of PRP injection, co-intervention and frequency and duration of intervention.

Outcomes

Data on fertility outcomes & ovarian reserve markers (both pre and post-PRP) were reported as means, standard deviations (SD) and the number of subjects in the studies.

Pregnancy outcomes(core reproductive outcome) were represented as dichotomous data (as the number of events occurred) and the remaining outcomes (AMH, AFC, FSH, number of oocytes retrieved, number of embryos formed) were represented as continuous data(means).

Quality of evidence

Assessment of risk of bias

The risk of bias was assessed using a National Institute of Health (NIH) Quality Assessment Tool for Before-After (Pre-Post) Studies (Table 1). The quality rating for each of the studies included was presented as Good, Fair, or Poor by two reviewers (risk of bias table). The studies were assessed for quality based on the NIH risk assessment tool. The studies ranged from being fair to good based on the NIH risk assessment tool (6 good-quality and 6 fair-quality studies). No major side effects were reported after PRP injection in the included studies which is similar to the studies where PRP was used in other faculties of medicine [15, 16].

Assessment of publication integrity

We used the reappraised checklist tool to systematically evaluate the included studies in 11 categories for publication integrity [17]. The integrity rating for each included study was presented as Good, Poor and Unclear in all the categories (Table 2).

The studies were assessed for quality of integrity using the REAPPRAISED checklist tool Nature checklist [17] on 11 categories. The quality of integrity of the studies was assessed as good, poor, and unclear. In the categories of No Plagiarism, 12 studies [10, 12, 23–32], Productivity 11 studies [10, 12, 24–32], Analysis & Methods 11 studies [10, 12, 24–32] were assessed as good. In the error reporting category, 8 studies [10, 24–29] out of 12 studies were assessed as unclear and 4 studies were assessed as poor [12, 23, 31, 32] and none of the studies were good and more than 3 studies were unclear in the research governance [12, 27, 29, 30], ethics[23, 24, 27, 29, 30], authorship[24–27, 29], no data duplication categories[10, 12, 23, 30] (Fig. 1).

Summary of findings and assessment of the certainty of the quality of evidence

We have prepared a summary of the findings table using GRADE pro software and Cochrane methods [18] for the outcomes and graded the evidence quality as low, very low, or moderate level of certainty of evidence. The significance of the quality of evidence grading on the outcomes in clinical practice is mentioned in the discussion section under the heading meaning of our findings (Tables 3, 4 and 5).

Results

A total of 17 studies were identified and scrutinized in full text, out of which 12 studies were included in the meta-analysis and 5 were excluded for reasons (Fig. 2 PRISMA). Two studies [10, 31] included only POI subjects, eight studies [1, 12, 23, 26–28, 30, 32] included POR subjects, and two studies [2, 24] included combined POI and POR subjects.

Included studies

All the twelve studies included in the meta-analysis were prospective and their details are mentioned in Table No. 3 [10, 12, 23–32].

Among the 12 included studies, five studies had recruited 20 patients or less, [23, 25, 26, 29, 32] while one study had only five patients [23].

The studies differed concerning the quantity, timing, and frequency of injection of PRP into the ovaries.

Table 1 NIH quality assessment tool for risk bias [10, 12, 23–32]

Criteria	Cakiroglu et al 2020	Melo et al 2020	Abdulla et al 2019	Petryk et al 2020	Stojkovska et al 2020	Paranov et al 2020	Tandulwadkar et al 2020	Aflatoonian et al 2021	Selvaraj et al 2021	Sfakianoudis et al 2020	Sills et al 2020	Farimani et al 2019
(1)Was the study question or objective clearly stated?	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	Yes	Yes
(2) Were eligibility/selection criteria for the study population pre-specified and clearly described?	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(3) Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(4) Were all eligible participants that met the pre-specified entry criteria enrolled?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(5) Was the sample size sufficiently large to provide confidence in the findings?	Yes	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD
(6) Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(7) Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	CD	CD	Yes	Yes	No	Yes	Yes	yes	Yes	Yes	No
(8) Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Yes	No	No	No	No	No	No	No	No	No	No	No
(9) Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(10) Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
(11) Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	No	No	Yes	No	Yes	No	Yes	No	Yes	No	No
(12) If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Yes	NC	NC	No	NC	No	NC	No	No	No	No	No
Quality rating: Good, fair, poor	Good	Fair	Fair	Fair	Good	Fair	Good	Good	Fair	Good	Fair	Fair

CD Cannot Determine, *NC* Not Commented

Legend: Green-Good, Yellow-Fair

Table 2 Showing quality of publication integrity REAPPRAISAL checklist tool [1, 10, 12, 23–28, 30–32]

Studies	Farimani et al	Aflatoonian et al	Petryk et al	Stojkovska et al	Tandulwadkar et al	Sills et al	Sfakianoudis et al	Abdullah et	Selvaraj et al	Paravanov et al	Cakiroglu et al	Melo et al
Categories												
Research Goverence	Good	Good	Unclear	Unclear	Good	Good	Good	Good	Poor	Unclear	Good	Unclear
Ethics	Good	Good	Unclear	Unclear	Good	Good	Unclear	Good	Unclear	Unclear	Good	Good
Authorship	Good	Unclear	Unclear	Unclear	Unclear	Good	Unclear	Good	Good	Good	Good	Good
Productivity	Good	Good	Good	Good	Good	Good	Good	Good	Poor	Good	Good	Good
No Plagiarism	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Research Conduct	Good	Good	Good	Unclear	Good	Good	Good	Unclear	Unclear	Good	Good	Good
Analysis & Method	Good	Good	Good	Good	Good	Good	Good	Good	Poor	Good	Good	Good
Image Manipulation	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Statistics & Data reporting	Good	Good	Good	Good	Unclear	Good	Good	Poor	Poor	Unclear	Good	Good
Error Reporting	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Poor	Poor	Poor	Unclear	Poor
No Data Duplication	Good	Good	Good	Good	Good	Good	Good	Good	Unclear	Unclear	Unclear	Unclear

