

## Research Article

# Clinical Approach of Novel Autologous Stem Cell Therapy for Primary Ovarian Insufficiency and Endometrial Regeneration

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## Abstract

Bone Marrow-Derived Mesenchymal Stem Cell Fraction (BMSCF) therapy has various applications as potential use in regenerative medicine. Here, we present an original case of Primary ovarian insufficiency associated with poor ovarian reserves and thin endometrium in a woman who achieved a live birth with BMSCF supplemented with PRP (platelet rich plasma). The age between 24 to 42-year-old woman (n=10) came to our centre with primary infertility. Her husband's sperm count and quality was normal. The patient was advised for fertility enhancing surgery and advised stem cell therapy for poor ovarian reserve and thin endometrium. Several attempts of IVF with Hormone Replacement Therapy (HRT) were made, but the desired thickness of the endometrium was not achieved. Intra ovarian and sub endometrial injection of BMSCF was given, followed by HRT for three months, which resulted in improved endometrium and ovary function. The treatment resulted in the conception and delivery of a 2.9 kg baby through lower segment caesarean section.

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Recently, there has been substantial interest in stem cells as a novel regenerative therapy for the regeneration of human endometrium disorders and poor ovarian reserves.

**Keywords:** Bone marrow; Platelet rich plasma; Poor ovarian insufficiency, Stem cell; Thin endometrium

## Introduction

Researchers have characterized stem cells and evaluated their therapeutic effects in various animal models of degenerative diseases [1]. Based on the considerable data on the feasibility of stem cells for various degenerative diseases, clinical trials are ongoing to develop new stem cell-based treatment strategies in regenerative medicine. However, there are few reports on the effects of stem cells in reproductive diseases [2]. In reproductive medicine, ovarian function is important in the health of both young and old women. Stem cell therapy has become a promising, particularly for indications not possible to treat medically or surgically to improve the condition. Stem cells have the ability to self-renew and differentiate into specific lineage [3]. MSCs can be isolated from various sources, including bone marrow, placenta, dental pulp [4-6]. The advantages of autologous MSCs are that they do not raise any ethical concerns; they have no immunogenicity and immunomodulatory function. Premature Ovarian Insufficiency (POI) is a clinical syndrome defined by loss of ovarian activity before the age of 40 years. POI is characterized by menstrual disturbance with raised gonadotropins, low Anti-Mullerian Hormone (AMH), and estradiol level [7]. Autologous BMSCF s was tried in POI to increase the follicular recruitment and avoiding the need for oocyte donation program and regeneration of endometrium. This study analyses the role of autologous BMSCF in POI and thin endometrium. In the absence of stem cell therapy, accepting oocyte donor program or adoption would have been the only viable options for this patient for which she was not ready. In particular, POI defines a state of female hypogonadism which causes a loss of ovarian function before the age of 40 years. POI can be caused by side effects of anticancer chemotherapy or by surgical means [8]. This condition can be diagnosed based on a decrease in the number of follicles, abnormalities in the menstrual cycle, and infertility. There are several preclinical studies of stem cell therapy to treat ovarian dysfunction in several animal models and endometrium regeneration [9,10].

## Methodology

Ten patients, who had a history of cancelled cycles due to inadequate endometrial growth (less than 7 mm) in the past FET cycles despite standard treatments and POI, were recruited into the study performed in the IVF centre, in 2021. After approval from the Institutional Ethics Committee, 10 patients was selected after written informed consent after explaining the pros and cons of this procedure were included in the study. This prospective interventional study was designed for intraovarian instillation and endometrium infusion of BMSCFs along with PRP in 10 patients who are poor responders for fertility.

### Inclusion criteria were as follows:

Age group of 20-45 years

1. Poor responder (the expected poor responder group where AFC <5 and anti-Mullerian hormone (AMH) <1.1 ng/ml)
2. Normal karyotype
3. Normal semen parameters

### Exclusion criteria were as follows:

1. Abnormal karyotyping
2. Autoimmune diseases
3. POD due to chemotherapy or radiotherapy
4. Active viral infections

The AFC by transvaginal ultrasound and serum AMH levels were considered markers of ovarian response. Both were recorded in all patients under basal conditions before and 5 weeks after the procedure.

