Impact of bilateral intraovarian platelet-rich plasma in women with poor ovarian response or primary ovarian insufficiency: a retrospective study

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Objective: To investigate the association of autologous platelet-rich plasma (PRP) treatment with functional ovarian reserve parameters and in vitro fertilization (IVF) outcomes of poor ovarian responders and women with primary ovarian insufficiency (POI) who refused oocyte donation.
Design: Observational, retrospective, multicentric cohort study
Subjects: Three hundred fifty-three women who underwent PRP treatment, including 207 poor responders and 146 diagnosed with POI.
Exposure: Intraovarian PRP injection.
Main Outcome Measures: Main outcomes were antral follicular counts (AFCs) and serum antimüllerian hormone (AMH). Secondary outcomes were IVF parameters and reproductive outcomes.
Results: In the poor responders' cohort (40.0 ± 3.8 years old, $AMH_0 = 0.43 \pm 0.54$ ng/mL; $AFC_0 = 2.6 \pm 2.4$), intraovarian PRP was associated with significantly improved AFCs at each follow-up visit ($AFC_0 = 2.6 \pm 2.4$ vs. $AFC_1 = 5.3 \pm 3.6$; $AFC_2 = 4.5 \pm 3.5$; $AFC_3 = 4.0 \pm 2.4$; $AFC_4 = 3.6 \pm 2.7$) compared with the pretreatment levels. There were 100 pretreatment and 231 posttreatment ovarian stimulation cycles initiated in 111 poor responders with similar yields of metaphase II oocytes (Pre-PRP: 2.4 ± 3.0 vs. Post-PRP: 3.0 ± 3.4) and blastocysts obtained (Pre-PRP: 0.5 ± 0.7 vs. Post-PRP: 0.6 ± 1.1). However, we found novel positive associations between PRP and oocyte quality-related parameters such as maturation (Pre-PRP: 65.8% vs. Post-PRP: 80.8%) and fertilization rates (Pre-PRP: 61.6% vs. Post-PRP: 75.8%), although statistically significant differences were not reached for implantation (Pre-PRP: 9.4% vs. Post-PRP: 35.1%), and biochemical pregnancy rates (Pre-PRP: 12.5% vs. Post-PRP: 41.5%). We identified 23 clinical pregnancies (17 after embryo transfer and six natural conceptions) with seven live births in poor responders who received PRP. In the POI cohort (38.7 ± 4.3 years old, $AMH_0 = 0.1 \pm 0.1$ ng/mL; $AFC_0 = 1 \pm 1.2$), PRP treatment was only related to higher AFCs ($AFC_1 = 2.1 \pm 1.9$; $AFC_2 = 1.9 \pm 1.9$; $AFC_3 = 1.9 \pm 1.8$, $AFC_4 = 1.9 \pm 1.7$), but improvements in IVF or reproductive outcomes were not detected.
Conclusion: Our results suggest that PRP did not induce quantitative effects on the ovaries, as oocyte and embryo yields were not increased. However, in poor responders, retrieved oocytes seemed more capable of maturing and being fertilized. For POI patients, intraovarian PRP treatment did not improve IVF or reproductive outcomes, and thus, alternatives are still required. Prospective randomized clinical trials are recommended to validate these retrospective findings and elucidate potential mechanisms for PRP-induced ovarian reactivation. (Fertil Steril® 2025;124:496–505. ©2025 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Antral follicular count, ovarian reactivation, platelet-rich plasma, poor ovarian response, primary ovarian insufficiency

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Ovarian aging is a physiological process characterized by the declining quantity and quality of oocytes (1). Its effects become clinically relevant when women reach their late thirties and are exacerbated until menopause (2). As couples postpone parenthood, advanced maternal age has become a leading cause of infertility (3). Low ovarian reserve is considered the most relevant risk factor for poor ovarian responders; however, some poor responders might present an accelerated ovarian aging, that progresses faster than expected according to chronological age, which may be caused by genetic or acquired risk conditions (4).

Approximately 6%–35% of patients referred to an infertility clinic have poor ovarian response (5) and this number seems to increase each year. Existing strategies to manage poor responders focus on optimizing ovarian stimulating protocols but were unsuccessful (6), likely because of the few remaining hormone-responsive follicles (7). Oocyte donation is recommended for these patients, however, some women and couples have difficulty accepting this option because of the related psychological burdens and emotional distress (8).

Similarly, oocyte donation remains the only effective treatment for patients with primary ovarian insufficiency (POI) (9) or hypergonadotropic hypogonadism, characterized by the loss of ovarian function before 40 years of age, manifesting as amenorrhea, hypoestrogenism, and subsequent infertility (10). Primary ovarian insufficiency was estimated to affect 3.7% of the general population according to a recent meta-analysis (11). The pathogenesis of POI is driven by genetic and non-genetic causes, including iatrogenic, environmental, and chemical factors (12). As these factors often cause irreversible damage to the ovaries, existing research efforts have mainly focused on early screening and timely intervention or counseling (12).

Ovarian reactivation is an emerging application of regenerative medicine. Autologous platelet-rich plasma (PRP) therapies are derived from whole blood samples and are enriched in bioactive factors with anti-inflammatory, tissue repair, and neo-angiogenic properties (13, 14). Several groups investigated whether intraovarian PRP injections could promote or restore ovarian function in poor responders and POI women. In 2016, Pantos et al (15) were the first to postulate that intraovarian PRP infusion reactivates human folliculogenesis, based on evidence that this treatment restored menses in eight peri-menopausal women. Subsequent observational studies in both poor responders and POI patients suggested that PRP increases the antral follicle count (AFC) and serum antimüllerian hormone (AMH) levels (16–20), however there was considerable heterogeneity of patients, methods, follow-up periods and outcomes, making it difficult to standardize a clinical approach and reliably establish the efficacy of the technique.