Legend- Green-Good, Yellow-Unclear, Red-Poor

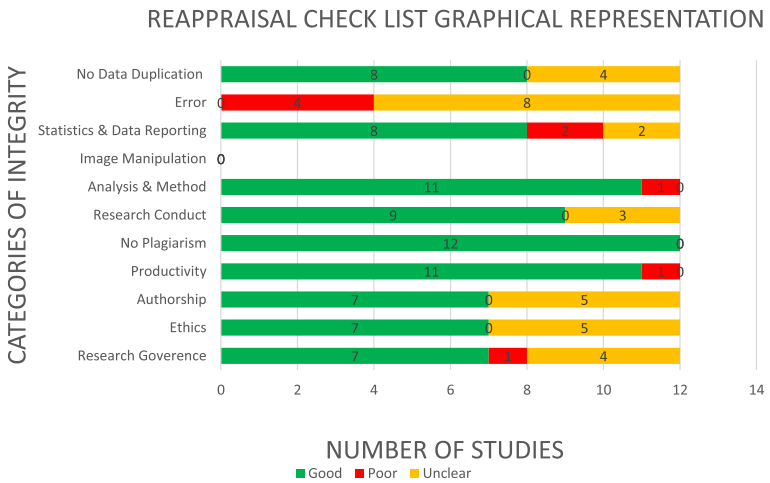

Fig. 1 Reappraisal checklist graphical representation

The volume of PRP injected ranged from 0.2 ml to 4 ml. Six studies have reported changes in at least one fertility outcome and ovarian reserve marker [12, 23, 24, 26, 27, 30]. Three studies reported only changes in at least one ovarian reserve marker [28, 29, 31] while 3 studies have commented on at least one of the fertility outcomes [10, 25, 32].

Excluded studies

Five studies were excluded from the analysis for the reasons explained in Table No. 2 [1, 19–22]

Ovarian reserve marker

Among the ovarian reserve markers, four studies included all three markers of ovarian reserve, i.e. AMH, AFC, and FSH [11, 13, 25, 32] while four studies included AMH and FSH [23–26]. The study by Tandulwadkar et al. [26] and Parvanov et al. [30] included AFC and AMH. Stojkosov et al. [29] included only FSH as a marker of ovarian reserve.

Embryology and fertility data

Three studies have included oocytes and embryos [24, 30, 32], while five studies have commented on pregnancies [10, 23–25, 32].

Outcomes

A) Comparison of fertility outcomes (both pre and post-PRP):

- Pregnancies: Among the 12 studies included in the meta-analysis, only 5 studies have reported pregnancies [10, 23–25, 32]. A total of 59 pregnancies

Table 3 Summary of findings table -GRADE pro quality of evidence

Summary of findings:

PRP compared to PrePRP in POI.POR.

Patient or population: POI.POR. **Setting:** Subfertility **Intervention:** PRP **Comparison:** PrePRP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PrePRP	Risk with PRP				
Pregnancy (Preg) assessed with: Clinical Pregnancy timing of exposure: range 2 months to 12 months	**Study population**		**OR 2.03** (0.13 to 3.92)	438 cases 438 controls (12 non-randomised studies)	⊕⊕⊕◯ Moderate[a,b]	PRP probably increases pregnancy. The effect of smaller studies need to taken with caution and also possibility of high publication bias
	14 per 1,000	**27 per 1,000** (2 to 52)				
	Moderate					
	14 per 1,000	**28 per 1,000** (2 to 53)				
Embryos	The mean embryos was **1**	MD **1.34 higher** (1.05 higher to 173 higher)	-	348 (3 non-randomised studies)	⊕◯◯◯ Very low[b]	
Oocytes	The mean oocytes was **1**	MD **0.84 higher** (0.02 lower to 1.8 higher)	-	348 (3 non-randomised studies)	⊕⊕⊕◯ Moderate[b]	
Antral Follicle Count (AFC) assessed with: TVS	The mean antral Follicle Count was **1**	MD **1.78 higher** (0.73 higher to 2.84 higher)	-	1346 (6 non-randomised studies)	⊕⊕◯◯ Low	The mean difference in improvement in antral follicle count is 1.78 after PRP
Anti Mullerian Hormone (AMH) assessed with: Blood	The mean anti Mullerian Hormone was **1**	MD **1.11 higher** (0.16 higher to 2.05 higher)	-	1584 (9 non-randomised studies)	⊕⊕◯◯ Low	The mean difference of improvement of 1.11 of AMH but it is not have any clinical importance
Follicle Stimulating Hormone (FSH) assessed with: Blood	The mean follicle Stimulating Hormone was **1**	MD **0.62 lower** (1.57 lower to 0.33 higher)	-	1838 (10 non-randomised studies)	⊕⊕◯◯ Low	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

resulted from 438 patients after (post) PRP in comparison to 6 pregnancies before (pre) PRP. 36 of 59 conceived spontaneously and 23 with ART after PRP administration. 44 pregnancies were with a mean age of < 35 years [10, 28] and 15 pregnancies with a mean age of > 35 years [23, 25, 32]. Pregnancies reported after PRP in the age group above 40 years were less than those below 40 years (4/40 vs 3/30). The estimated overall effects size of random log odds ratio (OR) (log OR = 2.03; 95% CI = 0.13 to 3.92; P= 0.04; I^2=0.42) significantly favoured post PRP and is depicted in Figure II. Intra-ovarian PRP did increase pregnancy rates.

