Efficacy of intra-uterine infusion of PRP for pregnancy related outcomes in women with recurrent implantation failure; systematic review and meta-analysis of published trials

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Abstract

Background: We aim in our systematic review and meta-analysis to summarize and evaluate the efficacy of intra uterine infusion of PRP for improving pregnancy related outcomes compared to a control group during infertile treatment in women suffering from recurrent implantation failure (RIF).

Methods: Our systematic review (SR) and meta-analysis (MA) was carried out according to the PRISMA guidelines for randomized studies. we searched PubMed, Web of Science, Scopus, and Cochrane library for included studies. We chose randomized controlled trials (RCTs) assessing the efficacy of PRP in women with RIF, then we used Review Manager Software to pool the outcomes of our MA.

Results: We included seven studies in our analysis. The results were significant and favor PRP group regarding clinical, biochemical pregnancy rate and endometrial thickness as following [RR=1.79 CI 95% (1.37-2.32)], [RR=1.97 CI 95% (1.40-2.79)], and [RR=1.79 CI 95% (1.13-2.44)] respectively.

Conclusion: PRP has the ability to improve clinical and biochemical pregnancy rate. Also, it has the ability to increase endometrial thickness in women with RIF.

Keywords: platelet-rich plasma (PRP); Implantation rate (IR); multiple pregnancy rate; miscarriage rate; assisted reproductive technique; IVF/ICSI; controlled ovarian hyperstimulation; repeated implantation failure.

Introduction

Implantation failure (IF) may happen in any stage of the implantation process which are apposition, adhesion, and invasion. There are many causes of IF which are categorized into main 4 classes; change in the endometrial receptive state, embryonic causes, abnormalities in endometrial to embryo crosstalk and immunological causes(1). It is well

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known that the state of the uterine cavity and endometrium thickness have a golden role to ensure pregnancy process (2). Nearly, 13% of the global population have difficulties to conceive for many different reasons (3). If we are talking about the normal natural menstrual cycle, the receptivity of the endometrium is best five to seven days after ovulation which is the same time needed to reach blastocyst stage(4). Endometrial thickness fewer than 7 mm is probably related to disappointing conception outcomes such as, (RIF) and subsequently decreasing pregnancy rates(5).

To increase both quality and endometrial thickness many drugs and interventions have been tried like, different forms of estradiol hormonal(6); vasoactive components like sildenafil(7), intrauterine granulocyte colony-stimulating factor (G-CSF)(8), vitamin E (9)and even pentoxifylline(9); scratching the endometrium(10), immune-modulators usage(11), and correcting the endometrial cavities using hysteroscopy(12). All of which were used as and adjuvant management modality to improve the receptive state and thickness of the endometrium.

In the last decades, there has been a great progress in the treatment of RIF and increasing endometrial thickness such as the usage of platelet rich plasma (PRP). PRP are widely used in many medical fields such as plastic surgery(13), derma(14), ortho(15), and cardio-thoracic surgery(16). It is an autologous conditioned platelets concentrated in plasma and are derived from fresh whole blood, centrifuging it in order to remove red blood cells(17).

PRP has grown in prominence in the field of reproduction in recent years, and several studies have previously looked into its influence on ovarian "rejuvenation" by rousing dormant oocytes in humans, such as those with low ovarian reserve.(18), cases with premature ovarian failure (POF)(19), patients in the post-menopausal period(19, 20).

The main idea of PRP mechanism of action in patients with previous RIF is thought to be mediated through the endometrium itself where the expression of growth factors and cytokines is increased significantly (21).

in our systematic review (SR) and meta-analysis (MA), we are aiming to investigate the previous studies that estimated the efficacy of PRP infusion intra-uterine for infertile females with RIF.

Methodology

Our systematic review (SR) and meta-analysis (MA) was reported according to the guideline reported in the PRISMA statement and that mentioned in "Cochrane handbook for systematic reviews of interventions(22).