### Bone marrow aspiration

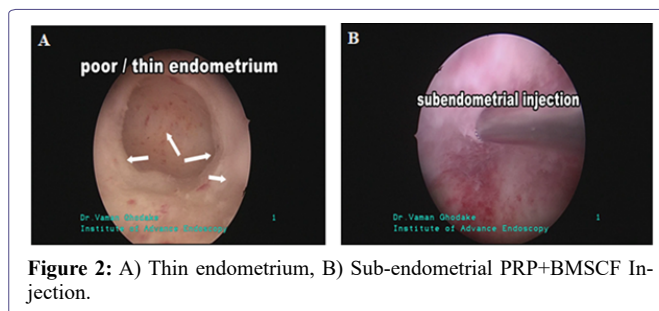
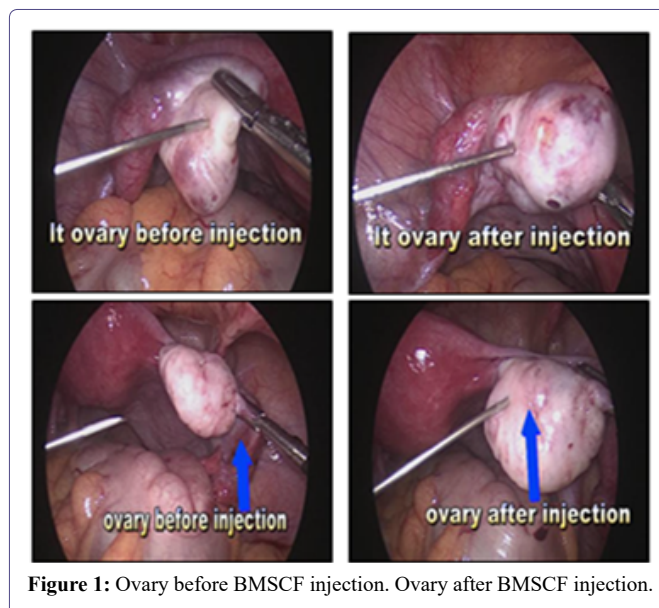
Age between 24-45-year-old poor ovarian failures, poor ovarian reserve, thin endometrium female, came to our fertility clinic. Their AMH level was low 0.4 ng/mL and AFC  $\leq$  2. On ultrasonography, ovaries were unremarkable with antral follicle count of one. It was thought to use autologous BMSCF for the rejuvenation of functioning ovarian tissue and optimizing the success rate of achieving pregnancy through assisted reproduction. Patients with POD, undergo diagnosis and screening confirming diagnosis including history and physical exams, labs and diagnostic procedures. Following final approval and under anaesthesia, bone marrow aspiration with separation of the Bone Marrow Derived Stem Cell Fraction (BMSCF) will be performed. BMSCF harvested from the anterior superior iliac crest region. Bone marrow aspiration procedure (BMAP) was carried out by local anaesthesia with light sedation monitored by an anesthesiologist for access to the posterior superior iliac crest.

### Preparation of Autologous Bone marrow-derived mesenchymal stem cell fraction

Bone marrow aspiration was done from the posterior superior iliac spine under local anaesthesia using the Jamshidi needle (13G) and 20-ml syringe prewashed with heparin maintaining strict asepsis. Prewashed the syringe avoids clot and coagulation, which can diminish the ultimate yield from the aspiration. Approximately 80-100 mL of bone marrow is aspirated. BMSCF were isolated by using automated closed-circuit centrifugation unit. By this method, we got 20 mL of stem cell concentrate. The stem cell mixed with PRP for the entire patient for transfusion. BMSCF were counted using a Neubauer chamber and cell viability was determined by counting the blue (dead) and transparent (alive) cells by trypan blue (Sigma) staining.

### BMSCF infusion

Considering the small size of ovaries, we preferred laparoscopic instillation of BMSCF in ovaries. Ovaries were held at the cranial and caudal position with forceps and intra-ovarian instillation of about 1-2 ml of BMSCF at 3-4 sites performed bilaterally and sub endometrial 1-2 ml stem cells injected for endometrial regeneration (Figures 1&2).



## Results and Discussion

The bone marrow is promising sources of MSCs, and although its aspiration is invasive technique for the MSC isolation, it is the most evaluated approach for cell therapy. MSC differentiation potential and the viability of the bone marrow MSCs decrease with age. PRP is defined as a plasma fraction of autologous blood. It has been shown to improve tissue regeneration with the expression of cytokines and growth factors [11]. A few studies have evaluated the role of intrauterine instillation of PRP in endometrium regeneration [12-14]. It has been shown to improve embryo transfer and vascularity through releasing cytokines and growth factors, containing Vascular Endothelial Growth Factor (VEGF), transforming growth factor, platelet-derived growth factor, and epidermal growth factor [15]. These factors regulate cell proliferation and differentiation, and promote extracellular matrix accumulation.

