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Original Research Article

Effects of autologous stem cell therapy for fertility enhancement among women with premature ovarian insufficiency

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ABSTRACT

Background: Premature ovarian insufficiency (POI) is a condition where the ovary loses its normal reproductive potential earlier than 40 years, compromising fertility. There is no treatment for POI, only ovum or embryo donation. Autologous stem cell ovarian transplant (ASCOT) may be a procedure that creates new eggs in the ovaries of women with POI. The aim of the study was to find out the efficacy of ASCOT in patients suffering from POI.
Methods: A total of 50 patients were included according to inclusion and exclusion criteria in this prospective observational study. POI was confirmed with low levels of anti-mullerian hormone (AMH) (<0.5 ng/dl), high level of follicle stimulating hormone (FSH) >25 ng/ml, and or a low number of antral follicle count (AFC) (<3 in each ovary).
Results: Results showed that after stem cell therapy, mean AMH values increased by 0.48±0.306 and mean FSH values increased by 2.73±3.98 but the difference was not statistically significant. AFC values significantly decreased by 1.33±0.625 at 1st post-stem-cell cycle. During the second cycle, AMH and AFC increased by 0.110±0.051 and 4.63±1.49, respectively, and FSH decreased by 7.4±2.78. In third cycle, AMH & FSH was significantly increased by 0.820±0.44 & 4.120±0.470 and FSH has been decreased by 2.150±3.625. The increase in AMH & AFC was statistically significant, and the decrease in FSH was not statistically significant compared to baseline values.
Conclusions: The study showed that autologous stem cell therapy can have a significant effect on women's ovarian function and fertility. It showed that ASCOT can increase AMH and AFC, and decrease FSH in patients with POI, with a total pregnancy rate of 4% after the third cycle follow-up.

Keywords: Autologous, Ovarian, Pregnancy, Fertility, Infertility, Stem-cell

INTRODUCTION

The development of human oocytes begins during fetal life and the follicular pool reaches its maximum at 20 weeks of fetal development.[1] Follicular depletion has been started before birth and at the time of delivery, only about 1 million follicles remain in the ovary. By the time of menarche, each ovary contains about 400,000 follicles and ovarian reserve continues decreasing as women age increases.[2] So, the decline in oocyte quantity and quality during women's reproductive life is a normal physiological process but in some women, ovary deterioration occurs abruptly and they become prematurely infertile.[3] Premature ovarian insufficiency (POI), is a condition characterized by loss of ovarian function before the age of 40, which is characterized by menstrual disturbances (oligo-menorrhea or amenorrhea), high gonadotrophins, low anti-mullerian hormone (AMH), and estradiol level.[4]