Search strategy

We conducted online search of the database till December 2021. The following keywords were used to our database: Intrauterine OR autologous OR platelet-rich plasma (PRP) OR Implantation rate (IR) OR multiple pregnancy rate OR miscarriage rate OR assisted reproductive technique OR IVF/ ICSI controlled ovarian hyperstimulation OR repeated implantation failure to identify the studies that meet our PICO criteria. We also searched the references to identify any other eligible study. We managed our references by Endnote X8.0.

Study selection process and outcome measurement

As mentioned above, we conducted Our SR&MA according to the PRISMA checklist for Randomized controlled trials (RCT).

Inclusion criteria:

RCTs in English with available full text met the following criteria: 1) age between 18 to 45Y 2) infertile women with primary or secondary infertility; 3) with regular menstrual cycles;

4) normal semen parameters of the husband; 5) BMI less than 35k/m2; 6) history of thin endometrium or poor endometrial response, 7) history of RIF

The exclusion criteria:

1)Patientsagedmorethan40years;2)endocrine and thyroid disorders; 3) tubal infertility as detected by Hysterosalpingogram (HSG); 4) cardiovascular, renal, or hepatic disorders; 5) congenital uterine deformities (Asherman Syndrome, fibroid), 6) endometritis; 7) tubal factors such as hydrosalpinx).

The outcome measured were as following clinical pregnancy rate; biochemical pregnancy rate; and ongoing pregnancies.

Data extraction

Data extraction including baseline characteristics (such as, patients age, (BMI) etc.) and outcomes (clinical, biochemical pregnancy rate, and ongoing pregnancies). RCTs were assessed by using the Cochrane Handbook for SR, the 2nd edition(23).

Statistical analysis

This MA was done using Rev-Manager 5.4.0 (Cochrane Collaboration, Oxford, UK). When describing the results of this study, researchers used RR and 95% CI (DerSimonian and Laird 1986). The degree of heterogeneity was established using Cochrane's Q tests and I2 stats. There is considerable heterogeneity if the I2 is more than 50% and the P-value is less than 0.1. To decrease the heterogeneity, the study used a random-effect model. When the p-value was more than 0.1, it was deemed significant statistically. There wasn't subgroup analysis due to lack of data in the included papers.

Results

characteristics of included studies

72 articles were concluded in the searched databases. 15 articles were excluded after title and abstract screening. Of the remaining 25 articles, we ruled out 18 articles. Finally, seven studies were involved. (24-30) All of them were included (fig 1). Summary and baseline characteristics of included studies mentioned in **Tables 1 and 2**.

