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Case Series

Evaluation of the synergistic application of bone marrow aspirate concentrate and platelet-rich plasma therapy in women experiencing premature ovarian failure and poor ovarian reserve: a case series

Srinivasan Vyjayanthi[1]*, Sharada Golconda[1], Kurapati Krishnaiah[2]

[1]KIMS Fertility Centre, Krishna Institute of Medical Sciences, Secunderabad, Telangana, India
[2]Department of Orthopedics, Krishna Institute of Medical Sciences, Secunderabad, Telangana, India

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***Correspondence:**
Dr. Srinivasan Vyjayanthi,
E-mail: svyjayanthi99@gmail.com

ABSTRACT

Autologous bone marrow-derived stem cells (BMSCs) and platelet-rich plasma (PRP) separately were found to be effective in restoring ovarian function in infertile women. The present study aims to study the synergistic effect of bone marrow-derived aspirate concentrate (BMAC) and PRP in women diagnosed with poor ovarian response (POR) and premature ovarian failure (POF) undergoing *in vitro* fertilization (IVF). A total of 10 patients participated in the study. Eight patients were diagnosed with POR, while two patients had POF. Intraovarian BMAC-PRP injection was given to all the patients via the laparoscopic or transvaginal route. Group 1 before starting the IVF cycle, group 2-intracycle-post ovum pick-up and group 3-POF patients. Outcomes assessed include improvement in antral follicular count (AFC), Anti-Mullerian hormone (AMH), response to ovarian stimulation at subsequent IVF cycle and clinical pregnancy. In group I POR patients (n=4) post-instillation, an increase in AFC count was observed and subsequently, these patients underwent IVF, however, no clinical pregnancies were achieved. Group II POR patients (n=4), who received BMAC-PRP instillation intracycle post-OPU there was improvement in AFC and better response with more oocytes and embryos in the subsequent IVF cycle, leading to three pregnancies in this group. In group III-POF patients (n=2) who received BMAC-PRP instillation, one of them spontaneously conceived post 3 months of instillation. The synergistic application of BMAC-PRP was found to be effective in improving ovarian function in POR and POF patients.

Keywords: Bone marrow derived aspirate concentrate, Platelet rich plasma, BMAC, PRP, Poor ovarian response, premature, Ovarian failure, *In vitro* fertilization

INTRODUCTION

In recent years, with the advent of regenerative medicine, studies have shown that stem cells or PRP can rejuvenate the ovaries. BMSCs, mostly isolated from the bone marrow, can self-renew and specialize into different types of tissue. These stem cells are immunomodulatory and non-immunogenic.[1] The stem cells release a range of growth factors, cytokines and chemokines that play a crucial role in tissue repair, follicular development, paracrine signaling, angiogenesis and ovarian response to controlled ovarian stimulation (COS).[2] Research conducted on animal models and humans demonstrated that stem cells migrate directly and spontaneously to the site of damage and repair. Stem cells on stimulation by various factors, lead to reactivation of folliculogenesis, restoration of ovarian hormone production, and improved ovarian recovery.[3-5] PRP is a component derived from processed autologous peripheral blood, characterized by platelet concentrations that exceed baseline levels. PRP comprises approximately 700 functional proteins, hormones, growth factors and immunomodulators. At the

PRP injection site, these released factors increase tissue angiogenesis, anabolism, cell migration, differentiation, and proliferation.[6] PRP treatment was found to improve reproductive outcomes in POI and POR patients.[7]

In recent years, a combination of PRP and BMSC was found to be an effective treatment option. PRP serves as a storage vehicle for growth factors, attracting stem cells to the injury site and enhancing their proliferation and differentiation.[8,9] Hence, based on prior studies and our experience, the present study aims to study the synergistic effect of PRP and BMAC on the reproductive outcomes of 10 patients diagnosed with POI and POR. This is the first case series to study the effect of the BMAC-PRP instilled during various phases or timings of the IVF cycle.

CASE SERIES

The study was done at Krishna institute of medical sciences (KIMS) fertility centre, KIMS hospital, Secunderabad from March 2022 to August 2024. The study was approved by the ethical committee (KIMS/IECBHR/225/102-05). Patients were informed and a written consent form was taken prior to the study.

A total of 10 patients were included in the study. Of them, 8 patients were diagnosed with POR and 2 patients with POF.

