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CASE REPORT

Ray of Hope for Decreased Ovarian Reserve: India's First Two Spontaneous Conceptions After Autologous Bone Marrow-Derived Stem Cells Therapy for Ovarian Rejuvenation

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Introduction

Decreased ovarian reserve is characterized by premature depletion of ovarian follicles. The only solution available for the fertility defect in such women is ovum donation but such therapy comes with a lot of psychological, social and religious restrictions.

Intraovarian stem cell therapy is a ray of hope for ovarian rejuvenation. It acts on small pool of quiescent primordial follicles which remain in the ovaries. Many studies have proved that autologous bone marrow-derived stem cells (ABMDSCs) are capable of providing growth enhancing environments. The stem cells secrete a variety of growth factors, cytokines and chemokines, which are involved in tissue repair, follicular growth, stem cell signaling, angiogenesis, variability and ovarian response to controlled ovarian stimulation (COS) [1].

Based on this information, we present two case reports of successful application of autologous bone marrow-derived stem cells mixed with platelet-rich plasma for ovarian rejuvenation resulting in successful spontaneously conceived pregnancies.

Case Report

First Case

A 26-year-old woman was referred to us with irregular cycles, secondary infertility and decreased ovarian reserve. Married since 3 years, she had conceived naturally in 2016 but had spontaneous abortion at 6 weeks which was medically managed. She underwent IVF in view of decreased ovarian reserve at some other center which failed. Her transvaginal ultrasound showed right ovary measuring ~ 0.6 cc, left ovary ~ 1.2 cc but contained mostly stroma with 2–3 follicles, and uterus was seen to be normal in size with thin endometrial lining. Her Serum AMH was 0.6 ng/ml, FSH–28 IU/l. Thyroid profile and prolactin levels were normal. Karyotyping done was normal. She had been receiving DHEA, Coenzyme Q and vitamin C since 9 months. Intraovarian instillation of ABMDSC mixed with PRP was performed laparoscopically after due consent. Follow-up ultrasound after 4 weeks showed excellent response in the left ovary. Left ovarian volume was seen to be increased from 1.2 cc to 8 cc with appearance of 7–8 follicles. The right ovary however did not show acceptable changes and was still atrophic ~ 0.8 cc. Serum AMH remained same. The patient was recruited for IVF 6 weeks post-procedure, and two Grade A–8 cell and three Grade B -6 cell embryos were formed after two ovum pickups done 3 months apart. Embryo transfer done, however failed. Financially exhausted, patient wanted to try for natural cycle. Since the patient had appreciable follicular count in left ovary,

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tubo-ovarian relationship was found to be normal during laparoscopy, and semen analysis was normal, and the fact that she had conceived naturally once and had resumed having regular cycles (5 months post-procedure), she was advised for timed intercourse. After 11 months of trying naturally (22-month post-intraovarian ABMDSC therapy), the patient conceived spontaneously in November'21 and delivered a healthy baby of 2.7 Kgs in July 2022.

Second Case

A 33-year-old woman was referred to us with secondary amenorrhea, high FSH (45 IU/L) and a normal karyotype (46,XX). Her husband's semen analysis and rest of the investigations were normal. She had normal regular menses until 2019. Her first conception was a spontaneously 8 years back, but resulted in a missed abortion at 7 weeks which was surgically managed. She had extremely low AMH ~ 0.01 ng/ml, FSH–45 IU/L and non-specific B/L ovaries with absent follicles (volume of right ovary–0.8 cc and left ovary 0.9 cc). Patient was given option for third-party reproduction in view of extremely low AMH but she refused donor eggs. After due consent and counseling, intraovarian instillation of ABMDSC mixed with PRP was performed laparoscopically. Transvaginal ultrasound done after 4 weeks showed ovarian volume increased to 6 cc and 12.8 cc, respectively, on right and left side. Right ovary had appearance of 4–5 follicles and left ovary showed 2 follicles. Serum AMH post-procedure was 0.12 ng/ml. Second patient underwent ovum pickup 6 week post-procedure where only one grade B embryo could be obtained. Patient was informed about the need for repeat pickup and success rate with transfer of such embryo; however, she was not willing for any further treatment because of financial constraints. She also reported to have resumed menses 7-month post-procedure. 2–3 follicles per ovary were appreciated in 6 monthly follow-up done for the patient, and she continued to take vitamin C supplementation. After 15 months of unprotected intercourse (15-months post-intraovarian ABMDSC therapy), she conceived spontaneously in June'21 with an ongoing healthy pregnancy of 9 months at the time of reporting the case.

Preparation of Autologous Bone Marrow-Derived Stem Cells

Bone marrow aspiration was done from the posterior superior iliac spine under local anesthesia using the Jamshidi needle (13G) and 20-ml syringe prewashed with heparin maintaining strict asepsis. Around 150 ml of bone marrow was aspirated. Sixteen milliliter of BMDSC was separated using the fully automated cell separator, which uses optical sensor technology and simultaneous application of centrifugation and sedimentation. Processing of bone marrow sample was carried out in a completely closed-circuit centrifugation unit. By this method, we got 10 mL of stem cell concentrate mixed with PRP for both the patients.

Laparoscopic Intraovarian Instillation of ABMDSC with PRP

Under general anesthesia, laparoscopic instillation of harvested ABMSC's mixed with PRP was done (3 ml in right ovary and 7 ml in left ovary in the first case and 5 ml in each ovary in the second case). Injection was done using a 3-mm injecting needle. An assistant firmly stabilized the ovary with an atraumatic grasper. The surgeon then inserted the needle through the ovarian capsule via one entry and slowly injected the concentrated cell sample into the subcortical region over a 5-min time period.

Discussion

The first baby of autologous stem cell therapy in DOR is a reality and hope. In 2018, Tandulwadkar and Gupta et al. [2] reported the world's first successful case of application of ABMDSCT in a 45-year-old female to give successful birth to a healthy baby. In 2016, Edessy et al. [3] used ABMDSCs in 10 POI younger women (26–33 years old) with positive results showing return of menses in two patients and one ongoing pregnancy, with one live birth. In 2020, Yan L et al. [4] injected mesenchymal stem cell through the transvaginal route under sonography guidance in POI patients and was able to achieve four pregnancies in 60 patients out of which three were through IVF and one was spontaneously conceived.

Though there are reports of pregnancy after intraovarian stem cell instillation, the mean duration for which their effect remains is still not fully understood.

In our cases, the patient underwent cycle of IVF after stem cell therapy. The sonographic findings were suggestive of better ovarian volume, blood flow and antral follicle count. However, it did not show positive result in the form of successful pregnancy. Keeping in mind the good ovarian response after stem cell therapy and the financial constraints of the patient, the patients were counseled to keep on trying naturally with the hope that the effect of stem cell therapy will remain in the subsequent cycles. The patients were followed up for 6 months with ultrasonography and conceived spontaneously in the subsequent years.

But this therapy comes with some limitations as it cannot be used in patients with known genetic and karyotype abnormalities. Apart from that there is a risk of introducing infections if sterility not maintained.

To conclude, our case report gives a new hope of spontaneous conception after stem cell therapy. Hence, we need to keep a long term follow-up of our patients to know the effect of this therapy on the ovaries and in the field of assisted reproduction.

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Declarations

Conflicts of interest The authors have no conflicts of interest to disclose.

Consents for Publication The authors certify that they have obtained all appropriate patient consents for publication of the clinical information in the journal.

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