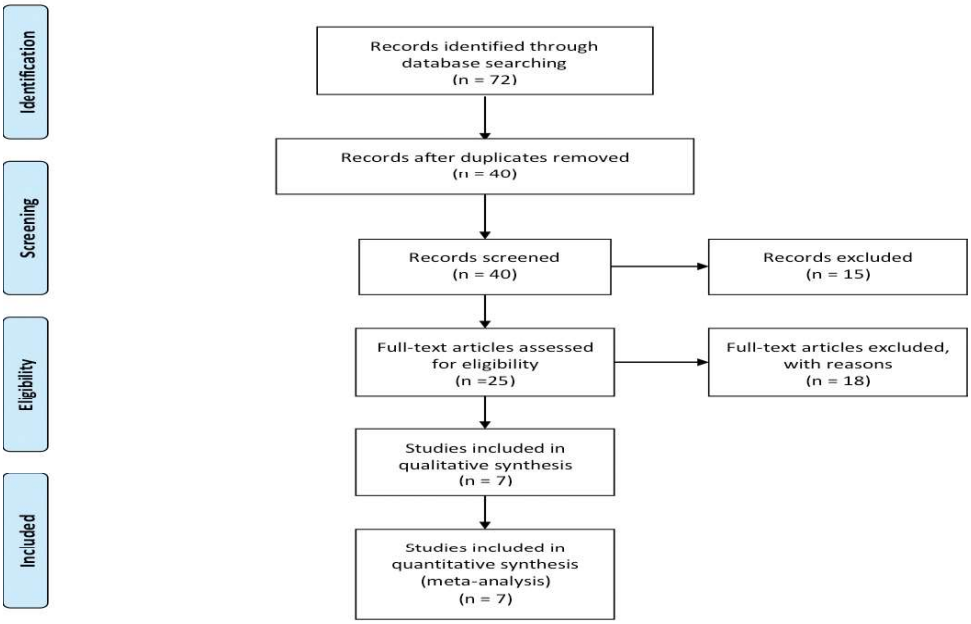

Fig1; Prisma flow diagram

study ID	Study arms	Age of cases	BMI	Basal FSH	AMH level	Endo-metrial thickness	Previous pregnan-cy	Dura-tion of infertility (years)	Trans-ferred blasto-cysts	Previ-ous ET cycles	History of abor-tion
Tehranine-jad 2020	PRP group: 42	33.5 ± 2.5	26.2 ± 2.8	6.4 ± 2.2	2.4 ± 3.7	7.7 (7.0–8.9)	20 (47.6%)	8.9 ± 6.2	2 (2–2)	4 (3–5)	18 (42.9%)
	control group:43	32.9 ± 3.0	26.3 ± 3.3	6.3 ± 2.4	2.0 ± 2.7	7.7 (7.0–8.8)	21 (48.8%)	11.0 ± 7.0	2 (2–3)	4 (3–5)	19 (44.2%)
Bakhsh 2022	PRP group	35	25.3	7		.	.	4.5	2.8	.	.
	control group	32.7	25.9	5.4		.	.	6.5	3.3	.	.
Nazari 2022	PRP group: 49	35.73 ± 3.49	25.61 ± 3.13	.	.	.	.	.	1.9 ± 0.8	5.38 ± 2.3	.
	control group:48	34.95 ± 4.23	25.46 ± 2.68	.	.	.	.	.	1.7 ± 0.6	4.97 ± 2.8	.
Coksuer 2019	PRP group: 34	29.41 ± 4.54	26.35 ± 4.41	7.3 (4.6–9.5)	.	10 (8–14)	.	7 (4–16)	9.32 ± 0.47	.	.
	control group:36	28.89 ± 3.91	26.78 ± 3.79	6.9 (3.5–9.7)	.	10 (8–13.5)	.	8 (5–15)	9.39 ± 2.46	.	.
Chang 2019	PRP group: 34	34.77± 0.75	22.42± 0.42	5.91± 1.77	.	6.32±0.54	.	3.57±1.82	.	.	.
	control group:30	32.64± 1.70	22.39± 0.80	6.36± 1.84	.	6.39±0.72	.	3.71±1.66	.	.	.
Mehrafza 2019	PRP group: 34	31.85± 5.22	25.52± 3.47	4.59± 1.71	3.02±1.85	.	.	.	3(2-9)	.	.
	control group:30	33.46± 5.17	26.44± 3.61	5.29± 2.18	2.08±2.59	.	.	.	2(2-5)	.	.
Russell 2022	100 patients	37.07 ± 3.77	22.44 ± 2.99	.	.	.	.	1.64 ± 2.32	.	2.19 ± 0.95	22% (19)

Table 2 baseline of included studies

Study ID	set-ting	Study design	study period	Study arms and sample	Inclusion criteria	Exclusion criteria	inter-vention group	control group	results
Tehranine-jad 2020	Iran	nonran-domized CT	between 2016 and 2018	PRP: 42 patients control: 43 patients	patients with RIF	age ≥35 y, ET <7 mm, FSH >10 mIU/Ml, males with azoo-spermia, intrauterine disorders, thrombophilia thyroid dysfunction, positive antiphospholipid antibodies or chromosomal abnormality in a couple.	PRP	non	no role for PRP in improving pregnancy outcomes
Bakhsh 2022	Iran	RCT	.	.	age less than 40 years BMI less than 30kg/m2.	hematological, hormonal, im-munological, chromosomal, and genetic disorders, and cancers	PRP	non	PRP im-prove all pregnancy outcomes
Nazari 2022	Iran	RCT	2016 and 2017	PRP: 49 patients control: 48 patients	age less than 40 years (BMI) less than 30 kg/m2	uterine abnormalities (con-genital or acquired), hormonal disorders, immunological and hematological disorders, azoospermia, testicular sperm extraction or aspiration, ana-tomical disorders of the male genital tract, varicocele and chromosomal abnormalities	PRP	non	PRP im-prove all pregnancy outcomes

