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Treatment of premature ovarian insufficiency using autologous bone marrow concentrates through a transvaginal approach under ultrasound guidance: A Case Report

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Abstract

Premature ovarian insufficiency (POI) is a clinical syndrome characterized by an early loss of ovarian function, manifested by menstrual irregularity or amenorrhea with elevated levels of gonadotrophin hormones and low levels of estrogen and anti-Mullerian hormones. Regenerative medicine treats a variety of diseases by using cells or biological products instead of conventional drugs or other interventions. The autologous use of stem cells from bone marrow or adipose tissue (stromal vascular fraction) or growth factor products such as platelet-rich plasma are safe alternative minimally manipulated products that can potentially solve this clinical problem without an oocyte donation program. The current study reports the application of regenerative medicine: autologous bone marrow aspirate concentrate is used to treat premature ovarian insufficiency using minimal manipulation combined with minimal surgical intervention through an intravaginal approach under ultrasound guidance. **In conclusion,** to the authors' knowledge, this is the first case study that reports the treatment of ROI via a transvaginal approach in delivering bone marrow aspirate concentrate.

Keywords: Anti-Mullerian hormone, autologous bone marrow concentrate, premature ovarian insufficiency.

Introduction

Premature ovarian insufficiency is a clinical syndrome characterized by the early loss of ovarian function (typically less than 40 years of age) manifested by menstrual irregularity or amenorrhea with elevated levels of gonadotrophin hormones and low levels of estrogen and anti-Mullerian hormones. The average menopausal age in the developed world is 50-52 years. At the same time, it is believed that about 1% of women less than 40 years of age and 0.1 less than 30 years of age develop premature ovarian insufficiency (1). The etiology of POI may be genetic, chromosomal, or auto-immune. Additional etiologies relate to cancer treatments and surgical causes.

Hormonal replacement therapy is recommended for POI patients to alleviate vasomotor symptoms in addition to preventing osteoporosis and ischemic heart disease (2).

Regenerative medicine is a new medical approach to treating a variety of diseases involving many tissues or organs in the human body (3). It uses cells or biological products instead of conventional drugs or other interventions.

The autologous use of stem cells from bone marrow or adipose tissue (stromal vascular fraction) or platelet-rich plasma are alternative safe, minimal manipulative products that can provide a solution to this clinical syndrome.

Only a few cases in the literature have mentioned the use of autologous stem cells for the treatment of POI, including bone marrow or adipose-derived stem cells and mesenchymal stem cells expanded in vitro.

The current case report aims to introduce application of autologous bone marrow aspirate concentrate using a transvaginal approach under ultrasound guidance to treat POI.

Case Report

A 38-year-old female patient presented to our fertility clinic with a 1-year history of oligomenorhea. Her Anti Mullerian Hormone level was low 0.01 ng/ml. On ultrasonography, the ovaries were unremarkable with an antral follicle count of 1.

Informed consent for the procedure of autologous bone marrow aspirate concentrate injection via transvaginal ultrasound approach was obtained, which included the nature of the experimental procedure as well as risks and alternatives. The consent methodology was approved by the fertility center's ethics committee.

In the current study the following were used:

1. Autologous cells.

1. Bone marrow aspiration was performed under local anesthesia with single skin insertion by multiple cortical penetrations and aspiration.
2. Bone marrow aspirate concentrate with the main product of 6 x 10^6 cells/ml^3 .
3. 95 % cell viability by trypan exclusion test

1. Transvaginal approach with ultrasound guide to inject small (1-2cc) bone marrow concentrates volume to both ovaries.
2. The result after 16 weeks was elevation in anti-Mullerian hormone and development of new follicles in both ovaries.

Procedures

Under local anesthesia, a posterior iliac crest bone marrow aspiration was performed by single trocar skin insertion, and multiple cortical bone penetrations. 30 cc of bone marrow aspirate was obtained and mixed with acid citrate dextrose in a 1:8 ratio, which was then centrifuged utilizing a closed kit system. The final bone marrow aspirate concentrate product consisted of a volume of 4 ml, containing approximately 6x10^6 mononuclear cells per cubic millimeter with a 95% cell viability by trypan exclusion test. Under general anesthesia the patient received 1-2 cc of the bone marrow aspirate concentrate in each ovary under ultrasound guidance using a transvaginal approach. After 16 weeks of the autologous ovarian bone marrow concentrate injection, a transvaginal ultrasound showed the presence of 2 follicles in each ovary (Figure.1). The anti-Mullerian hormone level elevated from 0.01 ng/ml pre-procedure to 0.2 ng/mL, and eventually to 0.97 ng/ml. In addition, her estradiol level increased from 28.25 pg/ml to

41.17 pg/ml. At the same time, the follicular stimulating hormone (FSH) level was reduced from 76.70 mIU/ml to 43.14 mIU/ml. (Table.1)