Bone marrow aspiration was done on all subjects from the posterior iliac crest under general anesthesia, utilizing a fenestrated bone marrow needle and a 60 mL VacLok syringe (Arthrex, USA) that had been prewashed with heparin (500 U/mL). Aspirated bone marrow (40 mL) was processed without delay using a closed-circuit centrifugation method, leading to 4 mL BMAC. The obtained BMAC contains platelets ($479.3\pm177.4\times10^3/\mu L$), nucleated cells ($113.2\pm27.5\times10^3/\mu L$) and progenitor cells including hematopoietic stem cells ($0.060\pm0.018\times10^3/\mu L$) and mesenchymal stem cells (843±169/mL) (Arthrex BMC kit, ABS-10072), which can vary from patient to patient. PRP was prepared using 40 mL of the patient's peripheral blood using a heparin-washed syringe (Arthrex, USA). Following double centrifugation, 4 mL of PRP was collected.

A combination of BMAC (2 mL) and PRP (2mL) was injected using a bevel tip needle no- 21G into the ovarian cortex away from the hilum transvaginally using ultrasound guidance under sedation. In patients where the ovaries were small and difficult to access, BMAC-PRP was injected using laparoscopy under anesthesia.

POR cases

A total of 8 POR patients were included in the study. The mean age of patients was 34.5±5.2 years, ranging from 26 to 42 years. The total AFC count increased from a minimum of 1 follicle to a maximum of 7 follicles. Figure 1A and B show the preinstallation and post instillation total AFC count and FSH values. The patients were further grouped based on diagnosis and timings of BMAC-PRP instillation.

Group I-BMAC-PRP instillation prior to the IVF cycle (n=4 POR patients)

In all the cases, the BMAC-PRP therapy was instilled into the ovary prior to further attempts at ovarian stimulation for IVF post BMAC-PRP instillation, total AFC count increased, leading to enhanced oocyte retrieval and embryo transfer. The first follow-up was scheduled one week after BMAC-PRP instillation, to assess the ovarian response (AFC, AMH, FSH). In the event of positive ovarian response, i.e., an increase in total AFC count to 3 or more follicles, COS with gonadotrophins was initiated. However, in all 4 cases, a clinical positive pregnancy at 10 weeks of gestation was not observed. Table 1 presents the group I patients' medical history and detailed clinical outcomes

Group II- BMAC-PRP instillation post-OPU (n=4 POR patients)

Group II includes four patients who experienced a failed first IVF cycle and demonstrated a POR. In the second IVF cycle, patients exhibited a continued inadequate ovarian response, resulting in the development of only one or two follicles. These patients received counselling regarding the intracycle instillation of BMAC-PRP immediately following oocyte collection. In three cases, BMAC-PRP was instilled intracycle post-ovum pick-up and in 1 case in between IVF cycles during hysteroscopy. COS was done either in the same cycle (1 week later), in which case the resultant embryos were cryopreserved (pooling of embryos), or in case of a negative cycle, the ovarian stimulation was reinitiated again in a subsequent IVF cycle. Subsequent IVF cycles led to enhanced oocyte retrieval and successful transfer of embryos. Cases 6, 7, and 9 all resulted in successful pregnancies, with extra frozen embryos still available for future pregnancies. However, in case 7, no follicular development was observed. Table 2 gives the group 2 patients' medical history and detailed clinical outcomes.

Group III-BMAC-PRP instillation (n=2 POF patients)

Group III includes two patients diagnosed with POF and amenorrhea. These patients were not open to oocyte donation therapy. BMAC-PRP was instilled in these patients to see if there are an ovarian response and growth of follicles.

In case 9, post-BMAC-PRP instillation, no ovarian response was observed. Three months after the intervention, she naturally conceived and had a healthy girl. In case 10, post instillation, no ovarian response was observed during the 3-month follow-up. The Patient later chose donor egg therapy (Table 3).

Table 1: Group I patients' medical history and detailed clinical outcomes.

Case no	Medical history				BMAC + PRP instillation procedure	AFC count		AMH (ng/mL)		FSH (IU/mL)		Time of COS post instillation	Post instillation IVF cycles-oocytes retrieved	Number of embryos transferred	Pregnancy
	Age (in years)	BMI (kg/m^2)	Cycles	Duration of infertility		Pre-installation	Post-installation	Pre-installation	Post-installation	Pre-installation	Post-installation				
Case 1	42	29.05	Irregular	2 years	Laparoscopically	RO-0 LO-0	RO-2 LO-6	0.0525	NA	53.2	20.00	1 week	1st IVF cycle-4	D2-2 ET 1×4 cell grade1 1×4 cell grade 2	Negative
Case 2	33	35.58	Regular	4 years	Transvaginally	RO-2 LO-2	RO-3 LO-4	0.166	NA	14	10	1 month	1st IVF cycle-6	D5-1 ET Early blastocyst-grade 2	Negative
Case 3	31	30	Irregular	4 years	Transvaginally	RO-1 LO-0	RO-4 LO-1	0.7	0.373	21.67	8.32	1 week	●1st IVF cycle -2 ●2nd IVF cycle-2 (2 oocytes frozen) ● 3rd cycle-1	●1st cycle: D2- 2 ET 1×4 cell grade3 1×2 cell grade 1 ●2nd cycle: no ET ●3rd cycle: D2-3 ET 3×4 cell grade 2	Negative
Case 4	34	31.23	Irregular	2 years	Laparoscopically	RO-0 LO-1	RO-2 LO-2	0.023	NA	35.45	23	1 month	1st IVF cycle-1	D3-1 1×5 cell grade 2	Negative

Table 2: Group 2 patients' medical history and detailed clinical outcomes.