After BMSCs transplantation in 45-year-old female to gives successful birth to a healthy baby. 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. The patients were counselled 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 6-8 months with ultrasonography and conceived spontaneously in the subsequent years. But this therapy comes

No	Pt / age / married	Diagnosis	USG	USG RT OVARY	USG LT OVARY	LAPAROS-COPY	HYS-TEROS-COPY	Clinical	Stem cell	result
1	KMC/27 /4	Twice aborted – blighted ovum Poor ovarian reserve	Uterus normal	19x13x16 mm= VOLUME 2.3 ml AFC = 0-2	13x19x20 mm= VOLUME 2.9 ml AFC 0-2	uterus normal ovaries smaller atrophic	Endometrial cavity normal	Non responding well ovulation induction drugs Poor follicular response Endometrium thin not growing more than 6 mm	Intra ovarian Subendometrial opu - -4 eoo-cystes  3 embryos	IVF 2950 gms Baby
2	VRM 24/ 2	Premature ovarian failure AMH = below 0.1 Fsh =70 Lh 24.56 Secondary amenorrhoea Responding well to medications	Atrophic smaller 35x25x17 mm Thin central endometrial echo	Smaller Could not be accessed properly	Smaller Could not be accessed properly	streak like smaller atrophic ovaries	cavity smaller twice metroplasty done	Ovarian failure Secondary amenorrhea Hormones correlating with post-menopausal age group Endometrium thin 2-3 mm Only spotting after withdrawal bleeding after medication	Sub-endometrial stem cells	Oocyte donation Husband sperms Ivf done Istivf aborted at 6 wks 2ndivf – Maximum endometrial thickness – 6.5 mm Presently 14 wks viable pregnancy
3	STJ 32 / 17	Poor responder	Uterus normal	20x25x29 mm Vol = 5.8 ml	25x17x21 mm Vol = 5.2 ml	Uterus normal Ovaries appears smaller	Endometrial cavity normal Poor endometrial quality	Endometrium is poor and took almost 2 yrs for endometrial preparation Finally endometrium was 7.4 mm thick with zone 5 vascularity IVF – FET done	Sub endometrial stem cells	Successful IVF conception
4	Spp 33 / 8	Poor responder Very poor response to the oral and injectable ovulation agents	Uterus Normal	16x17x16 mm Vol 2.4 ml AFC= 1-2	17x20x21 mm Vol 4.11 ml AFC= 0- 2	Uterus Normal Both ovaries appears smaller atrophic	Endometrial cavity normal Poor endometrial quality	Endometrium is poor and took almost 6 months for endometrial preparation Finally endometrium was 7.3 mm thick with zone 5 vascularity IVF – FET done	Intra ovarian stem cells  One blast formed	IVF FET DONE FAILED
5	MPG 35/13	Very poor response to the endometrial preparation Embryo are ready but endometrium is not well responding	Uterus normal Thin endometrium	Smaller in size atrophic	Smaller in size atrophic	Uterus Normal Both ovaries appears smaller atrophic	Endometrial cavity normal Poor endometrial quality	Embryos are ready but endometrium is not responding well Suggestive of poor endometrial response	Intraovarian and sub endometrial stem cells	Planning for endometrial preparation

6	SPM 24/4	Poor responder	Uterus rt unicornuate Poor responder AMH-0.8 FSH -8.5	UTERUS 31X23 MM UNICORNUATE	ovary small atrophic	ovary small atrophic	ENDOMETRIUM IS GOOD	Non responding well ovulation induction drugs Poor follicular respoce	Intraovarian Stem cells  Opu done 6 oocytes 3- M2 And 3 - abnormal oocytes  3 day 3 embryos	FET done Positive
7	SCG 29/7	Poor responder	Uterus normal	Smaller 26x17x20 mm	Smaller 23x18x21 mm	Uterus normal Both ovaries appears smaller atrophic	Endometrial cavity good	Non responding well ovulation induction drugs Poor follicular respoce	Intraovarian Stem cells  Opu done 3 oocytes 2- M2 And 1 - abnormal oocytes  1 day 3 embryos	FET DONE
8	Vsp 41/12	Poor responder Three abortions Two blighted ovum and one missed abortion	Uterus bulky adenomyotic One anterior wall fibroid One posterior wall fibroid Fibroids non indenting the endometrial cavity	Smaller 18x16x20 mm	Smaller 15x18x19 mm	Uterus bulky adenomyotic Smaller atrophic ovaries	Endometrial cavity appears normal	Intraovarian stem cells planned	3 oocytes 2 abnormal empty ooplasm One good m2 Failed fertilization	
9	MSS 25/5	Poor responder Premature ovarian failure AMH – 0.6 FSH – 9.7	UTERUS NORMAL	Smaller AFC = 1-2	SMALLER AFC = 0-1	uterus slightly bulky ovaries smaller atropic	endometrial cavity appears normal	Non responding well ovulation induction drugs Poor follicular respoce	intraovarin stem cell opu done 3 m 2 oocytes One ady 3 good embryo	FET Failed
10	Ssp 37/17	Poor responder Severe adenomyotic uterus Kinked endometrial cavity Non responding endometrium	Massive adenomyosis with kinked cavity poor endomyometrial differentiation Thin hazy non triple line endometrium with poor vascularity	Smaller atrophic	Smaller atrophic	Severe adenomyoic bulky uterus with smaller atrophic ovaries	Normal cavity capacity but poor endometrial quality	Nonresponding , thin hazy , nontriple line , typical adenomyotic endometrial response	Subendometrial stem cells	FET DONE TWIN PREGNANCY DELIVERED BABY -1 – 2.5KG AND BABY -2 – 2.3KG