The estimated overall effects size of random log odds ratio (OR) (log OR = 2.03; 95% CI = 0.13 to 3.92; P= 0.04; I^2=0.42) significantly favoured post PRP and is depicted in Fig. 3. Intra-ovarian PRP did increase pregnancy rates.

Table 4 Excluded studies

Author/country/year	Population studied	Number of patients studied	Interventions	Outcome	Reason for exclusion
Stojkovska et al. Macedonia /2019[1]	Women with poor ovarian reserve	40 (20 cases and 20 controls	3–5 ml of PRP into the ovaries Route: **transvaginal**	Live birth rates, Fertilization rates, Implantation rates, Clinical pregnancy rates	No pre and post-intervention data
Pantos et al. Greece/2019[20]	Women who had attained menopause	03 patients	4 ml of PRP in each ovary Route: **transvaginal route**	FSH, LH, AMH, E2, AFC, Menstrual recovery, Live birth rates	Case series less than 5 patients
Pantos et al. Greece /2016[19]	Perimenopausal women with DOR	08 patients	Intraovarian injection of PRP Route**: transvaginal**	FSH, LH, AMH, E2	Incomplete data
Hsu et al. Taiwan/2021[21]	Women with early menopause	12 patients	5 ml of PRP combined with 300 IU **recombinant- FSH** Route: **laparoscopy**	FSH, LH E2 Oocytes, fertilization	Excluded as FSH was injected Along with PRP
Anagani et al. India/ 2021[22]	Women with DOR and POI	12 patients with POI 7 pts with decreased ovarian reserve	1–2 ml of ABMDSC and 1 ml of PRP by laparoscopic route	FSH levels and clinical pregnancy rates	Inclusion criteria are not fulfilled

The estimated overall effect size of pregnancies after post-PRP in separate analysis between POI and POR did not have any significant difference (log OR -0.52;95%CI: -2.73-1.90;p=0.65) and similarly, the estimated overall effect size of post-PRP in separate analysis among under 35 years and over 35 years of age did not result in any significant differences in pregnancies (log OR-0.26;95%CI:-1.24-0.72;p=0.60).

- Embryos: Three studies reported the effect of intra-ovarian PRP injection on embryo formation [24, 30, 32]. Cohen's mean difference in embryo formation significantly favoured injection of PRP (post-PRP). The estimated overall effect size of mean difference (random model) with confidence intervals (CI) is 1.39; 95% CI = 0.56 to 2.21; P = 0.02; I2 = 46% and depicted in Fig. 4.
- Oocytes: Three studies reported the effect of ovarian PRP injection on oocyte formation [24, 30, 31]. Cohen's mean difference in oocyte formation favoured injection of PRP (post-PRP). The estimated overall effect size of means difference (random model) with confidence intervals (CI) is 0.84; 95% CI = -1.3 to 3.0; P = 0.24; I^2 = 93% and depicted in Fig. 5.
- No significant increase in pregnancy rates was noted in the present study. Also, the live birth rates were not calculated.

B) **Comparison of ovarian reserve markers (both pre and post-PRP)**

Out of 12 studies,9 studies reported on AMH [10, 12, 23–28, 31], while 6 studies reported on AFC [10, 12, 24, 26, 30, 32]. There are 4 studies, which have studied all three ovarian reserve markers, i.e. AMH, AFC and FSH [10, 12, 24, 31], while another four studies have evaluated AMH and FSH [23, 25, 27, 28]. Tandulwadkar et al. [26] and Parvanov et al. [30] studied AFC, AMH and AFC, FSH respectively. Stojkovska et al. [29] studied only FSH.

- AFC: Six studies reXported the effect of ovarian PRP injection on AFC [10, 12, 24, 26, 30, 31]. Cohen's mean difference in AFC favoured the injection of PRP (post-PRP). The estimated overall effect size of means difference (random model) with confidence intervals (CI) is 1.78; 95% CI = 0.73 to 2.84; P = 0.01. I2 = 97% and is depicted in Fig. 6. The AFC may increase by 1.78 after the PRP administration.
- The estimated overall effect size of mean difference after post-PRP in separate analysis between POI and POR did not have any significant difference (-2.97;95%CI:-2.11–8.04;p = 0.25) similarly, the estimated overall effect size of post-PRP in separate analyses among those under 35 years and over 35 years of age did not result in any significant differences in pregnancies (-2.89;95%CI:-1.46–7.22;p = 0.19).

Table 5 Included studies

Author/ country /year	Population studied / All are Prospective studies	Number of patients studied	Intervention	Outcomes	Quality risk assessment
Selvaraj et al. India/2021[23]	Women with decreased ovarian reserve	05	Injection of 1–2 ml of PRP into ovaries Route**: Transvaginal**	FSH, LH AMH, E2 Pregnancy rates	Fair
Cakiroglu et al. Turkey/2020[10]	Women diagnosed with premature ovarian insufficiency (POI)	311	2–3 ml of PRP into each ovary Route: **Transvaginal**	Number of retrieved oocytes, mature oocytes, number of 2 pronuclei embryos, Cleavage stage embryos and percentage of fertilization	Good
Melo et al. UK/2020[12]	Women with low ovarian reserve	86 patients. (46 cases and 37 controls)	200 µL of PRP into each ovary on days 7 and 9 of the menstrual cycle for 3 consecutive cycles Route: **Transvaginal**	Primary outcomes were changes in AFC, AMH, FSH Secondary outcomes were No. of oocytes obtained and fertilization rates after IVF-ICSI, Biochemical and clinical pregnancy rates, first-trimester abortions and live birth rates	Fair
Sfakianoudis et al. Greece/2020[24]	I. poor responders, II. perimenopausal women, III. women presenting with POI, IV. menopausal women	120 cases (30 in each group)	4 ml of activated PRP into each ovary Route: **Transvaginal**	In POR patients, primary outcomes were changes in the levels of AMH, AFC and oocyte yield in the IVF-ET cycle Secondary outcomes were—metaphase ii oocytes, number of embryos and cycle cancellation In POI, perimenopausal and menopausal patients, the primary outcome were -the restoration of the menstrual cycle, and FSH levels Secondary outcomes measures were AFC, AMH, LH and E2 levels	Good
Aflatoonian et al. Iran/2021[25]	Women with POI and POR	17 patients with poor ovarian responders 9 patients with POI	1.5 ml of activated PRP into each ovary Route: **Transvaginal**	In POR group- Biochemical, Clinical pregnancies and live birth rates In the POI group- menstrual restoration was monitored	Good
Tandulwadkar et al. India/2020[26]	Poor responders	20 patients	2 ml of PRP mixed with 16 ml of autologous bone marrow-derived stem cells(ABMDSCs) Route: T**ransvaginal route or laparoscopic route**	Primary outcomes were AFC and mature MII oocytes secondary outcomes were AMH levels and the number of Grade A and B embryos	Good