Coksuer 2019	.	retro-spective analysis	Jan 2014 and Jan 2017	PRP: 34 patients control: 36 patients	normal hys-teroscopy and karyotype, regular menstrual cycle of 21–35 days, FSH <10 IU/L, normal semen analysis, mean BMI 18 to 28, mean age 21 to 39, without systemic or immunologic disorders.	cases who obtained donor eggs, previously taken PRP, poor embryo quality	PRP	non	PRP im-prove all pregnancy outcomes
Chang 2019	Chi-na	prosp ective cohort	July 2015 to July 2016	PRP: 34 patients control: 36 patients	(1) age less than 40, FSH<10IU/L (2) endometrium thickness(<7mm) (3) no structural uterine anomalies	pelvic cancer, endometriosis, and adenomyosis	PRP	non	PRP im-prove all pregnancy outcomes
Mehrafza 2019	Iran	retro-spective cohort	during the peri-od from 2016-2017	PRP: 67 patients control: 56 patients	.	.	PRP	non	PRP im-prove all pregnancy outcomes
Russell 2022	Can-ada	retro-spective cohort	October 2018 to July 2021	100 patients	24–52y who diag-nosed with RIF or thin endometrium had PGT-A-tested euploid embryos received one or more intrauterine PRP infusions	inactive endometrium multiple embryos transferred genetic, hematologic, or auto-immune disease Diploid-aneuploid mosaic embryo transfers	PRP	non	PRP can improve both en-dometrial thickness and im-plantation rate

Summary of included studies: PRP: Platelet rich plasma; RIF: recurrent implantation failure; RIF: by mean is the failure to get pregnant following multiple embryo transfers (ET) cycles (three embryos of a high quality, or ≥ ten embryos on a different transfer cycles) or nonex-istence of sac on ultrasound at or after 5 weeks of ET.

Bias and quality assessment

Regarding the quality assessment of included RCTs, the included studies were of low risk of randomization, allocation, attrition bias, reporting bias, and any other biases. Regarding blinding, all studies reported that participants were not blind, and the nature of the interven-tion can explain this. Fig2

