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Intra-ovarian platelet-rich plasma administration plus successive accumulated embryo transfer could be a promising strategy for poor ovarian response management: a before-after study

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Abstract

Background The management of poor responders is a significant challenge for both patients and clinicians. The aim of this study was to evaluate the effectiveness of intra-ovarian injection of Platelet-Rich Plasma (PRP) combined with successive accumulated embryo transfer in improving the outcomes of patients with Poor Ovarian Response(POR) based on POSEIDON criteria.

Methods This single-center, retrospective before-after study was conducted at a private reproductive center, involving 49 women diagnosed with POR, indicated by an AMH level of less than 1.2 ng/ml. The participants, comprising 13 group 3 and 36 group 4 POR patients, underwent intra-ovarian injections of PRP followed by the accumulation of embryos over three successive cycles of mild stimulation IVF/ICSI from May 2021 to May 2022, before proceeding to the embryo transfer phase. The ovarian reserve markers, oocyte and embryologic outcomes were compared in all patients before and after intra-ovarian injection of PRP. The cumulative clinical pregnancy and cumulative live birth outcomes were presented. Statistical analyses were performed using SPSS version 25. A p-value < 0.05 denoted statistical significance.

Result(s) The mean age of all participants was 37.67 ± 4.15 years and their mean body mass index was 21.52 ± 2.80 kg/m^2. Autologous intraovarian PRP therapy significantly increased AMH levels, AFC and decreased FSH levels. Autologous intraovarian PRP therapy accompanied with 3 successive cumulated cycles, significantly increased No. of accumulated embryos and blastocysts. This strategy also significantly reduced the rate of cancelled cycle. Following this strategy, of 44 cases with accumulated embryos/blastocysts transfer, 20 (45.45%) achieved clinical pregnancy, of which 15 (34.09%) resulted in live births and 5 (11.36%) ended in miscarriage.

Conclusion(s) Intra-ovarian injection of PRP plus successive embryo accumulation following mild stimulation and accumulated embryo transfer appears to be an optimal strategy for POR management.

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Clinical trial number Not applicable.

Keywords Poor ovarian response, Platelet-rich plasma, POSEIDON criteria, Accumulation of embryos, Mild stimulation

Background

Despite the numerous advancements in reproductive medicine, certain issues persist without resolution. Among these, poor ovarian response stands out as one of the most challenging groups, presenting a persistent and vexing problem in everyday clinical practice that can be frustrating for both patients and clinicians [1].

Poor ovarian responders (PORs) account for approximately 9 to 24% of individuals receiving ovarian stimulation for in vitro fertilization (IVF) at assisted reproductive technology (ART) clinics [2]. The leading cause of POR is frequently linked to a reduced antral follicles count (AFC). In recent years, extensive efforts have been dedicated to addressing POR by employing a variety of controlled ovarian stimulation (COS) protocols, along with the integration of adjuvants either before or during the stimulation cycle. However, the outcomes of these strategies have been found to be unsatisfactory. There is a pressing need for alternative approaches to enhance the treatment outcomes for these poor responders. Notably, a limited reservoir of dormant primordial follicles persists in the ovaries of PORs, suggesting a potential avenue for improving the management of PORs [3].

