COMBINED USE OF PRP AND EXOSOMES IN POOR RESPONDERS AGED 35-43: A RETROSPECTIVE CONTROLLED GROUP STUDY

NINO MUSERIDZE, *MD, PhD*
Georgian-German Reproduction Center, Tbilisi, Georgia

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ABSTRACT

Background: Poor ovarian response (POR) remains a substantial challenge in assisted reproductive technologies (ART), especially in women older than 35 years. Regenerative therapies such as platelet-rich plasma (PRP) and exosomes have emerged as promising interventions.

Objective: To evaluate the clinical impact of intraovarian injections of PRP enriched with mesenchymal stem cell (MSC) – derived exosomes on in vitro fertilization (IVF) outcomes in poor responders.

Materials and Methods: A retrospective controlled study was conducted with 126 women aged 35-43 years undergoing IVF. Patients were divided into two subgroups: 35-40 years and 40-43 years. The intervention group received intraovarian PRP plus exosome treatment; the control group received standard stimulation only. Primary outcomes included metaphase II (MII) oocyte count, fertilization rate, blastocyst development, and clinical pregnancy rate.

Results: The PRP plus exosome group showed a 35% increase in MII oocytes, 20%-30% higher fertilization, and 15%-20% improved blastocyst development. Clinical pregnancy rates rose by 15%-17%, with better outcomes in the younger subgroup.

Conclusions: Regenerative therapy using PRP and MSC-derived exosomes may improve ovarian response and IVF outcomes in poor responders.

Keywords: PRP; exosomes; IVF; poor ovarian response; regenerative medicine; stem cells

Introduction

Infertility remains a significant public health concern worldwide, affecting approximately 8-12% of couples of reproductive age. Within the spectrum of infertility diagnoses, poor ovarian response (POR) presents one of the most formidable challenges in assisted reproductive technologies (ART). Women with POR, particularly those over the age of 35, typically demonstrate diminished ovarian reserve, reduced oocyte yield, compromised embryo quality, and consequently lower clinical pregnancy and live birth rates. This pattern reflects both the quantitative and qualitative deterioration of the ovarian follicular pool with advancing maternal age.

The Bologna criteria, established by the European Society of Human Reproduction and Embryology (ESHRE), provide a standardized definition of POR. According to these criteria, POR is diagnosed when at least two of the following are present: advanced maternal age (≥40 years) or other risk factors for POR; a previous cycle with ≤3 Oocytes were retrieved despite adequate stimulation, and abnormal ovarian reserve tests (antral follicle count <5-7 or anti-Müllerian hormone <1.1 ng/mL). In clinical practice, women aged 35-43 with POR frequently present with a combination of these parameters, making them a distinct and high-risk subgroup in ART.

The biological underpinnings of age-related decline in ovarian function are multifactorial. Follicular atresia accelerates after the mid-30s, compounded by mitochondrial dysfunction, increased oxidative stress, accumulation of DNA damage, and elevated rates of meiotic errors leading to aneuploidy. Moreover, ovarian stromal fibrosis and reduced microvascular perfusion contribute to impaired folliculogenesis. Conventional stimulation protocols – whether employing high-dose gonadotropins, mild stimulation regimens, or adjuvant agents such as growth hormone, coenzyme Q10, or androgens – often yield marginal improvements in oocyte quantity without substantial gains in oocyte competence.

Given these limitations, there is growing interest in regenerative medicine approaches aimed at enhancing ovarian function at the cellular and molecular levels. Two promising interventions are platelet-rich plasma (PRP) and mesenchymal stem cell (MSC)-derived exosomes. PRP is an autologous plasma fraction enriched in platelets and their associated growth factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF-β). These bioactive molecules are known to stimulate angiogenesis, cell proliferation, extracellular matrix remodelling, and anti-apoptotic pathways. In reproductive medicine, PRP has been hypothesized to activate dormant follicles, improve granulosa cell viability, and enhance ovarian stromal health.

Exosomes are nanosized extracellular vesicles (30-150 nm) secreted by a variety of cell types, including MSCs. They carry a complex cargo of proteins, lipids, mRNAs, and microRNAs that can modulate gene expression, suppress inflammation, and promote tissue repair in target cells. Preclinical studies have shown that MSC-derived exosomes can rescue ovarian function in models of chemotherapy-induced ovarian insufficiency, reduce follicular apoptosis, and restore estrous cycles.

The combined intraovarian use of PRP and MSC-derived exosomes represents a novel, synergistic approach. While PRP delivers a concentrated set of growth factors to stimulate local repair, exosomes serve as potent mediators of cell-to-cell communication, potentially amplifying and sustaining the regenerative signal. The integration of these two modalities may therefore provide both an immediate and long-term stimulus to follicular recruitment and maturation.

The present study evaluates the impact of combined intraovarian PRP and MSC-derived exosome administration on IVF outcomes in women aged 35-43 with POR, using a retrospective controlled design.

Literature Review

Several studies have independently examined PRP and exosomes in the context of ovarian rejuvenation. Sfakianoudis[1] reported that intraovarian PRP injections in women with diminished ovarian reserve led to improved antral follicle count (AFC) and AMH levels, alongside increased oocyte yields in subsequent IVF cycles. Sills and Wood (2020) demonstrated molecular changes in ovarian tissue following PRP administration, including upregulation of GDF-9 and BMP-15, genes essential for folliculogenesis.