**Table 1:** Table showing details of the synergetic effects of stem cells and PRP enhance and restoring various aspects of ovarian function, such as folliculogenesis, vascular formation, genetic stability and its clinical outcomes in various study subjects.

\*\*Note: Atrophic is a term given to signify a structure that is shrunken or diminished in size and function. In the case of the ovary this implies a decreased in the ovarian tissue volume and may be indicative of ovarian failure or interrupted ovarian blood supply.

with some limitations such as genetic and karyotype abnormalities. The present report described 10 IVF cycles in patients who underwent BMSCF therapy with PRP. For successful implantation, the endometrium needs to regenerate and proliferate properly. In this complex process, different type of cell such as endothelial, epithelial, and stem cells and fibroblasts are involved. Growth factors, pro-inflammatory cytokines, and local chemokines also have important role in tissue regeneration. The bone marrow-derived mesenchymal stem cells (BMSCs) could restore the structure and function of injured

tissues [16]. Recent studies suggest that stem cell therapy holds promise in treatment of variety of diseases including reproductive dysfunction. In a recent study, BMSC treated animals resumed ovarian function. In another investigation, granulosa cell apoptosis induced by cisplatin was reduced when BMSCs were migrated to granulosa cells in vitro [9]. In this study, chemotherapy-induced POI rats were injected with BMSCs. The BMSCs treatment group's antral follicle count and estradiol levels increased after 30 days, compared with untreated POI group. In a recent clinical trial evaluated the therapeutic potential

of autologous mesenchymal bone marrow stem cells transplantation in women with POI [17]. Patients with POI were selected and their ovaries were injected with autologous BMSC at time of laparoscopy. The results shown continuation of menstruation in after 3 months; showed focal secretory changes after having atrophic endometrium. According to these results, BMSC seem to have the ability to resuscitate prematurely failed ovaries both in their hormonal and follicular development abilities.

Researchers recently reported that stem cell transplantation improves ovarian function which suggests a therapeutic potential [18,19]. The therapeutic effects of stem cells can be measured by several factors, such as folliculogenesis, the Granulosa Cells (GC) apoptosis rate, vascular formation, the pregnancy rate and the regulation of hormone levels. Folliculogenesis can be endorsed by the stem cells transplantation, which can trigger oogenesis. ADSCs are known to augment the severity of theca cells and GCs, resulting in an ideal environment for folliculogenesis [20,21]. PBMC contain various multipotent progenitor cells and have the ability to restore organ function and regenerate tissues. The combination of Platelet-Rich Plasma (PRP) and PBMCs has a synergistic effect on restoring folliculogenesis when transplanted into the induced Premature Ovarian Insufficiency (POI) model [21]. Our study shown that synergetic effect of autologous BMSCF and PRP therapy in a 24-year-old blighted ovum poor ovarian reserve helped in procuring a pregnancy and delivery of a healthy 2.9 kg baby through assisted reproduction. It also help to improve endometrium thicken for embryo implantation for IVF treatment (Table 1).

## Conclusion

It is evident that combine effect of BMSCF and PRP therapies have potential in treating POD. The synergetic effects of stem cells and PRP enhance and restoring various aspects of ovarian function, such as folliculogenesis, vascular formation, and genetic stability. Since stem cells are a proven new therapeutic strategy for the future cure of ovarian dysfunction.

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