Case no	Medical history				BMAC + PRP instillation procedure	AFC Count		AMH (ng/mL)		FSH (IU/mL)		Time of COS post instillation	Pre-instillation IVF cycles-oocytes retrieved and embryos transferred	Post-instillation IVF cycles-Oocytes retrieved and embryos transferred	Pregnancy
	Age (in years)	BMI (kg/m^2)	Cycles	Duration of infertility		Pre-installation	Post-installation	Pre-installation	Post-installation	Pre-installation	Post-installation				
Case 5	33	22.8	Regular	3 years	Intracycle-post OPU	RO-1 LO-2	RO-4 LO-6	0.618	NA	NA	26.23	1 week	1st IVF cycle ●5 oocytes retrieved ●D2-2 ET 2×4 cell grade 2 2nd IVF cycle ●2 oocytes retrieved ●D6 1 embryo frozen, 1×Ex.blast AB	3rd IVF cycle ●6 oocytes retrieved ●D6 2 embryo frozen 2×Ex.blast BB ● FET-2 embryos 2×Ex.blast BB ●1 frozen embryo remaining	Positive
Case 6	26	33.3	Regular	4 years	Transvaginally intracyle-post OPU	RO-2 LO-1	RO-3 LO-2	0.288	NA	NA	NA	1 month	1st IVF cycle ●1 oocyte retrieved ●D3- 1 ET 1×8 cell grade 1 2nd IVF cycle ●2 oocytes retrieved ●D2-1 ET 1x5 grade 1	3rd IVF cycle ●4 oocytes retrieved ●D3-2ET 1×8 cell grade 1 1×6 cell grade 1	Positive
Case 7	36	32.03	Irregular	2 years	Transvaginally intracycle-post OPU	RO-0 LO-1	RO-1 LO-1	<0.010	0.01	76.3	25.7	2nd week	1st IVF cycle no response	2nd IVF cycle no oocyte retrieved 3rd IVF cycle only one follicle, cycle cancelled	negative
Case 8	41	25.08	Regular	3 years	Transvaginally in between IVF cycles during hysteroscopy	RO-0 LO-2	RO-4 LO-3	0.14	0.12	25.28	10.23	1 month	1st IVF cycle ●1 oocyte retrieved ●D2-1 ET 1×2 cell grade 1	2nd IVF cycle ● 4 oocytes retrieved ●D5- 2 ET 1×cavitating blast BC 1×cavitating blast CC	Positive

Table 3: Group 3 patients' medical history and detailed clinical outcomes.

Case no	Medical history				BMAC + PRP instillation procedure	AFC count		AMH (ng/mL)		FSH (IU/mL)		Time of COS post instillation	Post instillation IVF cycles-oocytes retrieved	Number of embryos transferred	Pregnancy
	Age (in years)	BMI (kg/m^2)	Cycles	Duration of infertility		Pre-installation	Post-installation	Pre-installation	Post-installation	Pre-installation	Post-installation				
Case 9	25	25.56	Irregular	1 year	Laparoscopically	RO-0 LO-0	RO-0 LO-0	<0.02	0.01	41.96	47.67	NA	NA	NA	Positive (spontaneously conceived)
Case 10	46	22	Irregular	2 years	Laparoscopically	RO-1 LO-0	RO-0 LO-0	0.1	0.016	59.5	50.7	NA	NA	-NA	Negative