In the last twenty years, the field of regenerative medicine has experienced significant progress [4]. The utilization of platelets to kick-start cell growth and the differentiation of tissues is now considered a highly effective approach within regenerative therapies [5]. When activated by events like bleeding or injury, platelets can unleash a multitude of bioactive substances and various growth factors. These elements are crucial for initiating clot formation, reducing inflammation, promoting vigorous new blood vessel formation, and facilitating repair in the affected tissues [6]. The extraordinary healing abilities of platelets have prompted the use of platelet-rich plasma (PRP), a concentrated form of blood obtained through centrifugation, which contains platelet levels up to seven fold higher than normal serum concentrations, across different areas of regenerative medicine [7]. The superior healing qualities of PRP are thought to be due to the increased presence of growth factors such as transforming growth factor-β (TGF-β), insulin-like growth factors 1 and 2 (IGF-1 and IGF-2), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF) [8]. As a crucial therapeutic approach, PRP has been effectively employed in various conditions, including eye diseases, myocardial infarction, nerve injuries, cosmetic surgery, tendinopathies, and other regenerative objectives [9]. Intrauterine PRP injection has been utilized in patients with thin endometrium since 2014 [10]. Intra-ovarian PRP injection was first used in patients with diminished ovarian reserve in 2018 [11]. Currently, PRP is being increasingly utilized in reproductive medicine owing to its regenerative capabilities. In recent years, numerous studies have effectively employed PRP for ovarian rejuvenation. A positive ovarian response was noted 6 weeks to 3 months following intra-ovarian PRP injection [12]. Furthermore, the positive ovarian response can be enduring, lasting between 6 to 12 months following a single procedure [13]. Uncommon instances of spontaneous pregnancy have been reported in women with Premature Ovarian Insufficiency (POI) or Premature Ovarian Failure (POF) following intra-ovarian PRP injection [14]. Nevertheless, the sustained implantation and live birth rates of IVF treatment are significantly higher than those of spontaneous conception. The impact of intra-ovarian PRP injection is limited to a specific timeframe, typically no more than one year. Therefore, for the majority of POR patients, repeated IVF cycles focusing on 'embryo banking' following intra-ovarian PRP may be necessary. In this study, our objective was to examine the effects of a single intra-ovarian PRP injection combined with successive accumulated embryo transfer on the IVF outcomes of POR patients.

Methods

Study design and patients

The retrospective before-after study was approved by and conducted according to the Medical Ethics Committee of Beijing Amcare Beisanhuan Women's & Children's Hospital. The inclusion criteria was considered as Patient-oriented Strategies Encompassing IndividualizeD Oocyte Number (POSEIDON) Group 3 and 4 poor responder patients undergone intra-ovarian PRP injection combined with accumulation of embryos through 3 successive IVF/Intracytoplasmic Sperm Injection (ICSI) cycles before transfer. POSEIDON Group 3 refers to young infertile women (< 35 years old), with low ovarian reserve markers (AFC < 5, AMH < 1.2 ng/ml), while POSEIDON Group 4 includes women ≥ 35 years old with similar characteristics to Groups 3 [15]. Patients with FSH > 25, current or previous IgA deficiency, a history of genital or non-genital cancers, treatment with anticoagulants, ovarian failure due to abnormal sex chromosomes, and prior pelvic surgery resulting in pelvic adhesions were excluded from the study [16]. Additionally, patients with anemia (hemoglobin ˂10 g/dl), indications of thrombocytopenia (platelet count ˂10^5/μl) and those who did not undergo PRP injection were also excluded [16].

Furthermore, patients who were unwilling to participate in the study were excluded as well.

Ovarian stimulation

Patients underwent sonography between days 1 and 3 of their menstrual cycle, followed by Controlled Ovarian Stimulation (COS) using a mild stimulation protocol. This involved administering 50 mg of clomiphene citrate and 2.5 mg of letrozole daily, starting on cycle days 2 or 3, alongside 150 IU of human menopausal gonadotrophin (hMG) daily. Letrozole was given for 5 days, while clomiphene citrate and hMG continued until the day before the final ovarian stimulation trigger. Ovulation was induced with a 0.25 mg dose of Human Chorionic Gonadotropin (HCG) when at least one follicle reached 18 mm or three follicles reached 17 mm in diameter. Oocyte retrieval was performed 36 h after HCG injection via a transvaginal ultrasound-guided method. No gonadotrophin antagonist was given at any time during the treatment cycle. Clomiphene citrate was administered throughout the entire cycle to prevent a premature LH surge in our mild stimulation protocol in accordance with methods documented in the literature [17, 18]. Ibuprofen was used to prevent premature follicle rupture.

Platelet-rich plasma preparation and intraovarian injection

PRP was prepared following established protocols as previously reported [19]. The PRP was obtained by drawing 27 ml of blood, combining it with sodium citrate, and undergoing a two-step centrifugation process utilizing the WEGO PRP preparation kit, resulting in 3 ml of concentrated platelet-rich plasma.