However, it has been estimated that premature ovarian failure affects 10% of the female population, and despite of young age, they have difficulty in conceiving.[5] The incidence of POI is age-specific affecting 1 in 250 women by the age of 35 and 1 in 100 by the age of 40.[6] Diagnosis is confirmed based on elevated follicle-stimulating hormone levels (>25 IU/ml) on 2 occasions 1 month apart, along with low estradiol level (<50 pg/ml) and amenorrhoea for at least 4 months in women younger than 40.[7] Evaluation is warranted, when POI is diagnosed the underlying etiologies should be ruled out. The main cause of POI is iatrogenic, other may be caused by surgery, chemotherapy, or radiation therapy. Other etiologies of spontaneous POI include Turner's syndrome or a variant of Turner mosaic, fragile X syndrome, and autoimmune disorders. In many cases, the etiology remains unknown.[8] Only 5-10% of women of with POI may have spontaneous pregnancy, especially during the first year after diagnosis.[9] However, ovulation is unpredictable and most women with POI have a low chance of pregnancy.[10] Ovarian rejuvenation is the procedure that may create new eggs in the ovaries of women who are unable to conceive because of POI, yet who wish to have their own biological child. These women are either unable to or unwilling for their own personal reasons, to use donor eggs or to adopt a child. Although, new eggs can't be produced naturally, new scientific attempts have gone through nowadays to regenerate their ovarian tissue and so they may have more possibilities for a successful pregnancy. The scientific research for the management of premature ovarian insufficiency started in the early 1950s including infertility due to aging or insults. It was restricted by the belief that ovaries are not amenable to renewal.[11] In 2004, studies with mice challenged the idea of a fixed ovarian reserve being endowed during the perinatal period.[12] Later many studies showed that ovarian aging may be reversible.[13,14] Regenerative medicine holds great promise to repair damaged tissues and organs and restore functionality by stimulating the body's own regenerative capacity. As a new source for multipotent stem cells, human adipose tissue has been introduced. The multipotency of MSCs, namely their ability to differentiate into cells of mesenchymal origin such as osteoblast, adipocytes, myocytes, and chondrocytes, brought interest to investigate their potential for future cell-based therapies.[15] Several mechanisms have been proposed to achieve tissue regeneration through adult stem cell therapy.[16] Subcutaneous adipose tissue consists predominantly of mature adipocytes and a heterogenous stromal vascular fraction (SVF), which induces fibroblasts, endothelial cells, pre-adipocytes, vascular smooth muscle cells, lymphocytes, monocytes, and ADCs. ADCs show the stem cell-specific combination of surface markers, such as CD90, CD105, CD73, CD44, and CD166 lack of expression of hemopoietic markers CD45 and CD34. ADCs also show a more effective collagen production. Moreover, the anti-apoptotic, anti-inflammatory, proangiogenic, immunomodulatory, and anti-scarring effects have been demonstrated for ADCs.[15] Results after autologous stem cell ovarian transplant (ASCOT) were promising for poor responders (PR). ASCOT resulted in a significant improvement in AFC two weeks after treatment. The team defined success as an increase in AFC ≥3 follicles and or two consecutive increases (two standard deviations) in AMH levels, and with this criterion ovarian function improved in 81.3% of women. Among 15 patients, five pregnancies were achieved: 2 after embryo transfer and 3 by natural conception.[17] At present, oocytes or embryo donation is the only proven method in the treatment of infertility in poor ovarian reserve. Ovum and embryo donation procedure is not ethically and religiously accepted in our country. So, women with premature ovarian insufficiency (POI) become hopeless and go to abroad for ovum donation. Ovarian rejuvenation with autologous mesenchymal stem cells from peripheral blood may be a good option for these women to regenerate follicles with the hope of reducing the need for ovum donation in ART procedures and also improving the oocyte quality and ovarian reserve. So, the present study aimed to decrease the need for ovum or embryo donation and also to increase the pregnancy outcome.

Objective

General objective

General objective of the study was to evaluate the effects of autologous stem cell therapy for fertility enhancement among women with POI.

Specific objectives

Specific objectives of the study were to compare the level FSH, AMH, and AFC count before and after the ovarian rejuvenation therapy with autologous stem cells.

METHODS

This was a prospective observational study conducted at the department of reproductive endocrinology and infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka. The study was conducted for 1 year, from July 2021 to June 2022, with a total of 50 infertile women diagnosed with premature ovarian insufficiency from outpatient department (OPD) or inpatient department (IPD) of BSMMU. Patients were selected through a purposive sampling technique. Inclusion criteria were infertile women diagnosed with premature ovarian insufficiency according to ESHRE guideline (infertile women with oligomenorrhea or amenorrhea, infertile women with AMH <0.5 ng/ml, infertile women with FSH >25 IU/ml, Infertile women with AFC <5 in number in both ovaries). Exclusion criteria were infertile male partner with testicular failure, POI due to genetic origins such as Turner's syndrome or chromosomal abnormality, and those affected with other chronic diseases. The procedure included bone marrow stem cell mobilization to peripheral blood by giving injectable granulocyte colony-stimulating factor (G-CSF) 5 µg/kg twice daily for three days and CD34+ count