This retrospective study aimed to determine whether intraovarian PRP injection modified the ovarian reserve biomarkers, response to stimulation, in vitro fertilization (IVF) outcomes and pregnancy rates in poor responders and POI patients with very poor reproductive prognoses who refused oocyte donation after previous failed assisted reproduction attempts.

MATERIALS AND METHODS

Study design and population

This observational, retrospective, multicentric cohort study included medical information from poor responders and POI patients who underwent a single treatment with intraovarian PRP at IVI Alicante Clinic (Spain) between June 2021 and May 2023. Participants were $\leq$45 years old, diagnosed as infertile at least 6 months before receiving the PRP, and classified as poor responders or with POI according to the European Society of Human Reproduction and Embryology Bologna criteria (4, 21). All POI patients were under 40 years at the time of diagnosis, presented with secondary amenorrhea or oligomenorrhea and were not undergoing hormone replacement therapy at the time of the PRP. Patients were excluded from the study if there was evidence of any malignant neoplasia, genetic or iatrogenic causes of ovarian insufficiency or infertility, endometriosis stage III/IV, pelvic adhesive disease, receiving consecutive PRP treatments or other ovarian reactivation treatments at any time.

Our main purpose was to investigate the impact of PRP on ovarian reserve parameters (i.e., AMH and AFC) during follow-up and response to ovarian stimulation (OS) (i.e., metaphase II (MII)-oocyte yield, maturation rate). Secondary measures included IVF and reproductive outcomes (i.e., implantation, pregnancy, and live birth rates). The IVF analysis was limited to only those patients who underwent OS cycles in one of the following IVI clinics: Alicante, Valencia, or Madrid (Spain). The poor ovarian response and POI groups were analyzed independently and with age-subgroup analyses when appropriate. In all cases, retrospective anonymized data was exported from internal electronic medical records, following personal data protection regulations in Spain. The PRP preparation, intraovarian injection, treatment follow-up and IVF procedures were developed as described in Supplemental Methods (available online).

Ethical approval

This study was approved by the Institutional Review Board of the Hospital Universitario y Politécnico La Fe, Valencia, Spain (2112-FIVI-109-SH).

Statistical analysis

A descriptive analysis of the functional ovarian reserve biomarkers (i.e., AFC and AMH), OS, IVF, and pregnancy outcomes was performed for poor responders and POI cohorts. Data from each posttreatment follow-up was compared with the pretreatment data and previous OS attempt when available. Continuous variables were reported as a mean $\pm$ SD, while categorical data were presented as a percentage (%) of the corresponding totals. For continuous variables, normality was assessed by the Shapiro-Wilk test. Clinical results were analyzed with the use of the Wilcoxon test when normality was not assumed, and a *t*-test was applied otherwise; proportions were analyzed by the χ^2 test. The ovarian reserve variables before and after PRP were compared for each patient with the use of a paired *t*-test. The IVF outcomes before and

after PRP for each cohort were compared by a non-paired *t*-test followed by a linear model, using the Generalized Estimating Equations approach to control for multiple cycle comparisons, as some women underwent subsequent OS cycles after PRP. In all cases, $P<.05$ was considered statistically significant. Results were expressed with their corresponding 95% confidence intervals (CIs). Statistical analyses were performed in R (v4.02, R Core Team 2020; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

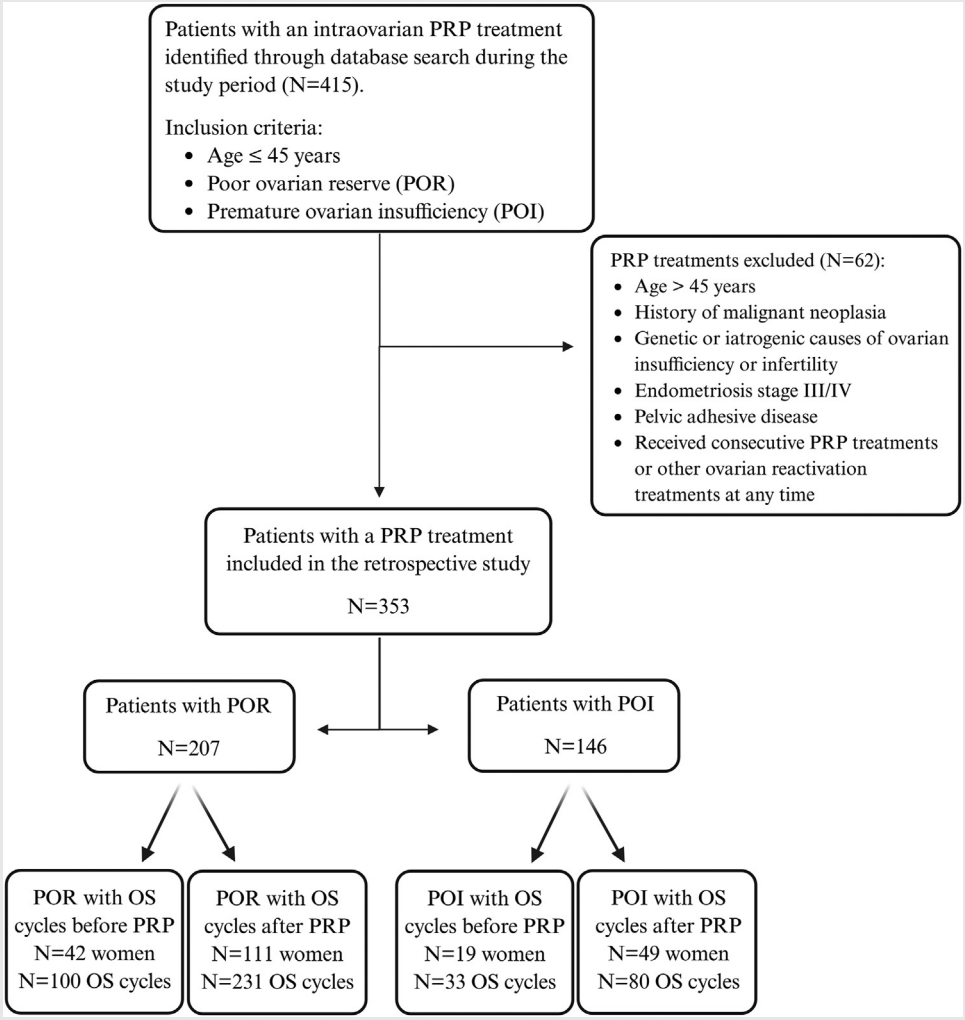
After screening our medical records, this study included 353 women (≤45 years old) who received a single treatment with intraovarian PRP injections for ovarian reactivation without any complications (flow chart in Fig. 1). These patients were then reclassified as poor responders (n = 207) or with POI (n = 146) according to the European Society of Human Reproduction and Embryology criteria (4, 21).