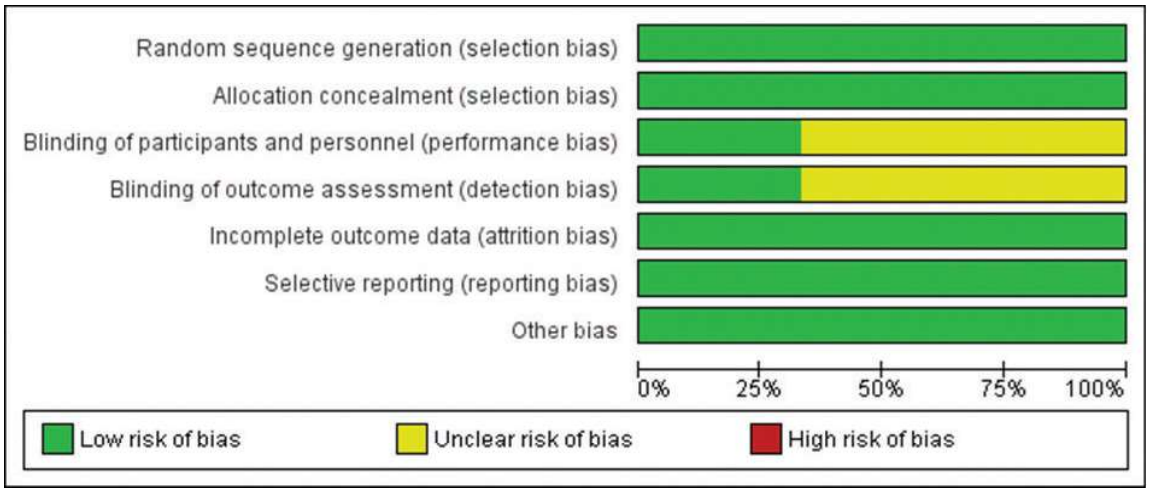

Fig2; risk of bias assessment

Clinical pregnancy rate:

Seven studies discussed the efficacy of PRP on the clinical pregnancy, of which 3 RCTs studies (total number of 59 in the intervention group and 25 in the control group) and 4 cohort studies (total number of 74 in the intervention group and 50 in the control group). (24-30) the results were significant and favor PRP (intervention) group and proved its ability to increase clinical pregnancies as following [RR=1.79 CI 95% (1.37-2.32)] (fig3. All our results were homogenous.

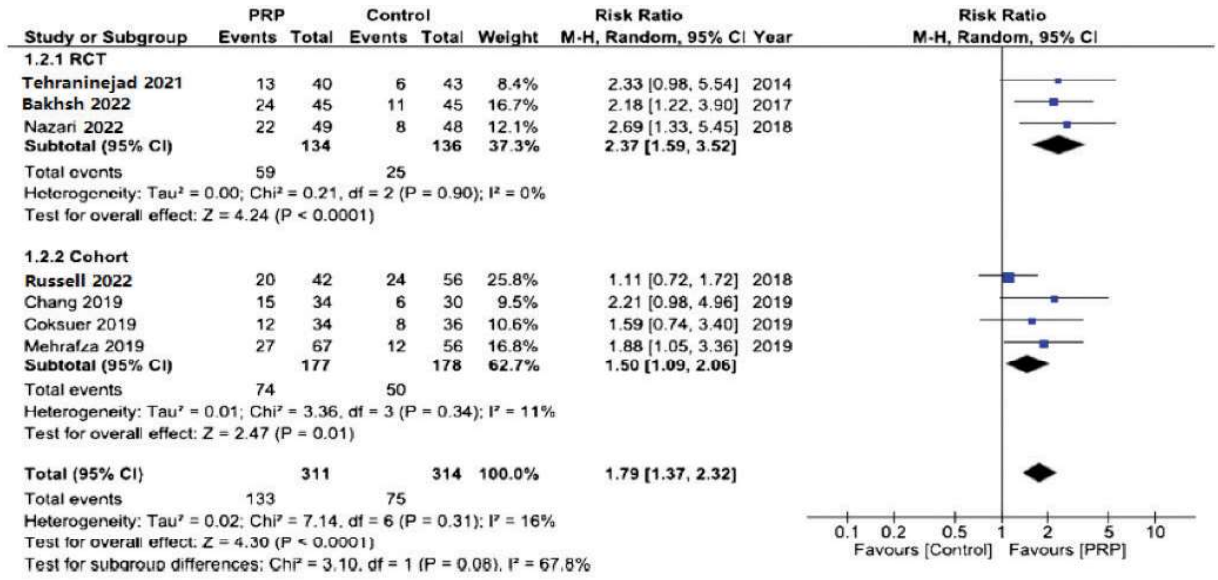

Fig3 Forest plot detailed for clinical pregnancy rate

Biochemical pregnancy rate:

four studies discussed the efficacy of PRP on bio-chemical pregnancies (24, 25, 27) with total number of 71 in the PRP group and 32 in the control group. Our results were significant and favor PRP group [RR=1.97 CI 95% (1.40-2.79)]. Our data was homogenous as following [(P = 0.83); I^2 = 0%] (fig. 4).