measured via flow cytometry for 2 times, WBC count was measured for three times, baseline and after the 4th dose and on the day of apheresis. On the fourth-day stem cell collection was performed if patients reached a threshold of CD34+ circulating cells in the peripheral blood ≥10 cells/µl and WBC count ≥20,000/cumm. Cell collection was performed by using the standard procedures including continuous flow apheresis via COM. TEC automated apheresis Fresenius Kabi machine. The used target to reach was a minimum of 4×10^6 CD34+ cells/kg. During the laparoscopic evaluation, 5 ml of pre-prepared autologous stem cells was injected into each ovary by an ovum pick-up needle. After laparoscopy and autologous stem cell injection, post-operatively patients have managed accordingly and were advised for monthly follow-up for three months on OPD of the REI department. To monitor the effect of autologous stem cell injection into the ovary, AMH, FSH, and AFC were measured at four weeks intervals in women who did not menstruate and in menstruating women (D2-5) for a period of at least three (3) months. And in all patients mature follicle was assessed and ovulation was detected. The aim and objectives of the study along with its procedure, alternative diagnostic and therapeutic method, risks, and benefits were explained to the patient's details in the easily understandable local language, and then voluntary informed written consent was taken from the patients before collecting data. Privacy, anonymity, and confidentiality were maintained during the procedure.

The study was also approved by the local ethical committee and the data was analyzed using statistical package for the social sciences (SPSS) V.25.

RESULTS

The mean age of the present study participants was 34.15 years. Among the total 50 participants, 62% had been from the age group of 31-39 years, 18% from 21-30 years, 14% had been of 40 years or older, and 6% had been of 20 years or younger (Table 1).

56% of the participants had primary infertility at the time of treatment, while 44% had previously been fertile and had been pregnant at least once (Figure 1).

Table 2 shows the mean±SD values of serum AMH, FSH, and AFC values at baseline, first cycle after treatment, second cycle after treatment, and third menstrual cycle after treatment.

Table 1: Age distribution of the study participants (n=50).

Age (years)	Frequency	Percentage
≤20	3	6
21–30	9	18
31–39	31	62
≥40	7	14
Mean age (years±SD)	34.15±6.0	

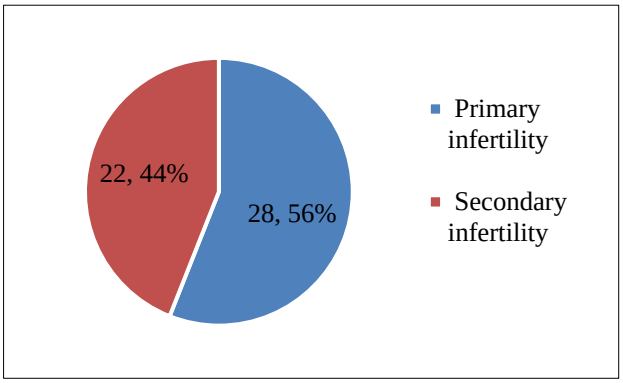

Figure 1: Distribution of the participants by type of subfertility (n=50).

Among the participants of the present study, mean AMH values had increased by 0.48 at 1st cycle after stem cell therapy, but the difference was not statistically significant. The mean FSH values had also increased by 2.73 but were similarly not significant. AFC values had significantly decreased at 1st post-stem-cell cycle, compared to baseline (Table 3).

Compared to baseline values, during the second cycle of post-stem-cell therapy, AMH and AFC had increased, while FSH had decreased. The increase in AMH and AFC was statistically significant, and the decrease in FSH was also statistically significant (Table 4).

During 3rd cycle of post-stem-cell therapy, FSH values had decreased compared to baseline, but the decrease was not statistically significant. Both AMH and AFC values had increased significantly compared to baseline values (Table 5).

Table 2: Number and mean values of the population having changes in ovarian reserve markers (AMH, FSH, AFC) post-stem cell transfer (n=50).

Parameter	Mean±SD (n=50)			
	Baseline	**At first cycle**	**At second cycle**	**At third cycle**
AMH (ng/ml)	0.39±0.63	0.80±2.16	1.43±0.32	1.21±0.27
FSH (IU/l)	25.94±14.87	25.67±23.92	15.54±12.87	20.79±20.88
AFC (count)	5.60±2.87	4.27±3.36	10.23±10.17	9.72±1.67

Table 3: Changes of AMH, FSH, and AFC (baseline versus first cycle post-stem cell injection values (n=50).

Parameters	Mean±SD (n=50)	1st cycle post stem cell therapy, mean±SD	Difference of mean±SD	P value
AMH (ng/ml)	0.39±0.16	0.80±2.16	0.48±0.306 (+)	0.12
FSH (IU/l)	25.94±14.87	28.67±23.92	2.73±3.98 (+)	0.49
AFC (count)	5.60±2.87	4.27±3.36	1.33±0.625 (-)	0.03

Table 4: Changes of AMH, FSH, and AFC (baseline versus second cycle post-stem cell injection values (n=50).