To enhance patient comfort, lower anesthesia and puncture injury risks, and reduce costs, intra-ovarian PRP injections were performed under ultrasound guidance right after the last follicular puncture during oocyte retrieval. The procedure involved 2–3 punctures per ovary using a 17-gauge needle, with a total of 1.5 ml PRP injected into the subcortical area of each ovary.

Successive accumulation of embryos

All valuable embryos were frozen on D3 or cultured to blastocyst stage for cryopreservation. Approximately 6 weeks later, during the second menstrual cycle post-PRP injection, laboratory tests and transvaginal sonography were performed. Patients then underwent a new mild ovarian stimulation cycle, mirroring the initial PRP cycle protocol, labeled as after PRP cycle 1. This process was repeated for after PRP cycle 2 and after PRP cycle 3, conducted at the third and fourth menses post-PRP injection, respectively.

Accumulated embryo transfer

Following three cycles of embryo accumulation post-PRP injection, the thawed embryos or blastocysts were transferred using either a natural cycle or artificial cycle based on the individual characteristics of the patients.

Outcome variables

The most sensitive markers for evaluating ovarian reserve, including participants' hormones such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), Anti-müllerian hormone (AMH) and antral follicle count (AFC) were assessed at two time points: prior to PRP therapy and at the sixth week following PRP therapy, specifically during the second menstrual cycle post-PRP injection. The number of oocytes retrieved, metaphase II (MII) oocytes, 2PN(pronuclear) zygotes, vitrified embryos and vitrified blastocysts was also assessed before and after PRP therapy. Day-3 embryo morphology followed Racowsky et al.'s criteria [20], with suitable embryos for freezing having ≥ 4 cells, < 26% fragmentation, and no or moderate asymmetry. Blastocyst quality was assessed using Gardner and Schoolcraft's guidelines [21], with those scoring ≥ 3BC considered for vitrification.

Statistical analysis

Continuous data were presented as mean ± SD, and categorical data as counts and percentages. Parametric and non-parametric data comparisons were conducted using the Paired T-test and Wilcoxon test, respectively. The chi-square or Fisher's exact test examined associations between categorical variables and outcomes. Statistical analyses were performed using SPSS version 25. A p-value < 0.05 denoted statistical significance.

Results

Demographic characteristics and ovarian reserve markers of the study population

A total number of 148 ovarian PRP injection POR patients from May 2021 to May 2022 were assessed in this study, with 49 patients being included and 99 patients being excluded based on the specified criteria. Among the participants, 13 were classified into the POSEIDON group 3 and 36 were in group 4. The mean age of all participants was 37.67 ± 4.15 years and the mean Body Mass Index (BMI) was 21.52 ± 2.80 kg/m^2. The BMI, baseline ovarian reserve markers and ultrasound findings of women in POSEIDON group 3 and group 4 were similar, except for age, as detailed in Table 1. The procedure was deemed safe, as there were no adverse effects related to intraovarian injection reported among the patients.

Table 1 Baseline characteristics of POSEIDON group3 and group 4

Variables	All Patients	POSEIDON3	POSEIDON4	*P*-value
PORs (n)	49	13	36	
Age (years)	37.67 ± 4.15	32.38 ± 1.55	39.58 ± 2.88	< 0.0001
BMI	21.52 ± 2.80	22.35 ± 1.08	21.22 ± 0.38	0.22
LH (IU/L)	Before PRP	5.15 ± 0.59	5.39 ± 0.49	0.79
FSH (IU/mL)	Before PRP	14.05 ± 2.42	14.75 ± 1.30	0.79
Estradiol (pg/mL)	Before PRP	47.68 ± 18.15	36.59 ± 4.20	0.39
AMH (ng/mL)	Before PRP	0.42 ± 0.11	0.41 ± 0.05	0.91
AFC	Before PRP	1.54 ± 0.27	2.19 ± 0.23	0.12

Table 2 Analysis of ovarian reserve metrics in all patients before versus after intra-ovarian injection of PRP