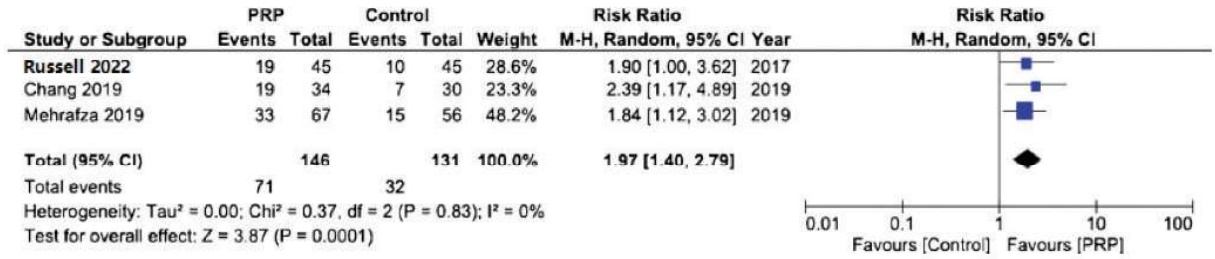

Fig4 Forest plot detailed for biochemical pregnancy rate

Endometrial thickness:

two studies discussed the role of PRP on patients with thin endometrium (24, 28). The results were significant and favor patients in the PRP group as following [RR=1.79 CI 95% (1.13-2.44)]. Our data was homogenous as following [(P = 0.10); I^2 = 64%] (fig. 5).

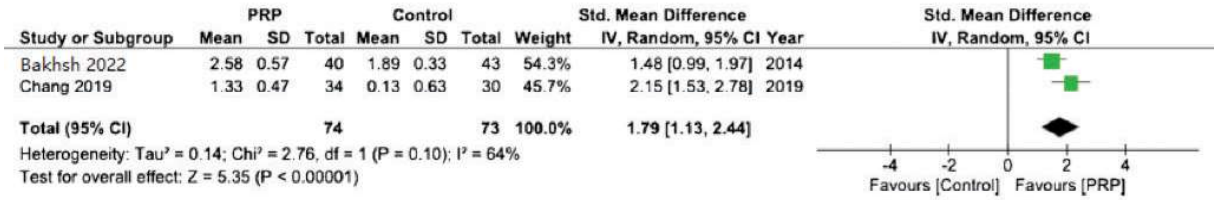

Fig5 Forest plot detailed for endometrial thickness

Discussion

seven studies were included in our meta-analysis that evaluating the efficacy of PRP as an add on therapy in fertile women with RIF. In the PRP group we noticed better improvement regarding the clinical and bio-chemical pregnancy rate. Also, the endometrium showed a significant increase in thickness. All of our results were homogenous.

PRP is an autologous condition where the platelets are found in an absolute concentration. Its injected through many different routes according to the used protocol(31). Our results go in the same direction with Bakhsh et al 2022(28). The study was done on 100 patients and could prove the magic role of PRP in increasing the pregnancy related outcomes in patients with RIF. On the other hand Tehraninejad et al 2021(29) said that PRP has no role in patients with RIF undergoing embryo transfer. Unfortunately, there aren't enough well-designed trials summarizing the efficacy and role of PRP in patients with thin endometrium, so we can't credit PRP's ability to improve the pregnancy outcomes in women with thin endometrium solely. As a result, future research should look into other endometrial receptivity markers.

Limitations and Strength points

Our study has several strength points (1) we conducted all steps in strict accordance with the Cochrane Handbook of Systematic Reviews for interventions, (2) we followed the standard reporting guidelines of PRISMA statement to report this work, (3) we ran a comprehensive search of multiple electronic databases to identify all relevant studies, and finally (4) Our study reported class 1 evidence about the efficacy of GDFT during pregnancy. Nonetheless, our study has a few limitations.