Intraovarian PRP injection for poor ovarian responders

The 207 poor ovarian response patients' baseline AMH, AFC, ovarian volumes, and the mean total volume of PRP administered are presented in Supplemental Table 1 (available online). Our records revealed that 72.0% (149) received the treatment during the follicular phase, 17.9% (37) during the luteal phase, and for 10.1% (21), this data was not available. At the time of data collection, we retrieved 184 records from the first follow-up visit (88.9%); 142 (68.6%), 82 (39.6%), and 46 (12.6%) from the second, third, and fourth visit, respectively.

Functional ovarian reserve parameters. Platelet-rich plasma treatment significantly improved the total AFC during the

FIGURE 1



Flowchart for patient and platelet-rich plasma (PRP) treatment selection strategy. Flow diagram of the PRP treatment selection, with detailed exclusion criteria and total number of patients, PRP treatments and ovarian stimulation (OS) cycles included in the retrospective study. Created with BioRender.com.

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TABLE 1

Comparison of ovarian reserve parameters in poor ovarian responders and premature ovarian insufficiency patients before and after bilateral intraovarian platelet-rich plasma treatment.

Poor ovarian responder patients

Parameters	Pretreatment	Posttreatment follow-up: First		Second		Third		Fourth	
	Mean ± SD, CI (N)	Mean ± SD, CI (N)	*P* value	Mean ± SD, CI (N)	*P* value	Mean ± SD, CI (N)	*P* value	Mean ± SD, CI (N)	*P* value
AMH (ng/mL)	0.43 ± 0.54, 0.35–0.50 (204)	0.47 ± 0.50, 0.40–0.54 (178)	.02	0.41 ± 0.46, 0.32–0.50 (115)	.33	0.39 ± 0.36, 0.30–0.48 (67)	.05	0.22 ± 0.19, 0.14–0.30 (26)	.42
Total AFC	2.6 ± 2.4, 2.3–2.9 (204)	5.3 ± 3.6, 4.8–5.8 (183)	< .0001	4.5 ± 3.5, 3.9–5.1 (141)	< .0001	4.0 ± 2.4. 3.5–4.6 (81)	< .0001	3.6 ± 2.7, 2.8–4.4 (46)	.007
AFC, RO	1.2 ± 1.3, 1.1–1.4 (205)	2.7 ± 2.0, 2.4–2.9 (184)	< .0001	2.3 ± 1.9, 2.0–2.6 (142)	< .0001	1.9 ±1.3, 1.6–2.2 (81)	< .0001	1.9 ± 1.4, 1.4–2.3 (46)	.01
AFC, LO	1.4 ± 1.4, 1.2–1.6 (204)	2.6 ± 2.1, 2.3–2.9 (183)	< .0001	2.2 ± 2.0, 1.8–2.5 (141)	< .0001	2.2± 1.6, 1.8–2.5 (82)	< .0001	1.8 ± 1.8, 1.2–2.3 (46)	.07

POI patients

	Pretreatment	Posttreatment follow-up: First		Second		Third		Fourth	
	Mean ±SD, CI (N)	Mean ± SD, CI (N)	*P* value	Mean ± SD, CI (N)	*P* value	Mean ± SD, CI (N)	*P* value	Mean ± SD, CI (N)	*P* value
AMH (ng/mL)	0.07 ± 0.12, 0.05–0.09 (145)	0.09 ± 0.14, 0.07–0.12 (121)	.08	0.08 ± 0.13, 0.05–0.1 (88)	.96	0.08 ± 0.11, 0.05–0.11 (63)	.46	0.04 ± 0.07, 0.01–0.08 (21)	.4
total AFC	1.0 ± 1.2 (145)	2.1 ± 1.9 (133)	< .0001	1.9 ± 1.9 (110)	< .0001	1.9 ± 1.8 (78)	< .0001	1.9 ± 1.7 (35)	.0019
AFC, RO	0.6 ± 0.8. 0.4–0.7 (146)	1.1 ± 1.1, 0.9–1.3 (133)	< .0001	0.9 ± 1.0, 0.7–1.1 (110)	.0006	0.9 ± 1.0, 0.7–1.1 (78)	.019	1.1 ± 1.0, 0.7–1.4 (35)	.011
AFC, LO	0.4 ± 0.7, 0.3–0.5 (145)	1.0 ± 1.2, 0.76–1.2 (133)	< .0001	0.9 ± 1.2, 0.7–1.2 (110)	< .0001	1.0 ± 1.1, 0.8–1.3 (78)	< .0001	0.8 ± 1.1, 0.4–1.2 (35)	.04

Note: Results are presented as the mean ± SD, 95% confidence interval and number of retrieved records/observations (N). *P*< .05 indicates statistical significance between the posttreatment and pretreatment ovarian reserve parameters. AFC = antral follicle count; AMH = antimüllerian hormone; LO = left ovary; N = number; POI = premature ovarian insufficiency; POR = poor ovarian reserve; RO = right ovary.