Parameters	Mean±SD (n=50)	2nd cycle post stem cell therapy, mean±SD	Difference of mean±SD	P value
AMH (ng/ml)	0.39±0.16	1.43±0.32	1.110±0.051 (+)	<0.001
FSH (IU/l)	25.94±14.87	18.54±12.87	7.4±2.78 (-)	0.009
AFC (count)	5.60±2.87	10.23±10.17	4.63±1.49 (+)	0.002

Table 5: Changes of AMH, FSH, and AFC (baseline versus third cycle post-stem cell injection values (n=50).

Parameters	Mean±SD (n=50)	3rd cycle post stem cell therapy, mean±SD	Difference of mean±SD	P value
AMH (ng/ml)	0.39±0.16	1.21±0.27	0.820±0.44 (+)	<0.001
FSH (IU/l)	25.94±14.87	23.79±20.88	2.150±3.625 (-)	0.554
AFC (count)	5.60±2.87	9.72±1.67	4.120±0.470 (+)	<0.001

After 3rd cycle follow-up, it was observed that 4% of the patients had become pregnant (Figure 1).

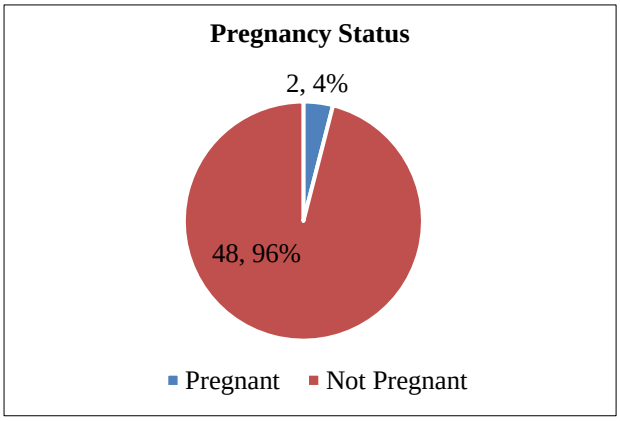

Figure 1: Incidence of pregnancy after 3rd cycle follow-up (n=50).

DISCUSSION

POI is characterized by amenorrhea brought on by ovarian function loss before the age of 40, according to ESHRE 2015. a condition of hypergonadotropic hypogonadism in women. Primary amenorrhea with onset before menarche or secondary amenorrhea, estrogen deficit, and decreased follicle numbers might be used to describe it. Some of the known causes of POI are chromosomal and genetic abnormalities, autoimmune processes, chemotherapy, radiation, infections, and surgery (idiopathic).[18] POI has some significant physical and psychological effects due to the symptoms of hypoestrogenism and long-term sex steroid deprivation. It also shortens life spans by increasing mortality rates.[19] It can affect 1–3% of women who are under 40 and in the reproductive age range, as well as 0.1–0.2% of women under 30.[20] Ovarian activity fluctuations cause only 5–10% of women with POI to become pregnant on their own.[21,22] It has been demonstrated that there are no effective therapies for women with POI to boost ovarian activity and the rate of natural conception.[18] There are currently few therapeutic options available, one of which is hormone replacement therapy, which is meant to alleviate fertility issues as well as difficulties brought on by the ovaries' decreased endocrine functioning. Especially for cancer patients, there are treatments for infertility in POI that can be employed before or during ovarian failures, such as ovarian cortex preservation, oocyte, and embryo preservation, oocyte or embryo donation, and adoption.[23] However, in a developing nation like ours, it is not always practical to explore every possibility. Therefore, it is necessary to investigate innovative techniques like stem cell transplantation. Autologous stem cell therapy, also known as stem cell transplant, is a procedure in which healthy stem cells (blood-forming cells) from a patient's blood or bone marrow are collected before treatment, stored, and then returned to the patient after treatment. An autologous stem cell transplant replaces a patient's stem cells that have been destroyed by radiation or high-dose chemotherapy treatment. Autologous stem cell transplantation is most commonly used to treat blood cancers like leukemia and lymphoma.[24] Although autologous stem cell therapy is intended to benefit cancer patients, it can also benefit other areas of health. ARTs are therapeutic approaches for infertility that involve the handling of either eggs or embryos, as opposed to conventional treatments that improve fertilization rates inside the womb.[25] Even with recent advances in ART, many couples are unable to have