Conclusion

In conclusion, our MA showed significant difference between PRP group and the control groups regarding clinical, biochemical pregnancy and endometrial thickness. So, PRP shows promising results in all pregnancy related outcomes. Also, PRP may provide benefit to healthy parturient women and their newborns

References

1. Diedrich K, Fauser BC, Devroey P, Griesinger G. The role of the endometrium and embryo in human implantation. Hum Reprod Update. 2007;13(4):365-77.
2. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS medicine. 2012;9(12):e1001356.
3. Bos-Mikich A, Ferreira MO, de Oliveira R, Frantz N. Platelet-rich plasma or blood-derived products to improve endometrial receptivity? Journal of assisted reproduction and genetics. 2019;36(4):613-20.
4. Cakmak H, Taylor HS. Implantation failure: molecular mechanisms and clinical treatment. Hum Reprod Update. 2011;17(2):242-53.
5. Dessolle L, Daraï E, Cornet D, Rouzier

R, Coutant C, Mandelbaum J, et al. Determinants of pregnancy rate in the donor oocyte model: a multivariate analysis of 450 frozen-thawed embryo transfers. Human reproduction (Oxford, England). 2009;24(12):3082-9.

6. Davar R, Janati S, Mohseni F, Khabazkhoob M, Asgari S. A Comparison of the Effects of Transdermal Estradiol and Estradiol Valerate on Endometrial Receptivity in Frozen-thawed Embryo Transfer Cycles: A Randomized Clinical Trial. Journal of reproduction & infertility. 2016;17(2):97-103.
7. Refai H, Hassan D, Abdelmonem R. Development and characterization of polymer-coated liposomes for vaginal delivery of sildenafil citrate. Drug delivery. 2017;24(1):278-88.
8. Zhao J, Tian T, Zhang Q, Wang Y, Li Y. Use of granulocyte colony-stimulating factor for the treatment of thin endometrium in experimental rats. PLoS One. 2013;8(12):e82375-e.
9. Acharya S, Yasmin E, Balen AH. The use of a combination of pentoxifylline and tocopherol in women with a thin endometrium undergoing assisted conception therapies--a report of 20 cases. Human fertility (Cambridge, England). 2009;12(4):198-203.
10. Gibreel A, El-Adawi N, Elgindy E, Al-Inany H, Allakany N, Tournaye H. Endometrial scratching for women with previous IVF failure undergoing IVF treatment. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology. 2015;31(4):313-6.
11. D'Hooghe TM, Debrock S, Hill JA, Meuleman C. Endometriosis and subfertility: is the relationship resolved? Seminars in reproductive medicine. 2003;21(2):243-54.
12. Margalioth EJ, Ben-Chetrit A, Gal M, Eldar-Geva T. Investigation and treatment of repeated implantation failure following IVF-ET. Human reproduction (Oxford, England). 2006;21(12):3036-43.
13. Chen S, Liu B, Yin N, Wang Y, Li H. Assessment of Bone Formation After Secondary Alveolar Bone Grafting With and Without Platelet-Rich Plasma Using Computer-Aided Engineering Techniques. The Journal of craniofacial surgery. 2020;31(2):549-52.
14. Bayat M, Yazdanpanah MJ, Hamidi Alamdari D, Banihashemi M, Salehi M. The effect of platelet-rich plasma injection in the treatment of androgenetic alopecia. Journal of cosmetic dermatology. 2019;18(6):1624-8.
15. Tabrizi A, Dindarian S, Mohammadi S. The Effect of Corticosteroid Local Injection Versus Platelet-Rich Plasma for the Treatment of Plantar Fasciitis in Obese Patients: A Single-Blind, Randomized Clinical Trial. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons. 2020;59(1):64-8.
16. Rainys D, Cepas A, Dambrauskaite K, Nedzelskiene I, Rimdeika R. Effectiveness of autologous platelet-rich plasma gel in the treatment of hard-to-heal leg ulcers: a randomised control trial. Journal of wound care. 2019;28(10):658-67.
17. Frantz N, Ferreira M, Kulmann MI, Frantz G, Bos-Mikich A, Oliveira R. Platelet-Rich plasma as an effective alternative approach for improving endometrial receptivity - a clinical retrospective study. JBRA Assist Reprod. 2020;24(4):442-6.
18. Melo P, Navarro C, Jones C, Coward K, Coleman L. 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. Journal of assisted reproduction and genetics. 2020;37(4):855-63.
19. Pantos K, Simopoulou M, Pantou A, Rapani A, Tsioulou P, Nitsos N, et al. A Case Series on Natural Conceptions Resulting in Ongoing Pregnancies in