Figure. 1: The ovarian Ultrasound showing the presence of two follicles

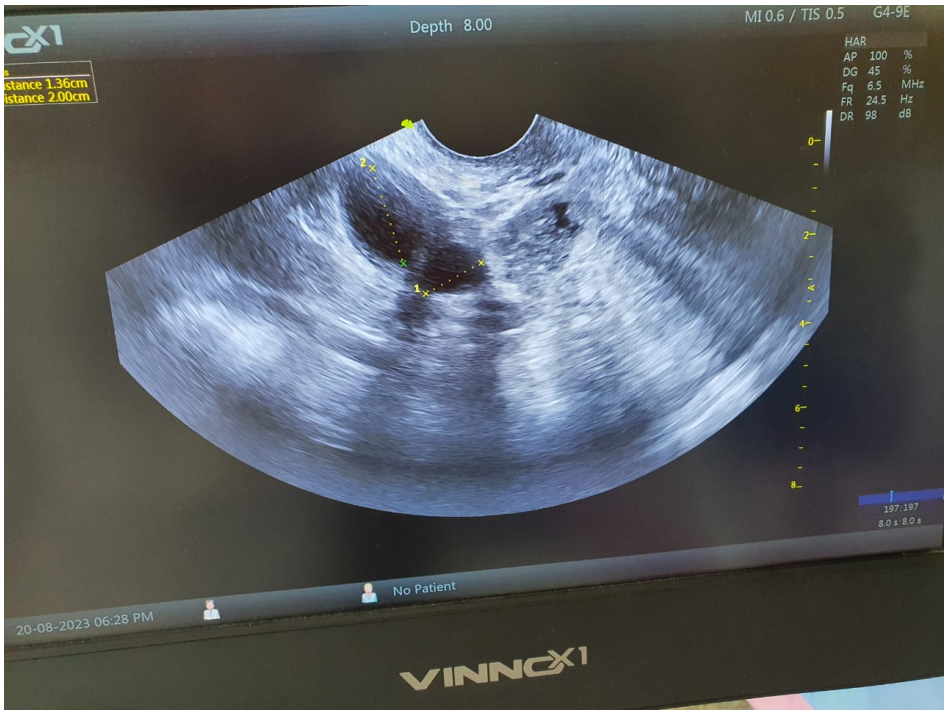

Table. 1: Hormone levels prior to and after the procedure

Hormone	**Before Procedure 05/25/2023**	**After Procedure 11/07/2023**
AMH	0.2 ng/ml	0.97 ng/ml
Estrogen	28.25 pg/ml	41.17 pg/ml
FSH	76.70 mIU/ml	43.14 mIU/ml
Date	25/5/2023	11/7/2023

Discussion

Premature ovarian failure is a complex syndrome, featuring hypoestrogenism, hypogonadotropic, amenorrhea, and infertility, as well as an increased risk of bone loss and ischemic heart disease (2). The current therapeutic approach to POI presents limited choices, which consist of hormonal replacement therapy to reduce symptoms and complications of hormonal loss and may provide some benefit for fertility, which is a more complex issue. Stem cell therapy offers an alternative approach, although many types of cells have been proposed for use in this scenario. This includes embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells, among others. For documented safety, the authors prefer using autologous cells with minimal manipulation from bone marrow sources with a transvaginal approach to be injected in both ovaries in small (1-2cc) increments.

It is well documented that stem cells are present in the body as a form of cellular backup to restore cells or tissue lost due to various causes. Autologous bone marrow-derived concentrate might be an alternative for follicular recruitment in POI, among the many other products currently being researched globally.

Bone marrow-derived stem cells also offer a promising therapeutic action through diverse mechanisms such as a reduction in granulosa cell apoptosis, improvement in angiogenesis through a paracrine effect, and secretions of growth factors. In addition to antifibrotic and immunomodulation, antioxidant and anti-inflammatory effects are also known properties of bone marrow (4) .

Intravenous infusions of autologous bone marrow cells promote follicular development in preclinical rat models and have shown some promising results in humans (5) .

Recent studies have shown that bone marrow mesenchymal stem cells delivered to the ovaries by laparoscopic approaches may show some efficacy in treating POI. In one clinical study of 10 cases, results showed that two cases (20%) recovered menstruation at 3 months after transplantation, and one of them (10%) became pregnant and delivered a healthy baby (5,6).

Another study of 30 patients, which utilized the laparoscopic approach to delivery of intraovarian bone marrow-derived mesenchymal stem cells, showed that estrogen and anti-Mullerian hormone (AMH) levels were rising in 86.7% of patients within 1 month after autologous bone marrow stem cell transplantation. This change continued throughout the 48-week follow-up period. In addition, 18 patients (60%) started to ovulate, with ovum sizes ranging from 12 to 20 mm, which indicated that the autologous bone marrow stem cells may improve the conditions in patients with POI (7).

The ovarian follicle population remains limited during the female reproductive life. When this store is depleted, the patient will enter reproductive senescence or menopause. Animal and experimental human trials have shown some promise in using stem cells from different sources. However, using autologous bone marrow-derived cells with minimal manipulation might be a preferred and safer method. Bone marrow cell aspiration from multiple rather than single sites may also yield a higher-quality aspirate. Also, a transvaginal ultrasound-guided ovarian injection is less invasive than the typical laparoscopic approach, which can have unintended complications such as bleeding and the formation of intra-abdominal adhesions.

The exact mechanism of the fertility restoration using autologous bone marrow derived stem cells in this syndrome needs to be further clarified. There is also a lack of clarity regarding the efficacy of mononuclear cells as opposed to isolated mesenchymal stem cells, as well as dosing and ideal patient selection parameters. However, the primary goal of these procedures consists of replenishing ovarian follicles and improving hormonal production, thus regaining fertility.

Conclusion

New and advanced regenerative medicine techniques are offering new hope for the treatment of premature ovarian insufficiency in a limited number of clinical trials and patients. However, the paucity and lack of efficacy of the current treatment options mandates exploring these techniques to improve ovarian function utilizing established stem cell methodologies in this novel application. This case report recorded a 38-year-old female patient with POI by using the safe technique of autologous bone marrow-derived aspirate concentrate that was injected under an ultrasound guide through a transvaginal

approach with resultant improvement in ovarian function. More studies are needed to clarify possible mechanisms and establish predictability in its clinical efficacy.

DECLARATIONS

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Competing interest statement

None

Ethics statement

The authors declare that the author approved that this research follows the journal's Attach Ethic Approval guidelines as appeared on the journal's author guidelines page.

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