Table 5 (continued)

Author/ country /year	Population studied / All are Prospective studies	Number of patients studied	Intervention	Outcomes	Quality risk assessment
Petryk et al. Ukraine /2020[27]	Women with low ovarian reserves and at least two unsuccessful attempts to receive their oocytes through IVF	38 patients	0.7 ml of PRP into each ovary Route: T**ransvaginal route or laparoscopic route**	Serum LH, FSH, AMH, and estradiol levels were analyzed Biochemical, clinical pregnancy rates, Live birth rates and number of oocytes retrieved	Fair
Sills et al. USA/2020[28]	Perimenopausal and menopausal women with infertility of > 1 yr. duration and at least 1 prior failed IVF	182 patients	1 ml of PRP into the ovary Route: **transvaginal**	AMH, FSH, E2	Fair
Stojkovska et al. Macedonia/2020[29]	Women with POR	15 patients	3–5 ml of PRP into the ovaries Route: **transvaginal**	FSH, AMH and AFC	Good
Parvanov et al. Italy /2020[30]	Women with POR undergoing IVF cycles	132 patients	Intraovarian injection of PRP Route**: transvaginal route**	AFC, FSH Number and quality of M2 oocytes, Fertilization rates and the number of quality of blastocysts	**Fair**
Abdullah et al. Iraq/2019[31]	Women with POR	50 patients	1.25 ml of PRP into each ovary Route**: transvaginal route**	FSH,AMH, AFC and mean ovarian volume	Fair
Farimani et al. Iran/2019[32]	Women with POR	12 patients	2 mL of PRP into the ovary Route**: transvaginal route**	No oocytes and embryos	Fair