healthy children unless they donate gametes or adopt. ART does not help infertility caused by gamete deficiency caused by genetic defects. However, most couples seeking infertility treatment want to resolve their own genetically related issues, which may be less invasive and less expensive than ART. In this regard, stem cells have provided new hope for overcoming infertility issues in the form of cell-based therapies in a variety of experimental preclinical and clinical models.[26-29] Stem cells are a type of cell that can self-renew and differentiate when they are undifferentiated in embryos and adult tissues. Stem cells in differentiated organs help to restore function by repairing organ damage. Stem cells are classified according to their origin as embryonic stem cells (ESC), adult stem cells (including mesenchymal stem cells MSC), induced pluripotent stem cells (iPSC), spermatogonial stem cells (SSCs), and ovarian stem cells.[30,31] The discovery of the rate of follicular atresia, as well as the death of oocytes and depletion of ovarian reserve in mice, led to the concept of Ovarian Stem Cells. The present study used this concept of stem cell therapy for fertility enhancement among women with premature ovarian insufficiency. Among the participants, the majority had been from the age of 31-39 years, with 14% being 40 years or higher. The normal age of ovarian insufficiency occurs in women after 40 years of age, and anything before that is considered POI.[32] Among the participants, 56% had primary infertility, and 44% had secondary infertility. At baseline, before the start of treatment, mean AMH was 0.39 ng/ml, much lower than normal values at reproductive age. The mean AMH values had increased by 0.48 ng/ml by the first post-stem-cell therapy menstruation cycle, but this increase was not statistically significant. Compared to the baseline, the AMH value increased by 1.11 ng/ml in the second cycle and increased by 0.82 compared to the baseline in the third menstrual cycle. This increase in AMH at both the second and the third cycle were statistically significant. In regards to FSH, the mean value at baseline was 25.94 IU/l, which was much higher than the normal range of women of reproductive age.[33] In the first post-therapy cycle, the FSH value further increased and went up to 28.67 IU/l, but this was understandable. According to previous findings, stem cell therapy initially increases ovarian function by increasing various serum values, including serum FSH.[34] It was further observed that by the second post-therapy menstrual cycle, FSH had dropped significantly, to near the normal range of 18.54 IU/l. AFC count had shown significant changes at each cycle. During the first cycle, the AFC count had a significant decrease of 1.33 count, with a P value of 0.03. In the second cycle, the AFC count had increased by 4.63 compared to the baseline, with a significant P value of 0.002. By the third cycle, the AFC count had increased by 4.120 compared to the baseline, which was a significant increase. AFC is a significant indicator of increased reproductive potential, and the significant improvement of AFC in the present study was similar to other studies.[17,35,36] Use of stem cells to prevent the degradation of follicles in the ovaries is not a recent process, but majority of related studies have mostly been clinical trails, and with animal hosts.[37-39] However, use of stem cells have also been observed in human trials as resisting DNA damage of natural aging to improve ovarian function.[40] A study by Feng et al had observed the use of human menstrual blood driven stromal stem-cell had significant impact on the recovery of premature ovarian insufficiency in rats, by regulating the CM-dependent FAK/AKT signaling pathways.[40] So, it can be said that depending on the usage process and selection of stem cells, the effects can greatly vary, from simply stopping ovarian follicles DNA destruction to restoration of ovarian follicles in case of POI.[37-41] During the study period, 2 patients got pregnant spontaneously, among them one patient had a miscarriage after 10 weeks, and another patient continued her pregnancy. And all the patients were managed by ART (IUI/IVF/ICSI) accordingly to their affordability and availability.

Limitations

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community. The duration of the study was only 3 months, but further follow-up with patients can provide a more detailed understanding of the situation.

CONCLUSION

The study showed that autologous stem cell therapy can have a significant effect on women's ovarian function by improving the AMH level, and AFC and decreasing the FSH level from the second cycle. Our results raised the possibility that promoting ovarian function by autologous stem cell infusion could be an alternative approach to improving follicular development in women with POI.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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