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entire follow-up period with respect to basal levels (Table 1). The total AFC peaked during the first visit (≈22.5 days posttreatment) and declined progressively thereafter. The improvements in AFC were also significant within each ovary until the third follow-up visit. However, serum AMH levels were only significantly higher at the first follow-up with respect to pretreatment levels (Table 1). Notably, 24 poor responders (13.5%) had improvements in both AFC and AMH, while 42 (22.9%) only had the AFC rise, and 87 (48.9%) only had higher AMH levels after PRP.

When the ovarian reserve biomarkers were compared for those poor responders receiving PRP during follicular (149) vs. luteal phase (37), no significant differences were found in the AMH and AFC during the follow-up between these two groups.

IVF and reproductive outcomes. After PRP treatment, we identified 231 OS cycles initiated in 111 poor responders undergoing IVF and embryo transfer in one of the three participating clinics. We first compared the results of the 231 posttreatment cycles and compared with those of the pretreatment cycles (N = 100; Table 2) by a non-paired *t*-test. The average time to initiate OS after PRP was 63.2 ± 46.5 days. Comparing pretreatment and posttreatment cycles in this cohort revealed that baseline serum AMH was significantly higher before PRP treatment, although no differences were observed between total gonadotropin doses, duration of stimulation, triggering method, baseline serum follicle-stimulating hormone levels and trigger day estradiol (E2) levels. There were comparable rates of cycles resulting in oocyte retrieval (79.0% vs. 80.9%, $P=.795$), cancellation or retrievals with empty follicles. The mean number of total oocytes retrieved and the MII-oocyte yield were also similar between pretreatment and posttreatment cycles (Table 2). Multivariate linear regression models adjusted for potential confounding variables (i.e., patient age, BMI, baseline AMH levels, and trigger day E2 levels) showed a non-statistically significant moderate positive correlation between PRP treatment and the number of oocytes retrieved in subsequent cycles in poor responders (r = 0.45; 95% CI, −1.59 to 2.49; $P=.66$).

Although the number of MII oocytes recovered did not significantly differ before and after PRP treatment, there were significant improvements in other measures of oocyte quality (Table 2), such as the oocyte maturation rate (65.8% ± 32.9% vs. 80.8% ± 27.5%, $P=.003$), fertilization rate (61.6% ± 36.2% vs. 75.8% ± 27.0%, $P=.011$), and embryo cleavage per MII oocyte (61.6% ± 37.3% vs. 73.9% ± 30.6%, $P=.03$). Based on the outcomes of 16 pretreatment and 43 posttreatment embryo transfers in poor responders (Table 2), and although these differences did not reach statistical significance, PRP increased the implantation rate (9.4% ± 27.2% vs. 35.1% ± 48.4%, $P=.07$), pregnancy rate per embryo transfer (12.5% vs. 41.5%, $P=.07$), and live birth rates (0% vs. 17.6%, $P=.18$). At the time of data collection, the ongoing pregnancy rate (22 weeks of gestation) per initiated OS cycle in the posttreatment was 7.4% compared with 2.0% in the pretreatment. We identified 23 clinical pregnancies among poor responders who received bilateral intraovarian PRP injections (17 after embryo transfer and 6 by natural conception), resulting in seven live births.

Finally, we included an additional paired comparison in a subset of 34 patients that performed 34 pretreatment and their corresponding first posttreatment cycle (Supplemental Table 2) in our clinics. This analysis limited to OS parameters, as an oocyte accumulation strategy was followed in the posttreatment cycles according to clinical practice, revealed no differences.

Maternal age-subgroup analysis of IVF outcomes in poor ovarian responders

To determine which age group PRP treatment benefited most (<38, 38–42, or >42), IVF cycles were analyzed according to poor responder patient age (Supplemental Table 3). Significant differences in maternal age before and after PRP treatment were detected for the subgroups of poor responders 38–42 and >42 years old ($P=.02$ and $P=.004$ respectively). Although all age groups presented with significantly lower baseline AMH levels in the posttreatment cycles, the number of MII oocytes recovered was comparable pretreatment and posttreatment. Further, intraovarian PRP was associated with increased oocyte maturation rates, although statistically significant differences were only reached in the 38–42-year-old group (<38 years: 9.7% increase, $P=.36$; 38–42 years old, 11.5% increase, $P=.032$; >42 years, 14% increase, $P=.055$). A similar pattern was also detected for fertilization and embryo cleavage rates although statistical significance was not reached. After PRP, the biochemical pregnancy rate rose by 47.8% in poor responders <38 years old, from 33.3% to 38.5% in the 38–42-year-old subgroup, and from 0% to 20% in women >42 years old.

Intraovarian PRP injection for women with POI

The 146 POI patients' baseline characteristics are presented in Supplemental Table 1. One hundred twenty-one POI patients (82.9%) had their first follow-up visit; 88 (60.3%), 63 (43.1%), and 21 (14.4%) returned for their second, third, and fourth follow-up visits, respectively.