Variables	Before PRP	After PRP	*P*-value
LH (IU/L)	5.32 ± 0.39	4.41 ± 0.35	0.09
FSH (IU/mL)	14.57 ± 1.14	11.42 ± 0.81	0.03
Estradiol (pg/mL)	39.53 ± 5.64	37.91 ± 8.49	0.87
AMH (ng/mL)	0.41 ± 0.05	0.65 ± 0.13	0.035
AFC	2.02 ± 0.19	2.94 ± 0.21	0.0013

Ovarian reserve parameters

Women treated with PRP exhibited significant enhancements in both biochemical and ultrasound indicators of ovarian reserve, as demonstrated in Table 2, when compared to their status prior to receiving PRP treatment across all patients. Specifically, AMH levels increased by an average of 59% following PRP ($P = 0.035$). FSH levels decreased by 22% in the PRP-treated group ($P = 0.03$). Furthermore, post-PRP treatment ultrasound observations revealed an average increase of 46% in antral follicles ($P = 0.0013$).

Characteristics of successive accumulated cycles

The oocyte and embryologic outcomes of all patients in POSEIDON group 4 and group3 patients before and after PRP intra-ovarian injection of 3 successive cumulated mild stimulation cycles were depicted in Fig. 1. PRP administration resulted in a significant increase in the number of oocytes retrieved, MIIs, 2PN zygotes, available embryos, vitrified embryos and vitrified blastocysts in across all 3 cycles following PRP intra-ovarian injection. The number of oocytes retrieved before PRP treatment cycle and in the 3 cycles after PRP intra-ovarian injection were 1.33 ± 0.16, 2.35 ± 0.24, 2.49 ± 0.33, 1.81 ± 0.31, respectively ($P = 0.003$). The number of MIIs were 1.02 ± 0.16, 2.06 ± 0.22, 2.20 ± 0.31, 1.71 ± 0.31, respectively ($P = 0.001$). The number of 2PN zygotes were 0.84 ± 0.15, 1.80 ± 0.21, 1.81 ± 0.25, 1.46 ± 0.30, respectively ($P = 0.002$). The number of available embryos were 0.75 ± 0.13, 1.78 ± 0.19, 1.89 ± 0.29, 1.33 ± 0.32, respectively ($P = 0.0004$). The number of vitrified embryos were 0.46 ± 0.08, 0.90 ± 0.11, 0.57 ± 0.14, 0.71 ± 0.16, respectively ($P = 0.02$). The number of vitrified blastocysts were 0.04 ± 0.03, 0.43 ± 0.09, 0.48 ± 0.13 and 0.33 ± 0.16, respectively ($P = 0.002$). The number of cancelled cycles, defined as those with no oocytes retrieved or no embryos and blastocysts cryopreserved were 28, 10, 12, and 8, respectively ($P < 0.0001$).

Autologous intraovarian PRP therapy, in conjunction with the accumulation of embryos through 3 successive