Menopausal and Prematurely Menopausal Women Following Platelet-Rich Plasma Treatment. Cell Transplant. 2019;28(9-10):1333-40.

20. Vural B, Duruksu G, Vural F, Gorguc M, Karaoz E. Effects of VEGF (+) Mesenchymal Stem Cells and Platelet-Rich Plasma on Inbred Rat Ovarian Functions in Cyclophosphamide-Induced Premature Ovarian Insufficiency Model. Stem cell reviews and reports. 2019;15(4):558-73.
21. Chang AM, Aeschbach D, Duffy JF, Czeisler CA. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(4):1232-7.
22. Zhang J, Han L, Shields L, Tian J, Wang J. A PRISMA assessment of the reporting quality of systematic reviews of nursing published in the Cochrane Library and paper-based journals. Medicine (Baltimore). 2019;98(49):e18099-e.
23. Cumpston MS, McKenzie JE, Welch VA, Brennan SE. Strengthening systematic reviews in public health: guidance in the Cochrane Handbook for Systematic Reviews of Interventions, 2nd edition. Journal of public health (Oxford, England). 2022.
24. Chang Y, Li J, Wei LN, Pang J, Chen J, Liang X. Autologous platelet-rich plasma infusion improves clinical pregnancy rate in frozen embryo transfer cycles for women with thin endometrium. Medicine (Baltimore). 2019;98(3):e14062.
25. Mehrafza M, Kabodmehri R, Nikpouri Z, Pourseify G, Raoufi A, Eftekhari A, et al. Comparing the Impact of Autologous Platelet-rich Plasma and Granulocyte Colony Stimulating Factor on Pregnancy Outcome in Patients with Repeated Implantation Failure. Journal of reproduction & infertility. 2019;20(1):35-41.
26. Coksuer H, Akdemir Y, Ulas Barut M. Improved in vitro fertilization success and pregnancy outcome with autologous platelet-rich plasma treatment in unexplained infertility patients that had repeated implantation failure history. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology. 2019;35(9):815-8.
27. Russell SJ, Kwok YSS, Nguyen TTN, Librach C. Autologous platelet-rich plasma improves the endometrial thickness and live birth rate in patients with recurrent implantation failure and thin endometrium. Journal of assisted reproduction and genetics. 2022;39(6):1305-12.
28. Bakhsh AS, Maleki N, Sadeghi MR, SadeghiTabar A, Tavakoli M, Zafardoust S, et al. Effects of Autologous Platelet-Rich Plasma in women with repeated implantation failure undergoing assisted reproduction. JBRA Assist Reprod. 2022;26(1):84-7.
29. Tehraninejad ES, Kashani NG, Hosseini A, Tarafdari A. Autologous platelet-rich plasma infusion does not improve pregnancy outcomes in frozen embryo transfer cycles in women with history of repeated implantation failure without thin endometrium. The journal of obstetrics and gynaecology research. 2021;47(1):147-51.
30. Nazari L, Salehpour S, Hosseini S, Sheibani S, Hosseinirad H. The Effects of Autologous Platelet-Rich Plasma on Pregnancy Outcomes in Repeated Implantation Failure Patients Undergoing Frozen Embryo Transfer: A Randomized Controlled Trial. Reproductive sciences (Thousand Oaks, Calif). 2022;29(3):993-1000.
31. Alves R, Grimalt R. A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification. Skin appendage disorders. 2018;4(1):18-24.