Functional ovarian reserve parameters. The total AFC and the AFCs for each ovary, were significantly improved in all posttreatment follow-ups, compared with the pretreatment levels (Table 1). The mean for the total AFC was highest at the first follow-up visit, approximatively 35.2 days posttreatment. On the other hand, PRP treatment did not improve serum AMH levels in POI patients during the follow-up period (Table 1). Analyzing individual response to the PRP treatment, we identified 19 POI patients (15.7%) with improvements in both AFC and AMH, 30 POI patients (22.5%) who only had higher AFC, and 45 POI patients (37.1%) who only had AMH levels rise, with respect to pretreatment ovarian reserve assessments.

IVF and reproductive outcomes. We identified a total of 49 POI women who underwent OS in one of the participating clinics before and/or after PRP treatment. There was a total of 33 pretreatment cycles and 80 posttreatment cycles with

TABLE 2

Controlled ovarian stimulation and in vitro fertilization/embryo transfer outcomes in poor ovarian responders before and after bilateral intraovarian treatment with platelet-rich plasma.

Poor ovarian responders	Pre-PRP, mean ± SD, CI	Post-PRP, mean ± SD, CI	*P* value
OS cycle outcomes			
Age (y)	39.7 ± 2.9, 39.0–40.4	39.8 ± 3.9, 39.2–40.4	.874
BMI (kg/m^2)	23.0 ± 3.7, 22.0–24.0	22.3 ± 3.7, 21.6–23.0	.250
OS cycles initiated (N)	100	231	
Patients who initiated OS (N)	42	111	
Baseline AMH (ng/mL)	0.87 ± 0.93, 0.67–1.08	0.54 ± 0.57, 0.57–0.62	.004
Baseline AFC	6.2 ± 4.5, 5.2–7.2	5.6 ± 4.0, 4.9–6.2	.271
Total gonadotropin dose (IU)	2,024 ± 1,248, 1,768–2,281	2,227 ± 1.411, 2,025–2,429	.221
OS duration (d)	11.4 ± 5.8, 10.3–12.6	12.7 ± 25.0, 9.4–15.9	.471
Trigger day E2 (pg/mL)	870 ± 664, 729–1,011	973 ± 821, 857–1,088	.266
Cycle cancellation rate	21%, 13.5–30.3	19.0%, 14.2–24.7	.795
Retrieval with no oocyte/empty follicle	10.1%, 4.5–19.0	5.9%, 3.0–10.3	.33
Oocytes retrieved	3.1 ± 3.6, 2.4–3.8	3.0 ± 3.2 2.6–3.4	.863
MII oocytes recovered	2.4 ± 3.0, 1.8–3.0	3.0 ± 3.4, 2.5–3.4	.120
Oocyte yield per antral follicle	49.9 ± 49.7, 38.8–61.0	54.6 ± 51.8, 46.6–62.7	.492
Oocyte maturation rate	65.8 ± 32.9, 57.3–74.3	80.8 ± 27.5, 76.2–85.4	.003
ICSI outcomes			
Fertilization rate	61.6 ± 36.2, 51.8–71.4	75.8 ± 27.0, 71.1–80.5	.011
Cleaved embryos	2.6 ± 2.3, 1.9–3.2	3.2 ± 2.7, 2.7–3.7	.127
Embryo cleavage rate	61.6 ± 37.3, 51.2–72.0	73.9 ± 30.6, 68.5–79.3	.03
Blastocysts	0.5 ± 0.7, 0.3–0.6	0.6 ± 1.1, 0.4–0.8	.173
Embryos transferred per stimulation cycle	0.2 ± 0.5, 0.1–0.4	0.2 ± 0.4, 0.1–0.3	.58
ET performed (N)	16	43	
Embryos per transfer	1.1 ± 0.2, 0.9–1.2	1.1 ± 0.3, 1.0–1.1	.93
ET outcomes			
Implantation rate	9.4 ± 27.2, –5.1–23.9	35.1 ± 48.4, 19.0–51.3	.07
BPR per ET	12.5%, 1.5–38.3	41.5%, 26.3–57.9	.07
LBR	0%, 0.0–20.6	17.6%, 6.8–34.5	.18

Note: Results are shown as the mean ± SD and the corresponding 95% confidence interval unless stated otherwise. $P < .05$ indicates statistical significance between the posttreatment and pretreatment measures. AFC = antral follicle count; AMH = antimüllerian hormone; BMI = body mass index; BPR = biochemical pregnancy rate; ET = embryo transfer; E2 = estradiol; ICSI = intracytoplasmic sperm injection; LBR = live birth rate; MII = metaphase II; N = number; OS = ovarian stimulation; PRP = platelet-rich plasma.

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no significant differences in gonadotropin doses, the duration of the stimulation, triggering method, baseline follicle-stimulating hormone levels, or trigger day E2 levels (Table 3). There were comparable rates of pretreatment and posttreatment cycles resulting in oocyte retrieval (45.4% vs. 41.2%, $P=.84$), cancellation or retrievals with empty follicles. There were no statistical differences in the mean number of oocytes retrieved or proportion of MII oocytes. Multivariate linear regression models accounting for confounding variables (i.e., patient age, BMI, baseline AMH, and trigger day E2 levels) showed there was no correlation between PRP treatment and the number of oocytes retrieved in subsequent cycles (r = 0.11; 95% CI, −0.72 to 0.94; $P=.79$). Indeed, the oocyte maturation rate, fertilization rate, and mean number of blastocysts were comparable. Overall, the pregnancy rate per initiated stimulation rose from 0% to 3.7% after PRP. We identified six clinical pregnancies among POI patients (3 after embryo transfer and 3 by natural conception), resulting in one live birth.