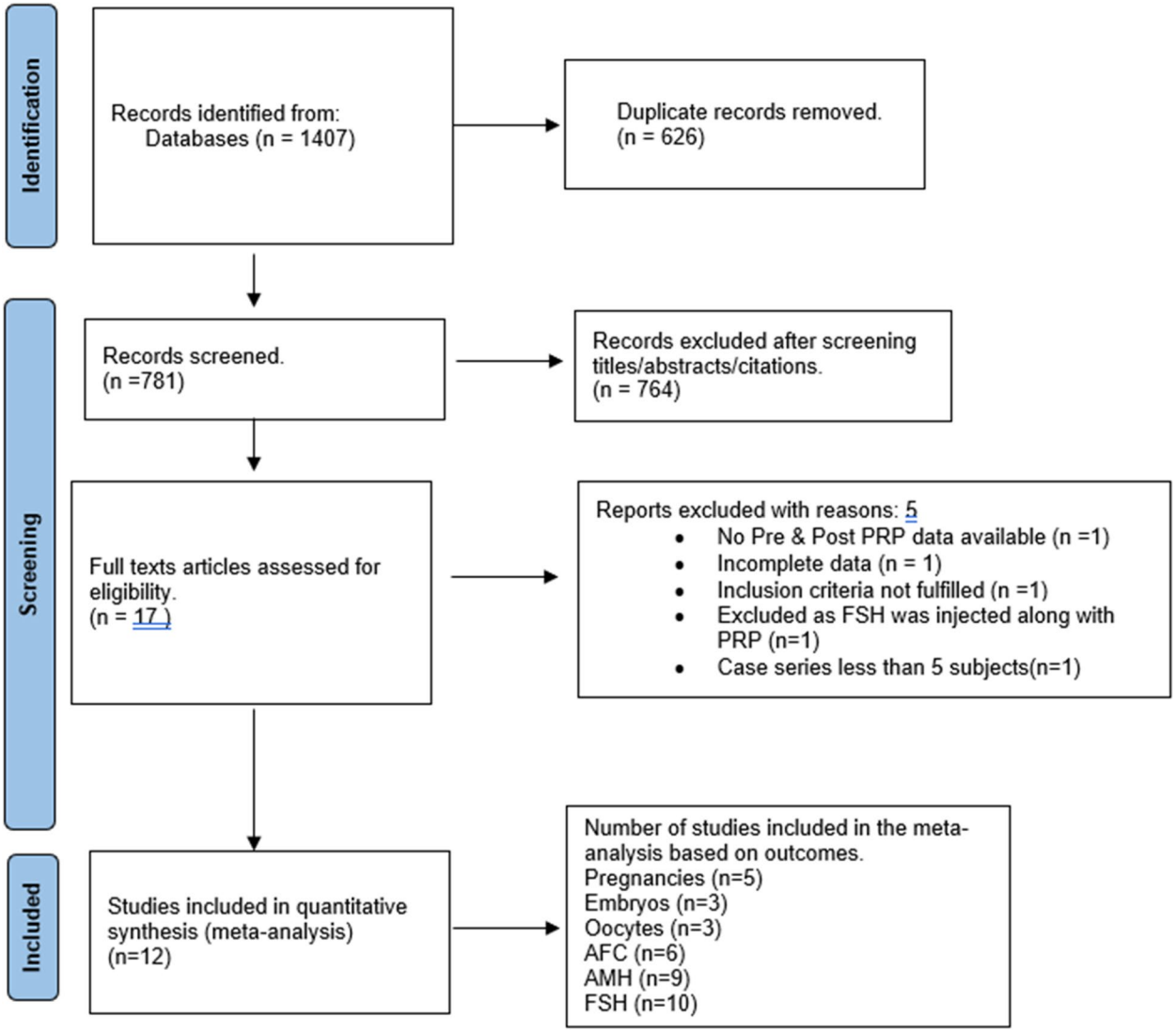

Fig. 2 Random model for pregnancies PRISMA flowchart

- AMH: Nine studies reported on the effect of ovarian PRP injection on AMH [10, 12, 23–28, 31]. Cohen's mean difference in AMH favoured injection of PRP (post PRP). The estimated overall effect size of means difference (random model) with confidence intervals (CI) is 1.11; 95% CI = 0.16 to 2.05; $P = 0.03$; $I^2 = 96\%$ and is depicted in Fig. 7. The AMH may increase by 1.11 after administration.
- The estimated overall effect size of mean difference after post-PRP in separate analysis between POI and POR. Post PRP favoured the POI group with significant difference (-3.08;95%CI:-2.11to-4.05; P = 0.00) however, the number of studies compared AMH are only two studies with high heterogeneity of 85% and wide confidence intervals.
- The estimated overall effect size of post-PRP in separate analyses among those under 35 years and over 35 years of age did not result in any significant differences in pregnancies (0.76;95%CI:-0.73–2.24; $P = 0.32$).
- FSH: Ten studies reported the effect of ovarian PRP injection on FSH [10, 12, 23–25, 27–31]. Cohen's mean difference in FSH favoured injection of PRP (post-PRP). The estimated overall effect size of means difference (random model) with confidence intervals (CI) is -0.62; 95% CI = -1.57 to 0.33; $P = 0.17$; $I^2 = 98\%$ and is depicted in Fig. 8. This is a non-significant decrease in FSH after PRP.