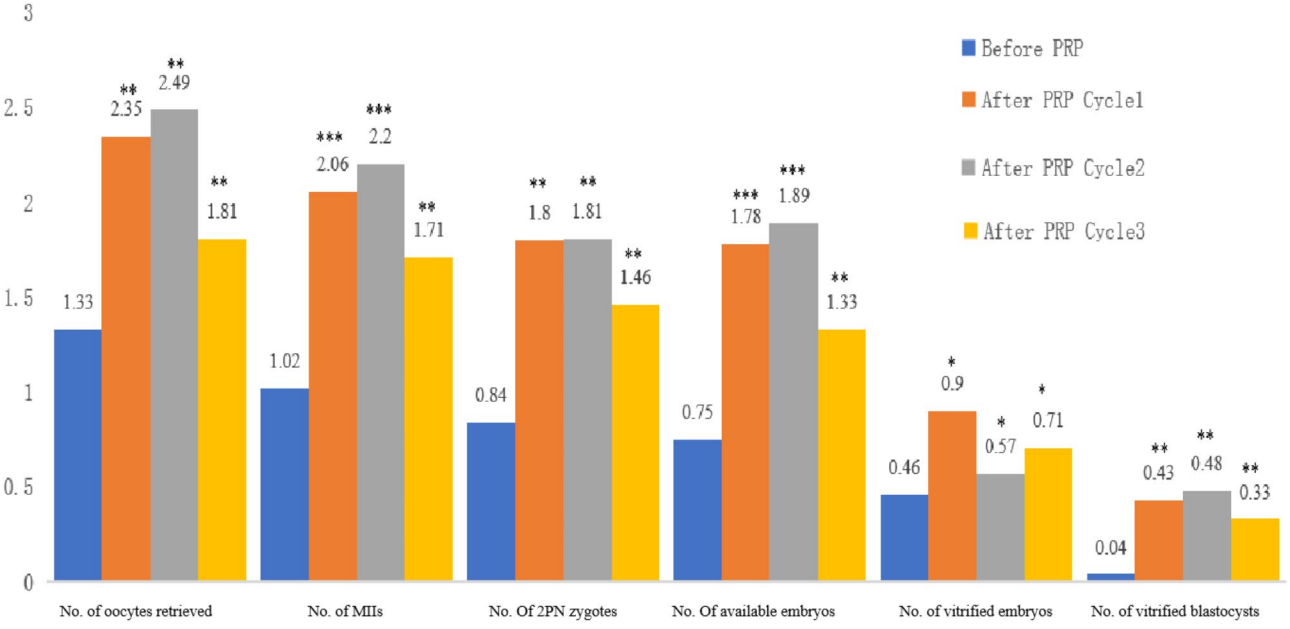

Fig. 1 Oocyte and embryologic outcomes of POSEIDON group 4 and group 3 patients before and after PRP intra-ovarian injection accompanied with 3 successive cumulated mild stimulation cycles

Table 3 Outcomes related to pregnancy and live births in all patients after PRP intra-ovarian injection with accumulated embryos transfer

Variables	All Patients	POSEIDON group 3	POSEIDON group 4
N	44	12	32
Clinical pregnancy	20	9	11
Live birth	15	7	8
Miscarriage	5	2	3
Twin pregnancy	5	4	1
Premature birth	3	3	0
Male babies	10	4	6
Female babies	9	6	3
Newborns	19	10	9
Average birth weight (g)	2988	2816	3179

mild stimulation IVF/ICSI cycles, resulted in a significant increase in the total No. of accumulated embryos (0.46 ± 0.08 vs. 2.18 ± 0.20, $P < 0.0001$) and blastocysts (0.04 ± 0.03 vs. 1.24 ± 0.14, $P < 0.0001$). Additionally, it significantly reduced the rate of cycle cancellations (57.13% (28/49) vs. 10.2% (5/49), $P < 0.0001$). The cumulative pregnancy and cumulative live birth outcomes were presented in Table 3. Following this strategy, one woman from POSEIDON group 3 and 4 women from POSEIDON group 4 did not have available embryos despite undergoing autologous intraovarian PRP therapy in conjunction with the accumulation of embryos through 3 successive mild stimulation IVF/ICSI cycles. Among the remaining 44 cases, which underwent more than 1 cycle of accumulated embryo/blastocysts transfer, 20 (45.45%) achieved clinical pregnancy, 15(34.09%) resulted in live birth and 5 (11.36%) experienced miscarriage. In the subset of 12 cases from POSEIDON group 3 who underwent accumulated embryos/blastocysts transfer, 9 (75%) achieved clinical pregnancy, 7 (58.3%) resulted in live births, 2 (16.7%) experienced miscarriages, 4 (33.33%) had twin pregnancies, and one of the twin pregnancies opted for selective embryo reduction. And Of 32 POSEIDON group 4 cases who underwent accumulated embryos/blastocysts transfer, 11 (34.38%) achieved clinical pregnancy, 8(25%) resulted in live birth, 3 (9.4%) experienced miscarriage, 1(3.14%) had a twin pregnancy. Among the 4 twin pregnancies, deliveries occurred at 35^{+3}, 35^{+6}, 36^{+2}, and 38 weeks gestation, with 3 cases of premature birth. There were a total of 19 healthy newborns, comprising 10 male babies and 9 female babies, with an average birth weight of 2988 g. All newborns were reported to be healthy.