DISCUSSION

This retrospective study aimed to investigate whether bilateral intraovarian PRP treatment promoted ovarian function and improved IVF and reproductive outcomes after embryo transfer in poor ovarian response and POI. Intraovarian PRP treatment significantly enhanced AFC in poor responders throughout the entire follow-up. Despite serum AMH levels being significantly lower at the beginning of each posttreatment cycle, the proportion of cycles resulting in oocyte retrieval and the quantity of mature oocytes recovered were similar to pretreatment cycles. Our results did not support that local PRP treatment improves the yield of MII oocytes from poor responders, which was a previously reported benefit in patients with diminished ovarian reserve (16–20). Although most of the existing studies investigated the effects of PRP on the quantitative variables and the overall pregnancy rate, in our study, oocyte quality and developmental competence were evidenced by PRP significantly improving the oocyte maturation, fertilization, and embryo cleavage rates. These results support previous findings in chemotherapy-induced poor ovarian response/reserve and POI mouse models, where PRP did not modify the MII-oocyte yield but improved fertilization and blastocyst formation rates, leading to increased numbers of good-quality blastocysts (22). However, statistically significant differences were not reached for improvements in implantation, pregnancy, and live birth rates for poor responders. This might be due to the limited number of embryo transfers performed before and after the PRP treatment (16 vs. 43 embryo

TABLE 3

Ovarian stimulation and in vitro fertilization/embryo transfer outcomes in women with premature ovarian insufficiency before and after bilateral intraovarian treatment with platelet-rich plasma.

POI	Pre-PRP, mean ± SD, CI	Post-PRP, mean ± SD, CI	*P* value
OS cycle outcomes			
Age (y)	38.6 ± 4.4, 35.4–41.7	39.0 ± 3.5, 37.4–40.5	.98
BMI (kg/m^2)	24.1 ± 5.1, 21.8–26.3	23.3 ± 4.3, 22.1–24.5	.63
OS cycles initiated (N)	33	80	
Patients who initiated COS (N)	19	49	
Baseline AMH (ng/mL)	0.20 ± 0.30, 0.05–0.35	0.10 ± 0.11, 0.08–0.13	.22
Baseline AFC	3.2 ± 2.4, 2.0–4.3	3.2 ± 2.2, 2.6–3.8	.97
Total gonadotropin dose (IU)	1,896 ± 1,463, 1,317–2,475	1,849 ± 1,460, 1,451–2,248	.98
Duration of stimulation (d)	14.4 ± 10.9, 10.5–18.2	15.3 ± 27.5, 9.2–21.4	.8
Trigger day E2 (pg/mL)	421 ± 407, 257–586	392 ± 427, 272–512	.67
Cycle cancellation rate	54.6%, 36.3–71.9	58.7%, 47.2–69.5	.84
Retrieval with no oocyte/empty follicle	20.0%, 4.3–48.1	21.2%, 9.0–38.9	1
Oocytes retrieved	1.0 ± 2.2, 0.2–1.8	0.6 ± 1.0, 0.4–0.8	.34
MII oocytes recovered	0.7 ± 1.4, 0.2–1.2	0.5 ±1.0, 0.3–0.7	.48
Oocyte yield per antral follicle	5.6 ± 13.6, −1.6 to 12.9	17.7 ± 32.3, 8.7–26.6	.21
Oocyte maturation rate	72.6 ± 38.9, 47.9–97.3	70.9 ± 36.3, 55.2–86.5	.75
ICSI outcomes			
Fertilization rate	78.3 ± 36.9, 51.9–104.7	74.8 ± 40.6, 55.8–93.8	.81
Cleaved embryos	1.70 ± 1.06, 0.94–2.46	1.37 ± 1.21, 0.78–1.95	.28
Embryo cleavage rate	78.3 ± 36.9, 51.9–104.7	73.5 ± 41.3, 53.6–93.4	.74
Blastocysts	1.00 ± 0.94, 0.33–1.67	0.74 ± 0.99, 0.26–1.21	.36
Embryos transferred per cycle	0.50 ± 0.71, −0.01 to 1.01	0.32 ± 0.48, 0.09–0.55	.56
ET outcomes			
ET performed (N)	4	10	
BPR per ET	0.0%, 0.0–60.2	30.0%, 6.7–65.2	.61
LBR	0.0%	0.0%	NA

Note: Results are presented as the mean ± SD, the corresponding 95% confidence interval unless stated otherwise. AFC = antral follicle count; AMH = antimüllerian hormone; BMI = body mass index; BPR = biochemical pregnancy rate; CI = confidence interval; COS = controlled ovarian stimulation; ET = embryo transfer; E2 = estradiol; ICSI = intracytoplasmic sperm injection; LBR = live birth rate; MII = metaphase II; N = number; NA = not available; OS = ovarian stimulation; POI = premature ovarian insufficiency; PRP = platelet-rich plasma.

Molinaro. Effect of platelet-rich plasma injection. Fertil Steril 2025.

transfers, respectively) or to the absence of significant effects that require further validation in randomized and control prospective studies. Nevertheless, our overall data suggest the regenerative effects of PRP, as external factors with positive effects on maturation, clinical pregnancy rate and live birth rate per embryo transfer, such as the use of dual trigger (23), were similar before and after PRP (45.5% vs. 48.8%). Indeed, improved maturation rates were also detected in the 38–42-year-old group and to a lesser extent in the > 42-year-old group of the poor ovarian response age subanalysis, although the statistical significance in some variables of this age-analysis was not reached due to the small size of the subgroups.