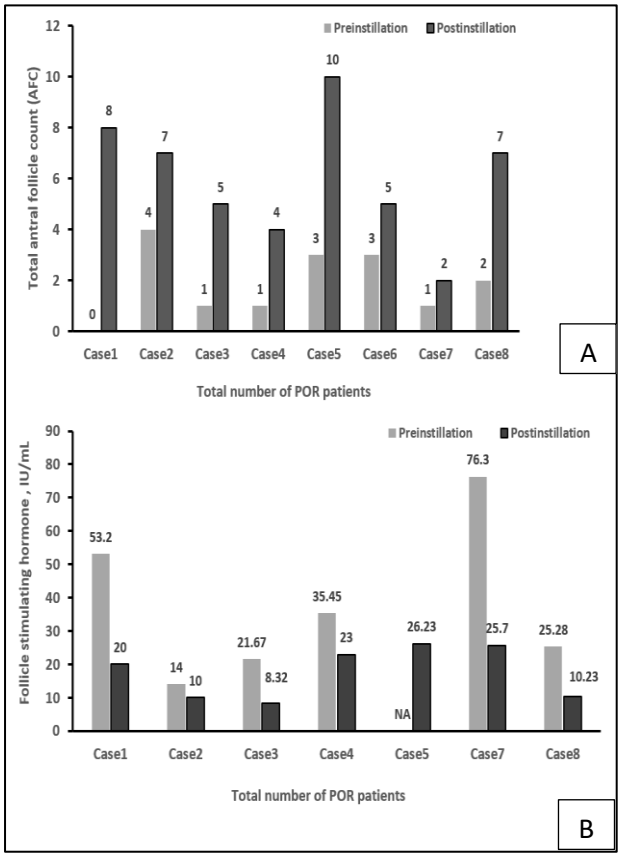

Figure 1 (A and B): Total AFC count-pre-instillation and post instillation of BMAC-PRP B. FSH values preinstallation and post instillation of BMAC-PRP. For case 6, FSH evaluation was not available (NA).

DISCUSSION

The combination of PRP and BMSCs demonstrated an enhanced capacity for regeneration compared to stem cells or PRP alone. Prior studies indicate an increase in ovarian volume, restoration of the menstrual cycle, improvement in endometrial thickness, increase in the total AFC count, estradiol, AMH levels and pregnancy rates.[8,10] A study with 20 patients categorized poseidon group 3 and 4 poor ovarian responders demonstrated that 6 weeks post combined BMSC and PRP transvaginal or laparoscopic instillation, there was an increase in the patients' AFC count to 7-9 follicles and AMH values increased to 0.3-1.1 ng/mL. The total mean number of oocytes retrieved was 4±1.654, and the number of day 3 embryos frozen was 2.5±1.051, indicating a restoration of ovarian reserve.[11] A case study on 10 patients suffering from POR on receiving combined BMSC and PRP instillation demonstrated improved ovarian function and endometrium. One of the patients' conceived naturally and delivered a healthy baby.[12]

In the present case study, group I patients who had repeated failed attempts of ovarian stimulation received BMAC-PRP instillation done prior to IVF cycle, resulted in increased folliculogenesis and improved ovarian function. Post instillation, more oocytes were retrieved and embryos transferred, but failed to result in any successful pregnancies. In a study conducted by Cakiroglu et al intraovarian stem cell treatment prior to ART cycles demonstrated a significant improvement in AMH and AFC values.[13] Nonetheless, in group 2 patients, when BMAC-PRP was instilled intracycle, especially post-oocyte pick-up, there was a significant enhancement in pregnancy outcomes. Clinical pregnancies were achieved in three out of four cases, suggesting a potential synergistic effect. Instillation post-OPU allowed tissue regeneration and follicular development ahead of future IVF cycles. A study conducted using only PRP injected during the ovum pick-up procedure on 3 patients resulted in positive pregnancies naturally.[14] Although the data that is currently available on the timing of instillation is limited, anecdotal evidence and initial case studies indicate a trend of enhanced ovarian function and response in women who are undergoing IVF.

In POF patients (Group III), the combination of BMAC-PRP was found to be effective. One of them spontaneously had a positive pregnancy and live birth. Similar findings were reported in a study conducted on a patient diagnosed with secondary amenorrhea. The patient was given BMSC-PRP laparoscopically. During the follow-up period, her period was resumed, followed by the development of 2 to 3 follicles. After 15 months post-BMSC-PRP therapy, the patient got pregnant spontaneously.[10] Research indicates that even in instances of apparent ovarian quiescence, stem cell-based therapies can reinstate endocrine function and result in follicle growth and oocyte retrieval.[15] However, the response to the therapy varied from case to case and is still being studied.

In a nutshell, our findings demonstrate that the combined use of BMAC-PRP effectively enhances ovarian function and follicular development, leading to 4 pregnancies in this very poor prognosis group. Nonetheless, the investigation utilized BMAC rather than entirely pure stem cells. Although BMAC is simple to prepare, its diverse cell composition, which includes both mesenchymal and hematopoietic stem cells, can result in varying potency. BMAC was used as the initial exploratory approach to investigate the effect of instillation on the outcomes. Further, pilot-scale study will be done using BMSCs to validate the present study findings.

CONCLUSION

The study findings show the potential therapeutic application of BMAC-PRP in patients with POR and POF. Following the instillation, there was an increase in oocytes retrieved and the number of embryos that could be transferred, indicating an enhanced ovarian response, leading to four clinical pregnancies. Further, pilot-scale randomized controlled trials and long-term follow-up studies need to be investigated to optimize the protocol and validate its safety and efficacy.

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