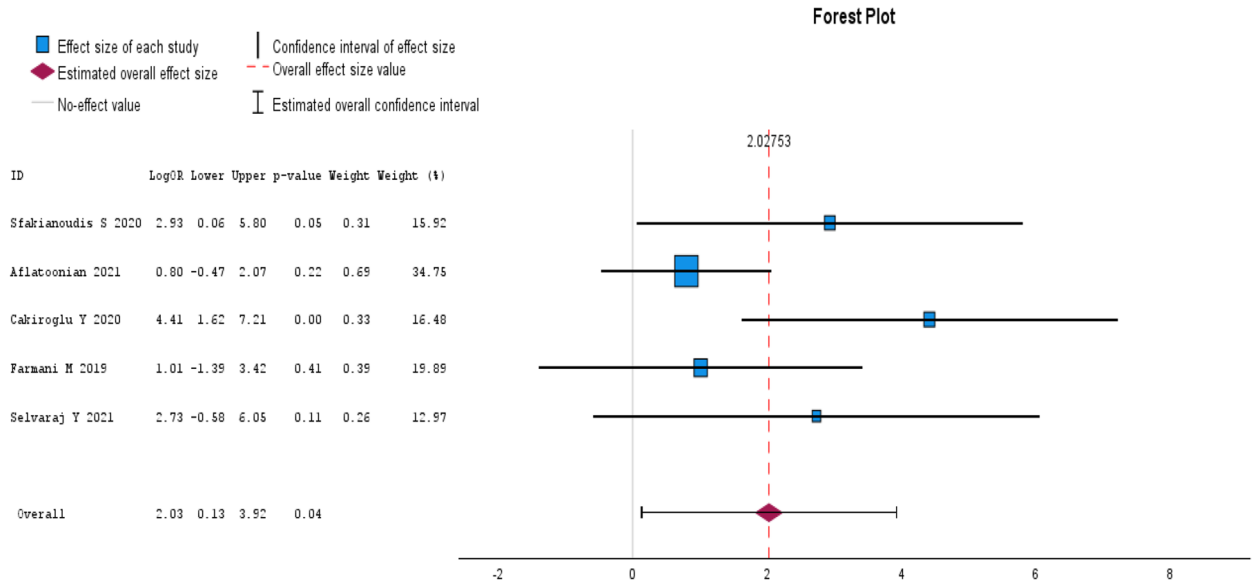

Fig. 3 Random model for pregnancies

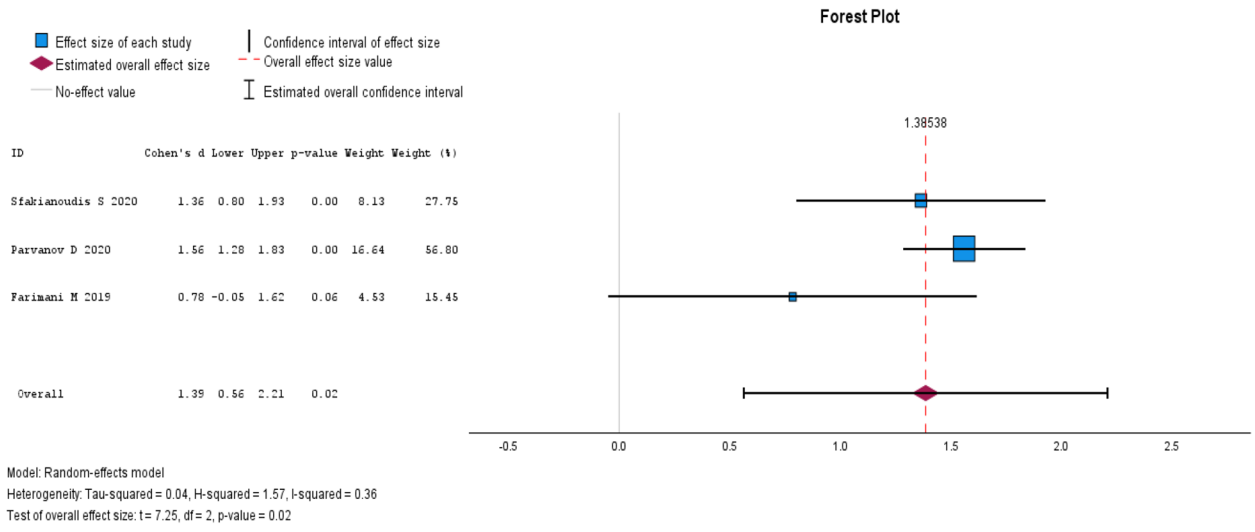

Fig. 4 Random model for embryo formation

Discussion

Meaning of our findings

Our study findings suggest that intraovarian PRP administration will increase pregnancy rates and better oocyte and embryo formation. Similarly, there was an improvement in the ovarian reserve markers (AFC, AMH) in POI/POR women.

Pregnancies: The studies reported an increase in pregnancy rates after PRP injection, but many of the pregnancies occurred in younger women (mean age ~ 35 years), and most of them were natural conceptions rather than IVF/ICSI. There was a tendency to favour spontaneous pregnancies in younger women with POI rather than controlled ovarian stimulation after PRP injection. This indicates that maternal age is the most important factor in pregnancy outcomes with or without PRP injection [12]. PRP probably increases pregnancy with the caveat that the quality of evidence is only moderate. The effect