Intraovarian treatment with autologous PRP is widely used and has already been investigated for poor responder women (17–20), however, these quality-related findings are quite new in the PRP scenario. Oocyte maturation and developmental competence are critical for successful IVF. Hosseini et al. (24) first described the possible benefits of PRP on oocyte quality in a preclinical study, demonstrating that thrombin-activated PRP improved maturation rates and oocyte viability in vitro. Similarly, Parvanov et al. (25) report that MII-oocyte yield, morphology, and blastocyst quality improved after two consecutive calcium gluconate-activated PRP injections, however, fertilization rates were comparable with the pretreatment ones. Aligning with our findings, a retrospective study by Cakiroglu et al. (18) found poor responder women had more MII oocytes retrieved and fertilized after PRP treatment, raising the number of blastocysts generated. In another non-randomized clinical trial including women with advanced maternal age (20), the number of MII oocytes, Society for Assisted Reproductive Technology embryo grade, and clinical pregnancy rates rose after three consecutive PRP treatments (once per menstrual cycle), whereas Farimani et al. (26) found the MII-oocyte yield particularly increased in women >35 years with low ovarian reserve biomarkers (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number group 4), however, the IVF outcomes were not reported. By contrast, a multicentric randomized clinical trial (RCT) (27) developed in young poor responder women (<38 year-old), receiving PRP during the early follicular phase, reported no benefits in terms of oocyte yield, blastocyst and euploid blastocyst number compared with no intervention when IVF cycles were started in the first menstrual cycle after treatment, comparable with that found in our paired comparison with the first posttreatment IVF cycle in a limited subset of 34 patients of the poor responders group. Similar results were reported by Barad et al. (19) in 28–54-year-old women who received no clinical benefits from intraovarian PRP, suggesting that treatment success could be age and patient dependent.

Interestingly, a recent double-blind RCT on intraovarian PRP treatment by Barrenetxea et al. (28) investigated the effect of PRP on subsequent ovarian simulations in poor ovarian response patients from Patient-Oriented Strategies

Encompassing IndividualizeD Oocyte Number groups 3 and 4. These patients who underwent three successive OS and received PRP or placebo during the first oocyte pick up showed an increased number of MII oocytes in the first to the third oocyte retrieval in both groups. This benefit for the total and mature oocyte yields was higher in the PRP group, suggesting that PRP bioactive factors play a role beyond the ovarian mechanical effect (29). Finally, the mean number of euploid blastocysts was similar in both groups. By this RCT, where both placebo and PRP-treated patients underwent similar medical attention and monitoring, the additional effect of this existing exceptional follow-up is excluded (28).

Systematic reviews suggested that autologous intraovarian PRP treatment could optimize the ovarian reserve as well as improve IVF and reproductive outcomes in poor responder patients, but additional randomized controlled trials are still needed to estimate treatment efficacy (30, 31) and elucidate the mechanisms of PRP action in the ovary (13).

Previous studies (15–20, 26, 30, 31) were heterogeneous in terms of PRP preparation protocols, activating PRP or reporting which activator was employed, the concentrations of platelets and growth factors, the number, site, and volume of injections, and the menstrual cycle phase when the intervention occurred, hampering the ability to compare treatment efficiency and standardize treatments. As PRP activation releases the bioactive proteins and molecules related to cell proliferation and differentiation, apoptosis regulation and angiogenesis (13, 14), this step is critical for treatment efficacy. In our clinics, PRP is generally activated using calcium chloride, which showed a more gradual and effective release of growth factors compared with other activation agents (32).

In summary, our PRP treatment did not induce increased numbers of oocytes retrieved or embryos generated in poor responders; however, it resulted in statistically significant improvements in quality-related parameters of the preexisting ovarian follicles, leading to oocytes showing increased ability to mature and be fertilized. This intervention resulted in a 41.5% pregnancy rate per embryo transfer, with a live birth rate of 17.6% for a limited number of women reporting data after delivery.

Although intraovarian PRP treatment promoted antral follicle development in POI patients, we found no significant improvements in their IVF or reproductive outcomes, suggesting a limited efficacy of this approach in our cohort of POI patients. Our results contrast those reported by Cakiroglu et al. (16), where intraovarian PRP significantly raised both serum AMH levels and AFC in younger POI patients (34.8 ± 4.3 years) although this cohort was not compared before and after PRP treatment to establish if these improvements were related to better IVF outcomes. Given that Cakiroglu et al. (16) identified a 7.4% spontaneous pregnancy rate and a 22.8% pregnancy rate after embryo transfer (overall live birth/sustained implantation rate of 8%), they were in favor of routine PRP treatment for young women with POI. However, we recommend treating POI women on a case-by-case basis. As these patients have a 5% chance of spontaneous pregnancy without any intervention (33), the benefit of PRP is slim, as we evidenced only 4.1% of patients achieving pregnancy. These sporadic responses to PRP in POI women seemed to be attributed to the intermittent resumption of ovarian activity (34) because, in some circumstances, ovarian failure may be transient and unpredictable.

The main limitations of our study include its retrospective nature, the lack of a non-treated independent control group, and the inability to analyze data from patients who were lost to follow-up, dropped out of the study, or continued their IVF cycles in other clinics. Thus, this study may over- or underestimate the IVF outcomes, pregnancies and live births facilitated by PRP treatment, especially in the POI cohort. Indeed, we cannot exclude the risk of potential bias derived from the fact that all pretreatment and posttreatment cycles were pooled together, although multiple cycle comparisons were controlled and an additional paired *t*-test applied. As some women underwent subsequent OS cycles, the possibility of only those with a positive response after PRP performing more stimulation attempts should be considered. Although prospective RCTs are needed to establish the optimal efficacy in a larger pool of participants, it will be important to keep in mind that most patients, particularly those with POI, might not want to risk being assigned to the control group or wait long periods before starting their IVF treatment. Finally, molecular studies may help elucidate the mechanism of action of PRP in ovarian reactivation and correctly define the target population for PRP intervention.