Discussion

To the best of our understanding, this research stands one of the few to evaluate the effectiveness of PRP intraovarian infusion in conjunction with an embryo banking strategy for women with POR. Additionally, it is among the few studies to provide follow-up data on intact live births following intraovarian PRP injection. The results suggest that PRP intraovarian infusion combined with embryo accumulation can significantly reduce the risk of not having an embryo for transfer in women with POR, and may improve cumulative live birth rates, offering a new approach for POR management.

Since the 1970s, PRP has been explored and applied, gaining widespread acceptance in routine clinical procedures as a regenerative treatment across multiple disciplines, including dermatology, plastic surgery, dentistry, orthopedics, among others [22]. Nevertheless, intraovarian PRP therapy remains a relatively novel alternative for women with POR. PRP intraovarian infusion has demonstrated effectiveness in restoring ovarian function and hormonal balance. Sills et al. were pioneers in utilizing intraovarian PRP in the field of reproductive medicine [11].In their study involving 4 patients with POR, they observed a reduction in FSH levels and an elevation in AMH levels following intraovarian PRP intervention. However, only the decrease in FSH levels was deemed clinically significant ($p < 0.01$), while the rise in AMH levels was not statistically significant ($p = 0.17$). Melo et al. conducted a prospective non-randomized comparative pilot study involving 83 women with diminished ovarian reserve [9]. Among the 83 women included in the study, 46 individuals who received PRP treatment exhibited a 63% rise in AMH levels, along with a 33% decrease in FSH levels. Notably, the autologous PRP group showed a 75% increase in the number of antral follicles during the 3-month follow-up period. Our study revealed a significant enhancement in biochemical and ultrasound indicators of ovarian reserve following intraovarian PRP injection including a 59% increase in AMH levels, a 22% decrease in FSH levels, and a 46% increase in the number of antral follicles. These findings not only corroborate previous reports but also strengthen the evidence supporting the effectiveness of intraovarian PRP injection in restoring ovarian function and hormonal profile. Farimani et al.'s study, however, showed some inconsistencies with our findings [23]. Although they found no significant improvements in FSH and AMH levels across four groups of POR patients after ovarian PRP injection, they did report an increase in the number of retrieved oocytes in all groups, and an increase in MII oocytes in groups POR1, 3, and 4, which aligns with our observations. Navali et al.'s before-after study with 35 POR women also demonstrated a significant increase in the number of oocytes and embryos following PRP treatment, consistent with our findings [16]. Melo et al. further noted a significantly elevated biochemical pregnancy rate and clinical pregnancy rate [9], with a live birth rate of 8.7% in the PRP group compared to 2.7% in the control group,