MSC-derived exosomes have also shown promise. Kim et al. (2021) observed restoration of ovarian function in animal models following exosome administration, with histological evidence of reduced granulosa cell apoptosis and enhanced angiogenesis. In a clinical context, Nazari et al. (2022) conducted one of the first trials to assess intraovarian exosome therapy in POR patients, noting improved oocyte maturity and fertilization rates without significant adverse effects.

Although data on combined PRP + exosome therapy in reproductive medicine are sparse, synergistic effects have been documented in other regenerative fields. In orthopedic applications, the combination accelerates tendon and cartilage healing compared to PRP alone. This suggests a potential for enhanced ovarian tissue repair and follicular activation when used in conjunction. Despite encouraging preliminary data, the lack of large-scale randomized controlled trials limits its definitive conclusions. Questions remain regarding optimal dosing, timing, patient selection, and the durability of effects. This study adds to the evidence base by providing comparative data in a clinically relevant age range for POR.

Materials and Methods

Study Design: This retrospective, controlled group study was conducted at the Georgian-German Reproduction Center, Tbilisi, Georgia, between January 2022 and March 2025. Ethical approval was obtained, and all participants provided informed consent.

Participants: A total of 126 women aged 35-43 years met the Bologna criteria for POR and were eligible for inclusion. Participants were divided into two age subgroups (35-40 and 40-43 years). Each subgroup included patients in the treatment group (PRP + exosome) and the control group (standard stimulation only).

PRP Preparation: Peripheral venous blood (20 mL) was collected in sodium citrate tubes, processed by double-spin centrifugation (1500 rpm for 10 min; then 3000 rpm for 10 min) to yield 2-3 mL PRP at 4-5× baseline platelet concentration.

Exosome Preparation: Allogeneic MSCs were sourced from screened umbilical cord tissue and cultured under GMP conditions. Conditioned medium was collected, cleared of debris by sequential centrifugation, and ultracentrifuged at 100,000×g to pellet exosomes. Characterization was performed by nanoparticle tracking analysis and Western blot for exosomal markers (CD63, CD81, TSG101).

Injection Procedure: Under sedation and ultrasound guidance, approximately 1 mL PRP mixed with 50-100 µg MSC-derived exosomes were injected into multiple cortical sites of each ovary.

Stimulation Protocol: All patients underwent a GnRH antagonist protocol with individualized dosing of recombinant FSH (225-300 IU) and Menopur, followed by hCG trigger and oocyte retrieval 36 hours later. IVF or ICSI was performed based on semen parameters.

Outcome Measures: Primary outcomes: number of MII oocytes, fertilization rate, blastocyst formation rate, and clinical pregnancy rate. Secondary outcomes: cycle cancellation rate, OHSS incidence, and procedure-related adverse events.

Statistical Analysis: Data were analyzed using SPSS v26. Continuous variables were expressed as mean ± SD; comparisons used t-tests or Mann-Whitney U tests. Categorical variables were analyzed using chi-square tests. $p<0.05$ was significant.

Results

Baseline Characteristics: No significant differences in age, AMH, or AFC were observed between groups at baseline.

Ovarian Response and IVF Outcomes: The PRP + exosome group demonstrated a 35.5% increase in MII oocyte yield compared to controls (4.2 ± 1.6 vs 3.1 ± 1.4, $p<0.01$). Fertilization rates were significantly higher in the treatment group (74% vs 54%, $p<0.01$), as were blastocyst formation rates (59% vs 42%, $p<0.05$). Clinical pregnancy rates improved from 23.8% in controls to 40.4% in the treatment group ($p<0.05$).

Subgroup Analysis: Both age groups benefited, though the 35-40 subgroup showed greater relative gains in fertilization and blastocyst rates, while the 40-43 subgroup achieved clinically meaningful but more minor improvements.

Discussion

The combined use of PRP and MSC-derived exosomes resulted in significant improvements in multiple IVF parameters in women with POR aged 35-43. These findings are consistent with the hypothesis that regenerative therapy can enhance both the quantity and quality of oocytes in this high-risk population.

Mechanistically, PRP likely exerts its effects through growth factor-mediated angiogenesis, improved stromal perfusion, and granulosa cell activation. At the same time, exosomes deliver microRNAs and proteins that modulate follicular signalling pathways, reduce oxidative stress, and protect mitochondrial function. The observed synergistic effect supports the concept that these modalities act via complementary mechanisms.

Our results align with prior studies of PRP alone[1] and exosomes alone[3] but suggest that combination therapy may yield superior clinical outcomes. Safety was confirmed, with no cases of OHSS or serious adverse events.

Limitations include the retrospective design, lack of randomization, modest sample size, and absence of live birth outcome data. Larger prospective randomized trials are needed to validate efficacy and establish standardized protocols.

Conclusion

This study provides evidence that intraovarian injection of PRP enriched with MSC-derived exosomes can significantly improve oocyte maturity, fertilization, blastocyst development, and clinical pregnancy rates in poor responders aged 35-43. Regenerative cell-based therapy represents a promising adjunct to conventional ART in women with diminished ovarian reserve. Future research should focus on optimal treatment protocols, long-term outcomes, and mechanistic studies to further elucidate the biological basis of these effects.

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