CONCLUSION

In conclusion, intraovarian treatment with autologous PRP did not improve IVF outcomes in our cohort of POI women, and thus, should be considered on a case-by-case basis until there is sufficient evidence of its therapeutic benefit for POI. On the other hand, intraovarian treatment with autologous PRP was related to greater oocyte quality rather than quantity in poor responders, as supported by the statistically significant improvements in oocyte maturation ($P=.003$), fertilization ($P=.011$), and embryo cleavage rates ($P=.03$) compared with IVF attempts before PRP, although increases in implantation and live birth rates did not reach statistical significance. All together, these findings provide hope for women whose oocytes cannot develop into good-quality embryos to transfer, and thus, must rely on oocyte donation. We highlight the need for additional well-designed prospective studies, with proper control groups and long-term follow-up, to validate the findings presented herein, establish the duration of the beneficial effects on reproductive outcomes, and finally, characterize which subgroups of patients may benefit most from this treatment.

CRediT Authorship Contribution Statement

Pietro Molinaro: Writing – original draft, Formal analysis, Data curation. **Ana Ballester:** Writing – original draft, Investigation, Data curation. **Juan A. Garcia-Velasco:** Writing – review & editing, Supervision, Resources, Conceptualization. **Manuel Muñoz:** Writing – review & editing, Supervision, Resources, Conceptualization. **Sonia Herraiz:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of Interests

P.M. has nothing to disclose. A.B. has nothing to disclose. J.A.G.-V. has nothing to disclose. M.M. has nothing to disclose. S.H. has nothing to disclose.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be found online at https://doi.org/10.1016/j.fertnstert.2025.05.143.

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Impacto del plasma rico en plaquetas intraovárico bilateral en mujeres con baja respuesta ovárica o insuficiencia ovárica primaria: un estudio retrospectivo

Objetivo: Investigar la asociación del tratamiento con plasma rico en plaquetas (PRP) autólogo con los parámetros de reserva ovárica funcional y los resultados de fecundación in vitro (FIV) en mujeres con baja respuesta ovárica o con insuficiencia ovárica primaria (IOP) que rechazaron la donación de ovocitos.

Diseño: Estudio observacional, retrospectivo y multicéntrico de cohorte.

Población: 353 mujeres que recibieron tratamiento con PRP, incluyendo 207 con baja respuesta y 146 diagnosticadas con IOP.

Intervención: Inyección intraovárico de PRP.

Variables de resultado principales: Los resultados principales fueron el recuento de folículos antrales (AFC) y la hormona antimülleriana (AMH) sérica. Los resultados secundarios fueron parámetros de FIV y resultados reproductivos.

Resultados: En la cohorte de baja respuesta (40,0 ± 3,8 años, AMH0 = 0,43 ± 0,54 ng/mL; AFC0 = 2,6 ± 2,4), el PRP intraovárico se asoció con una mejora significativa en los AFC en cada visita de seguimiento (AFC0 = 2,6 ± 2,4 vs. AFC1 = 5,3 ± 3,6; AFC2 = 4,5 ± 3,5; AFC3 = 4,0 ± 2,4; AFC4 = 3,6 ± 2,7) en comparación con los niveles previos al tratamiento. Se iniciaron 100 ciclos de estimulación ovárica antes del PRP y 231 después en 111 mujeres con baja respuesta, con un rendimiento similar de ovocitos en metafase II (Pre-PRP: 2,4 ± 3,0 vs. Post-PRP: 3,0 ± 3,4) y blastocistos obtenidos (Pre-PRP: 0,5 ± 0,7 vs. Post-PRP: 0,6 ± 1,1). Sin embargo, se encontraron nuevas asociaciones positivas entre el PRP y parámetros relacionados con la calidad ovocitaria, como las tasas de maduración (Pre-PRP: 65,8% vs. Post-PRP: 80,8%) y fertilización (Pre-PRP: 61,6% vs. Post-PRP: 75,8%), aunque no se alcanzaron diferencias estadísticamente significativas en tasas de implantación (Pre-PRP: 9,4% vs. Post-PRP: 35,1%) ni en tasas de embarazo bioquímico (Pre-PRP: 12,5% vs. Post-PRP: 41,5%). Se identificaron 23 embarazos clínicos (17 tras transferencia embrionaria y 6 concepciones naturales), con 7 nacidos vivos en mujeres con baja respuesta que recibieron PRP. En la cohorte con IOP (38,7 ± 4,3 años, AMH0 = 0,1 ± 0,1 ng/mL; AFC0 = 1 ± 1,2), el tratamiento con PRP solo se relacionó con un mayor AFC (AFC1 = 2,1 ± 1,9; AFC2 = 1,9 ± 1,9; AFC3 = 1,9 ± 1,8; AFC4 = 1,9 ± 1,7), pero no se detectaron mejoras en los resultados de FIV ni reproductivos.

Conclusión: Nuestros resultados sugieren que el PRP no induce efectos cuantitativos sobre los ovarios, ya que no aumentó la cantidad de ovocitos ni embriones. Sin embargo, en mujeres con baja respuesta, los ovocitos recuperados mostraron mayor capacidad de maduración y fertilización. En pacientes con IOP, el PRP intraovárico no mejoró los resultados de FIV ni reproductivos, por lo que aún se requieren alternativas. Se recomiendan ensayos clínicos prospectivos y aleatorizados para validar estos hallazgos retrospectivos y dilucidar los posibles mecanismos de reactivación ovárica inducida por PRP.