although this difference was not statistically significant ($p = 0.38$). The systematic review by Soumya et al. and the meta-analysis by Vahabi Dastjerdi et al. indicated that intra-ovarian autologous PRP infusion enhanced ovarian reserve parameters and improved ART outcomes, including an increase in the number of total oocytes, MII oocytes, and high-quality embryos [24, 25]. Vahabi Dastjerdi et al.'s meta-analysis, which included 13 studies with 1289 patients, reported significant improvements in ART outcomes and a prevalence of 22% for clinical pregnancy, 5% for spontaneous pregnancy, and 21% for ongoing pregnancy following PRP therapy, in line with our study's findings on the efficacy of PRP in improving fertility indices in women with POR. A recent randomized double-blind study of G Barrenetxea et al. revealed that while PRP can indeed increase the number of available oocytes, it does not enhance the likelihood of yielding euploid embryos [26]. They showed the percentage of clinical pregnancies was higher in the control group than in the treatment group (60% vs. 27%, $P = 0.018$). There was also a trend toward poorer outcomes in the treatment group when considering full-term pregnancies ($P = 0.170$). The effect of PRP on the cumulative live birth rate was seldom. The study of Meng et al. showed in routine IVF/ICSI without intraovarian PRP injection, the cumulative clinical pregnancy rate (CCPR) and cumulative live birth rate (CLBR) for women with POR at the third complete cycle were 35.83% and 19.95% respectively [27]. Furthermore, the study revealed that both conservative and optimistic estimates of the CLBR reached their highest point at the fourth complete cycle [27]. Therefore, they concluded that it is not recommended to proceed with more than four complete cycles for patients with POR, as the CLBR does not show further increase beyond this point. Our approach of three cycles of embryo accumulation following PRP injection, along with one cycle before PRP injection, is grounded on the study. Our study showed following 3 cycles of embryo accumulation post PRP injection, the CCPR and CLBR were 45.45% and 34.09% respectively. Despite the potential for variation in the CCPR and CLBR due to the relatively small sample size of our study, these outcomes offer valuable preliminary data that can inform future research, enhance patient counseling, and boost the confidence of both clinicians and POR families. The pregnancy outcomes for POSEIDON 3 patients are clearly superior to those in group 4. It is important to note that this is likely influenced by the age factor, as the quality of oocytes obtained from younger patients is generally better. As reported in the literature, the rates of aneuploidy in embryos and blastocysts for POSEIDON 3 patients are similar to those of non-POSEIDON patients of the same age group [28, 29].

Notably, none of our patients experienced adverse side effects or any reproductive system-related side effects, which aligns with existing literature on the subject [30, 31]. Furthermore, all newborns in our study were healthy. Several studies have emphasized that PRP growth factors pose no risk, as they are non-mutagenic and incapable of inducing tumor formation [32].

PRP comprises numerous active substances [33]. Nevertheless, the mechanisms of action of intraovarian PRP injection in general, and its specific effects on ovarian function, remain largely unclear. There is a notable absence of mechanistic studies aimed at elucidating the biochemical mechanisms of PRP. We hypothesize that the elevated concentrations of various growth factors including PDGF, TGF-β, IGF-1/2, VEGF and EGF found in platelet-rich concentrates [8] may play a crucial role in stimulating the growth of the limited reserve of dormant primordial follicles present in the ovaries, ultimately resulting in ovarian rejuvenation. As highlighted in the systematic review by Hajipour et al., growth factors present in PRP may influence distinct attributes of oocytes, resulting in an enhanced follicle survival rate when contrasted with the control group [34]. The authors speculated that PRP could potentially facilitate ovarian tissue regeneration and reactivation by activating dormant follicles, increasing cortical volume, and inducing neoangiogenesis in dysfunctional ovarian tissue [12, 35]. As Sills & Tan have eloquently reviewed [36], the promise of PRP in rejuvenating the ovaries is indeed fascinating. However, the clinical application of this treatment necessitates a cautious approach, given the intricate interplay of involved factors and the surrounding ambiguities related to 'ovarian rejuvenation' methods. Drawing insight from the engineering adage cited by Sills & Tan, "Inside every complicated problem is many smaller ones waiting to be noticed," it becomes clear that nuanced investigation is essential. Advancing our understanding of ovarian function through rigorous research should elucidate the mechanisms by which platelet cytokines impact and orchestrate this intricate process.

Although PRP has shown promising results in our results, we must admit the changes observed after the PRP injection might not be solely due to the intervention itself. Notably, other external factors could affect the results, like change in lifestyle factors (smoking, alcohol consumption, stress and psychological state, nutritional status and dietary habits), BMI and the characterized heterogeneity of study population due to the inclusion of patients with diverse IVF backgrounds and treatment histories. In our analysis, because of our retrospective study character and relatively small sample, we did not specifically stratify the results based on these influencing factors. This approach offers a relatively stronger representation of real-world clinical scenarios.