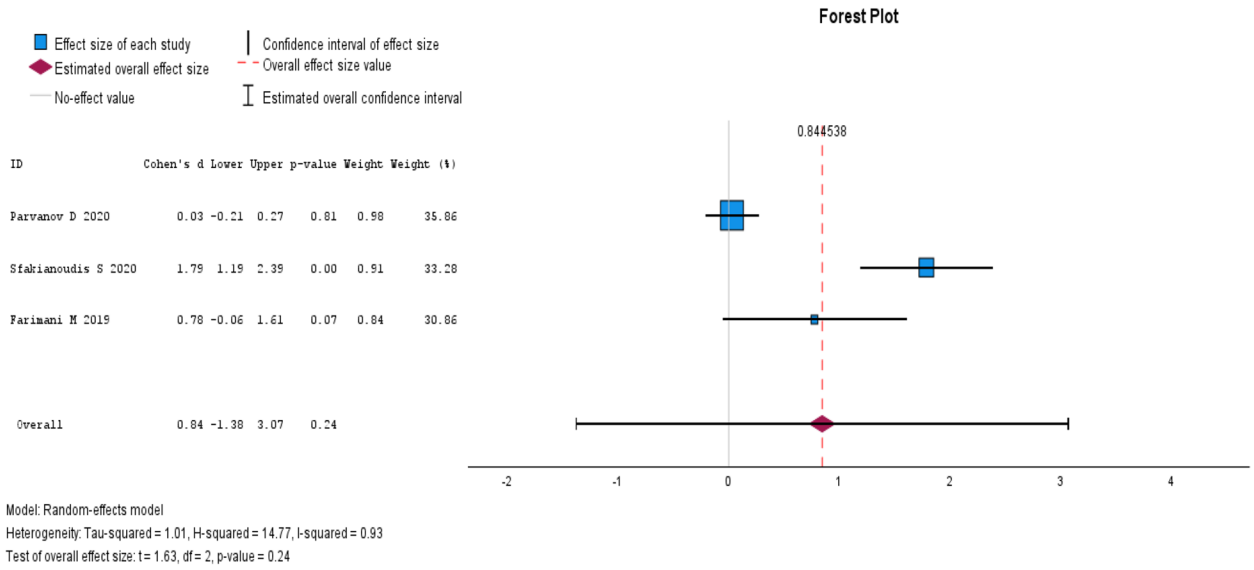

Fig. 5 Random model for oocyte retrieved

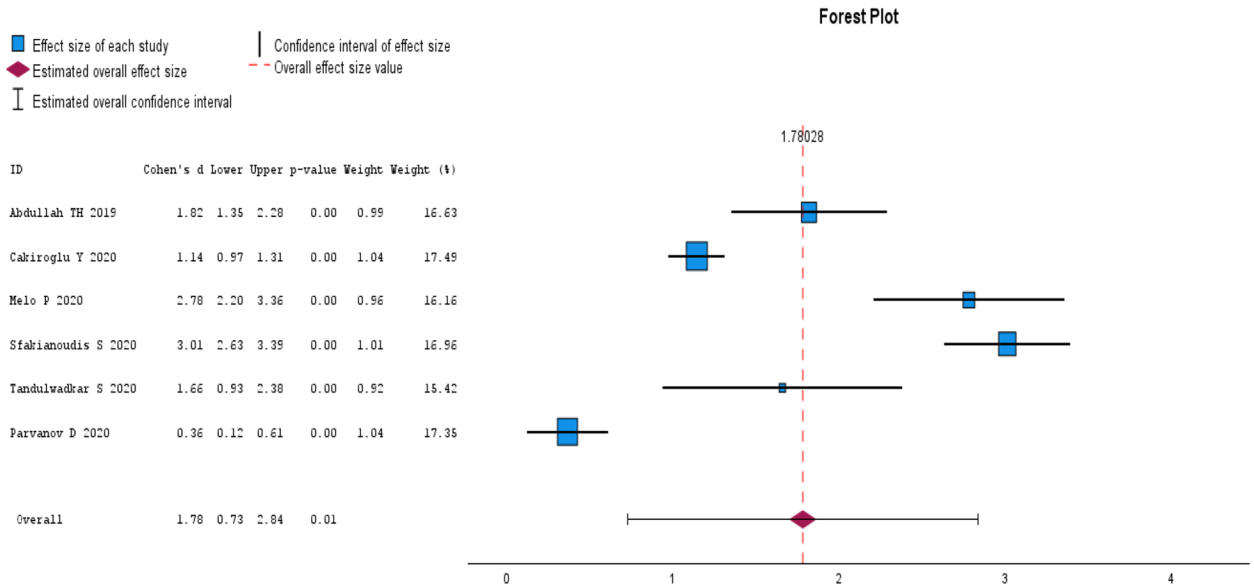

Fig. 6 Random model for AFC

of smaller studies needs to be taken with caution and the possibility of high publication bias, with one study having only five subjects [23].

AFC: Our study findings show statistically significant improvement in the AFC. In POI, apoptosis and atresia can occur in all stages of folliculogenesis, i.e. primordial follicle to the antral follicle [33, 34]. The autocrine and paracrine growth factors play a crucial role in all stages of folliculogenesis which can influence embryo quality and implantation potential [35]. We do not know at what stage of folliculogenesis, atresia/apoptosis occurred or what growth factor gene was expressed or mutated at the time of atresia/apoptosis [36]. Henceforth, we can hypothesize that the beneficial effect of PRP to halt