Despite the notable strength of being the seldom study to assess the effectiveness of PRP intraovarian infusion combined with an embryo banking strategy for women with POR resulting in live births, this study is constrained by several limitations. Primarily, it is an uncontrolled longitudinal study that lacks a placebo control group. Drawing from the findings of Kawamura et al., the observed effects of PRP may not definitively exclude a primarily mechanical role [37]. Zhang et al. also conducted an evaluation of follicle growth and pregnancy outcomes involving 80 women with POI following ovarian biopsy/scratch [38]. Given the absence of existing data on sham/vehicle injections for use as controls it is recommended that future studies include a control group to ensure the highest level of homogeneity for a valid comparison. The relatively small sample size represents a second limiting factor. An exclusive reliance on mild stimulation protocols for embryo banking represents the third limitation. Alternative approaches, such as the combination of dual ovarian stimulation protocols (duostim) with ovarian PRP injections, should be considered in future to improve pregnancy outcomes for patients with POR. This integrated strategy may offer a more effective means of increasing both the quantity and quality of embryos available for patients facing challenges with ovarian responsiveness. Furthermore, the inability to predict which individuals would benefit from PRP injection into the ovaries prior to treatment is a significant constraint. Research conducted by Cakiroglu and colleagues showed that subjects without an antral follicle during PRP administration had a lower likelihood of responding to the treatment in comparison to individuals possessing one or two antral follicle [14]. The researchers concluded that PRP facilitated the activation of present preantral and/or early antral follicles, suggesting that the quantity of residual follicles within the ovaries is likely to influence the magnitude of their response. Nevertheless, currently, it's not feasible to apply this observation broadly, and there's a definite need for future, rigorously designed studies to identify the specific subgroup that would most benefit from the combination of PRP intraovarian infusion and embryo banking strategy. It may necessitate invasive and ethically challenging procedures such as ovarian tissue sampling. Hence, in the future, it would be valuable and imperative to comprehensively elucidate the biological mechanisms through which PRP may influence ovarian function and to identify the specific group of women who can genuinely benefit from PRP.

Conclusions

In summary, for women experiencing POR, intraovarian PRP injection combined with accumulated embryo transfer (ACC-ET) across 3 consecutive mild stimulation IVF/ICSI cycles may offer an innovative alternative treatment. This strategy may offer a glimmer of hope to infertile couples hesitant about donor-assisted methods. However, larger studies and randomized controlled trials are needed to validate its efficacy and clinical outcomes before recommending it as a standard treatment for POR.

Abbreviations

ACC-ET	Accumulated embryo transfer
AFC	Antral follicles count
AMH	Anti-müllerian hormone
ART	Assisted reproductive technology
bFGF	Basic fibroblast growth factor
BMI	Body Mass Index
CCPR	Cumulative clinical pregnancy rate
CLBR	Cumulative live birth rate
COS	Controlled ovarian stimulation
E2	Estradiol
EGF	Epidermal growth factor
FSH	Follicle-stimulating hormone
HCG	Human Chorionic Gonadotropin
HGF	Hepatocyte growth factor
hMG	Human menopausal gonadotrophin
ICSI	Intracytoplasmic Sperm Injection
IGF-1	Insulin-like growth factors 1
IGF-2	Insulin-like growth factors 2
IVF	In vitro fertilization
LH	Luteinizing hormone
MII	Metaphase II
POF	Premature Ovarian Failure
POI	Premature Ovarian Insufficiency
POR	Poor Ovarian Response
POSEIDON	Patient-oriented Strategies Encompassing IndividualizeD Oocyte Number
PRP	Platelet-Rich Plasma
TGF-β	Transforming growth factor-β
VEGF	Vascular endothelial growth factor
2PN	2 pronuclear

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Author contributions

Data collection, drafting the manuscript and approving the final manuscript: Hongcui Zhao, Juan Wu, Yang Xu, Xiaofang Shen, Huanhuan Wang, Aihua Zhao, Fumin Cao, Xinna Chen. Hongcui Zhao and Xinna Chen performed the study supervision.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The retrospective before-after study was approved by and conducted according to the Medical Ethics Committee of Beijing Amcare Beisanhuan Women's & Children's Hospital. The authors declare their adhered to the 1975 declaration of Helsinki and its next revisions.

Consent for publication

Patients voluntarily provided their written informed consent for the publication/use of their medical data.

Competing interests

The authors declare no competing interests.

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