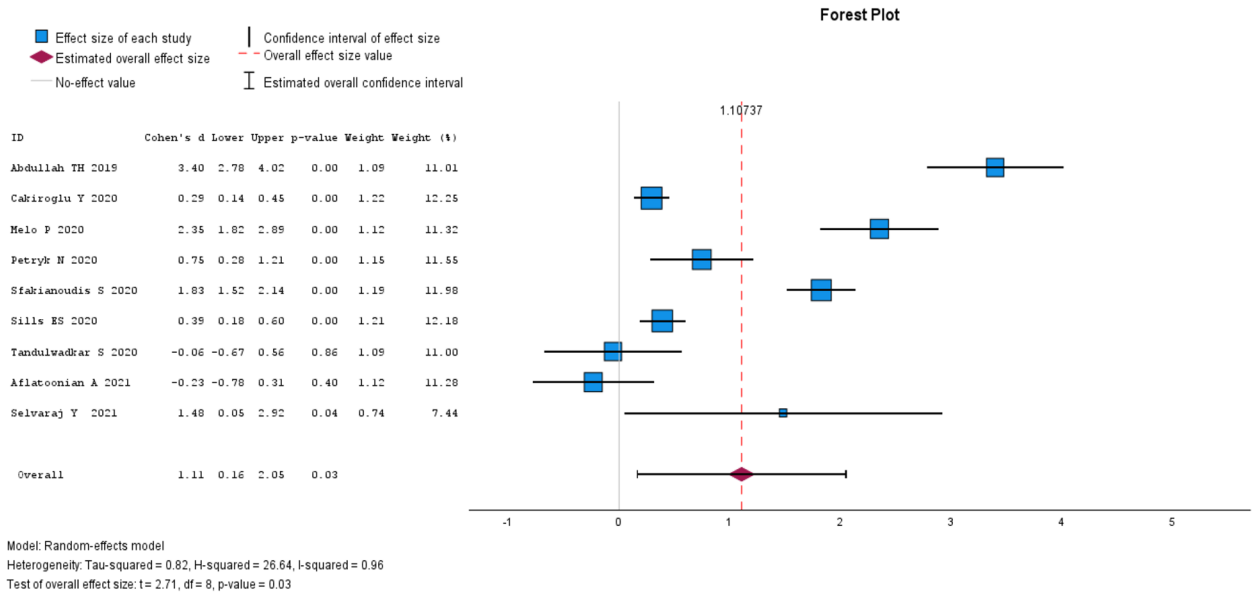

Fig. 7 Random model for AMH

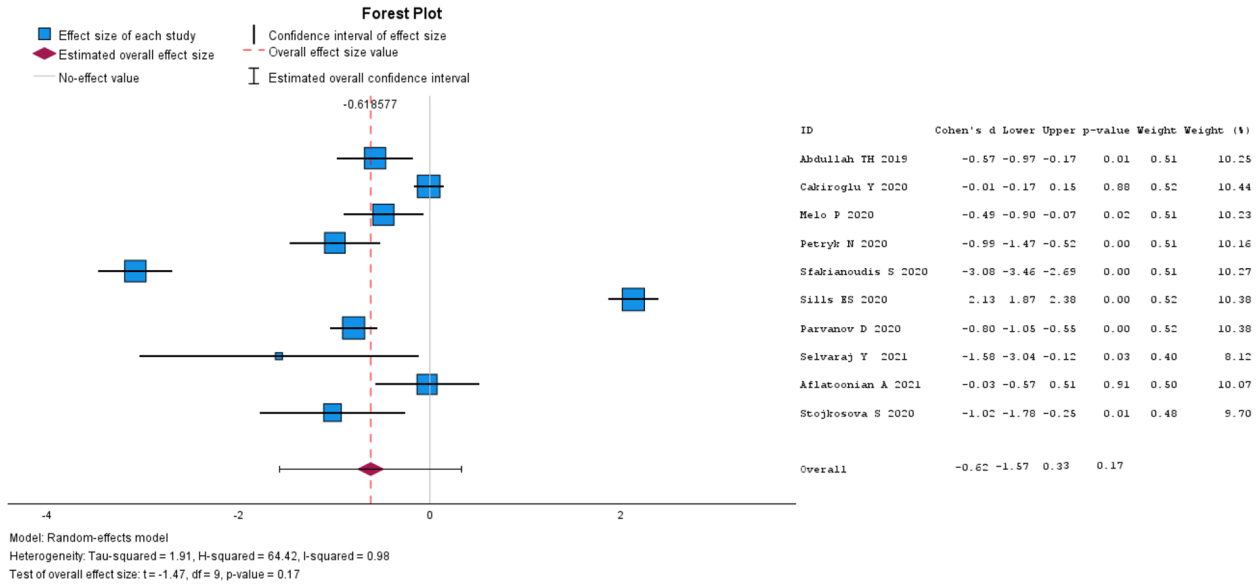

Fig. 8 Random model for FSH

the process of apoptosis depends upon the normal gene expression and abnormal gene mutation expression of growth factors at the time of apoptosis/atresia [35, 37]. If normal growth factor gene expressions persist more than abnormal growth factor gene mutations, then PRP might help in the promotion of the development of the remaining antral follicles or may slow down the process of apoptosis, which might quantitatively increase the number of AFC [36]. When the abnormal growth gene mutations are expressed more, then PRP may not necessarily reactivate the already atretic primordial follicle or will lead to low viability and implantation after PRP administration in POI [37]. The quality of evidence about improvement in antral follicle count after PRP is low(uncertain). The mean difference of just 1.78 after PRP has no clinical utilitarian value.

AMH: The AMH is primarily secreted by the granulosa cells of the developing follicles. POI results in the atresia

of the follicles and a decrease in the AMH. As mentioned above, PRP may halt the process of atresia but may not reactivate the atretic follicles thus resulting in some improvement in AMH levels [38]. Although the improvement was noted, it may not be clinically significant for good fertility outcomes [38]. The quality of evidence about improvement in AMH after PRP is low (uncertain). The mean difference of improvement of just 1.11 of AMH does not have any clinical utilitarian value.

The estimated overall effect size may favour POI and those under 35 years of age without any statistical significance after PRP concerning pregnancies, AFC and AMH without any clinical utility.

Comparison with other studies

PRP injection favoured more oocyte and embryo formation. The study by Sfakianoudis et al. [24] and Farimani et al. [32] showed an increase in the number of oocytes and embryos, while the study by Parvanov et al. [30] did not show any statistical increase in the number of oocytes and embryos. The age of patients studied ranged from 35–38 years in the study by Sfakianoudis et al. [24] and Farimani et al. [32]. The mean age of the patients in the study by Sfakianoudis et al. [24] and Farimani et al. [32] may be less than that of the mean age of patients in the study by Parvanov et al. [30], as the study by Parvanov et al. [30] did not mention the mean age. The most probable reason for the increase in the number of oocytes and embryos is that PRP may help to activate existing preantral and/or early antral follicles [24], and thus they respond better to fertility treatment.

Strengths and limitations

This study was undertaken to evaluate the effects of intraovarian PRP administration in POI/POR women on pregnancies and ovarian reserve markers. There are no randomized control trials, and all the studies included in our meta-analysis and review were observational studies, which led to a high risk of bias. Also, the number of studies which have reported on pregnancies was only five with one study with only 5 subjects.

Implications for clinical practice

Based on our findings, intraovarian PRP administration may have a role in improving pregnancies and ovarian reserve markers in POI/POR women, albeit the younger women conceived spontaneously in comparison to older women with or without ART.

Implications for future research

Given that there is scope to improve the pregnancy outcomes in POI/PORs, there is no standardized preparation method and PRP injection volume. There is a huge need for large multi-centred randomized trials to standardize the PRP preparation, volume & frequency of administration, duration of repeat PRP injections, and follow-up of patients to evaluate the improvement in fertility outcomes, till that time this procedure is deemed experimental.

Conclusions

Intraovarian PRP injections in POI or POR or low ovarian reserve women did not show significant improvement in the pregnancies (moderate level of evidence), AFC (low level of evidence), AMH(low level of evidence), and number of oocytes and embryos. Live birth rates were not calculated. There is no statistical difference between POI/POR and < 35 years and > 35 years. Large multicentric randomized control trials are required, especially concerning the type of PRP preparation, amount of PRP injected, number and frequency of PRP injections required and duration of follow-up to evaluate the effect of PRP injection, for clinical utility before it is incorporated in the management of POI/POR patients.

Abbreviations

AFC	Antral follicle count
AMH	Anti-Mullerian hormone
ART	Assisted reproductive technology
DOR	Decreased ovarian reserve
ESHRE	European Society of Human Reproduction and Embryology
FSH	Follicle stimulating hormone
IVF	In vitro fertilization
ICSI	Intracytoplasmic sperm injection
NIH	National Institute of health
PDGF	Platelet-derived growth factor
POI	Premature ovarian insufficiency
POR	Poor ovarian response
POSEIDON	Patient Oriented Strategies Encompassing Individualized Oocyte Number
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	Platelet-rich plasma
TGF	Transforming growth factor
VEGF	Vascular endothelial growth factor

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Code availability

PROSPERO Registration number: 2021 CRD42021245753.

Authors' contributions

Conception – Dr. Srisailesh Vitthala and Dr. Prashanth K Adiga. Acquisition – Dr. Srisailesh Vitthala and Dr. Prashanth K Adiga. Analysis- Dr. Ravishankar N and Dr. Nicola Marconi. Interpretation –Dr. Nicola Marconi. Drafting – Dr. Srisailesh Vitthala. Final approval—Dr. Prashanth K Adiga.

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Availability of data and materials

Data extracted from published papers.

Declarations

Ethics approval and consent to participate
Not applicable as it is a systematic review and meta-analysis.

Consent for publication
Not applicable.

Competing interests
The authors have no conflict of interest.

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