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Intra-ovarian injection of autologous menstrual blood-derived-mesenchymal stromal cells: a safe and promising method to improve pregnancy rate in poor ovarian responders

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Abstract

Background Poor ovarian response (POR) significantly reduces the success rates of fertility treatments. This study investigates the long-term efficacy and potential complications associated with autologous menstrual blood-derived mesenchymal stromal cells (MenSCs) therapy in improving fertility outcomes for women with POR.

Objective To evaluate the long-term efficacy and potential complications associated with MenSC therapy in improving fertility outcomes for women with POR.

Methods This longitudinal, single-center retrospective observational study included 105 POR patients who received autologous MenSC injections from August 2018 to September 2021. Participants were monitored for at least 3 years, and demographic, menstrual, and fertility data were collected. Potential complications were also assessed during this period. Statistical analyses were performed to determine pregnancy rates and possible complications.

Results The average age of participants at the time of injection was 37.91 years. During the follow-up period, 36.19% of women became pregnant, with a live birth rate of 30.48% per treatment cycle. The treatment showed no significant difference in pregnancy rates between women with regular and irregular menstrual cycles. The spontaneous pregnancy rate was also notably higher within the first three months post-injection. No significant complications such as endometriosis, ovarian malignancies, or autoimmune disorders were observed. Only one case of an ovarian cyst, which resolved without intervention, was reported. MenSC treatment did not increase the risk of congenital anomalies or infant mortality.

Conclusion Intra-ovarian injection of MenSCs is a safe and promising method for improving pregnancy outcomes in women with POR.

Keywords Poor ovarian response (POR), Menstrual blood-derived stem cells (MenSCs), Intra-ovarian injection, Stem cell therapy, Long-term safety

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Introduction

Poor ovarian response (POR) refers to a suboptimal response of the ovaries during the in vitro fertilization (IVF) or other assisted reproductive techniques. [1] According to Bologna criteria developed by the European Society of Human Reproduction and Embryology (ESHRE) in 2011, at least two of the following criteria are necessary to be considered as a poor ovarian responder:

1. Advanced maternal age (> 40 years).
2. Previous POR: cancelation of cycles or retrieval of three or fewer oocytes using a conventional stimulation protocol.
3. Abnormal ovarian reserve tests (ORT):
4. Anti-Mullerian hormone (AMH): Less than 0.5–1.1 ng/ml
5. Antral follicle count (AFC): Less than 5–7 follicles. [2]

Poor ovarian response presents significant challenges for individuals undergoing fertility treatments. Reduced chance of pregnancy: due to a decrease in mature follicles, Higher cancellation rate because of Inadequate follicle development, Financial burden as Multiple IVF attempts can be costly, and Emotional toll of repeated IVF failures can be significant. Addressing POR remains a complex task, providing compassionate care and support to those dealing with poor ovarian response is crucial. [3]

Despite the challenges, researchers and clinicians seek different treatment options including Growth hormone supplementations, Controlled Ovarian Hyperstimulation, adjunct therapy, acupuncture, and intra-ovarian injection of platelet-rich plasma. [4–8]

Numerous studies have explored the potential of stem cells in improving ovarian function. Menstrual blood-derived stem cells (MenSCs) have emerged as a fascinating source of mesenchymal stem cells (MSCs) with unique properties. [9] Although they may not directly differentiate to follicular cells, MenSCs play a crucial role in modulating immune responses. They can suppress inflammation and promote tissue repair in inflammatory diseases, tumors, and tissue injuries. [9, 10] MenSCs hold promise for treating infertility and ovarian dysfunction. Their ability to enhance folliculogenesis, regulate angiogenesis, and reduce ovarian stromal fibrosis makes them valuable for improving ovarian health. [11] MenSCs contribute to tissue repair and potential fertility restoration by improving the ovarian stromal environment. [12] MSCs can be sourced from various locations in the body, including bone marrow, adipose tissue, umbilical cord, and menstrual blood. [13] Unlike bone marrow or adipose tissue, MenSCs can be collected monthly during menstruation without invasive procedures, ethical concerns, and autoimmune rejection. [14]

In the previous phases of our clinical trial, we concluded that potential hazards associated with MSC application, particularly in specific cellular microenvironments, necessitate careful long-term monitoring and follow-up assessments. We emphasized the need for further randomized parallel studies with larger sample sizes and extended follow-up periods to definitively establish the impact of MenSCs on ovarian function and live birth rates. In this follow-up study, conducted years after the initial trial, our goal was to adhere to these recommendations by monitoring our patients' long-term efficacy and potential complications of MenSC therapy. [15, 16]

Method

Study design

This investigation constitutes a longitudinal, national single-center retrospective observational study encompassing all patients diagnosed with POR (n = 105) who underwent autologous MenSCs administration across three distinct phases of clinical trials from August 2018 to September 2021 [15, 16]. The detailed study protocol, selection criteria, and methodologies of cell therapy for POR patients have been articulated in preceding publications [15, 16]. Authorization for the clinical trial protocol and the associated consent documentation was obtained from the Biomedical Research Ethics Committee of the Academic Center for Education, Culture, and Research (ACECR). Patients participated in clinical evaluations at the Avicenna Fertility Center approximately at intervals of 3 months, 6 months, and 1-year post-cell therapy. Subsequently, they were directed to local facilities for annual evaluations, and pertinent medical information was extracted from their medical records. Following a minimum follow-up duration of 3 years (ranging from 3 to 6 years), a comprehensive questionnaire was developed, and a trained midwifery professional contacted all patients to collect the requisite information.

Data collection

We collected demographic and relevant information from electronic patient records and our previous publications. This included details such as age, number of injections, injection dates, pre/ post injection menstrual states, and IVF outcomes. [15, 16]

Every participant was assessed utilizing a long-term safety and efficacy assessment methodology. This technique involved analyzing the patient's medical history, imaging investigations, laboratory test results, and self-reported information to ascertain any problems, menstruation status, fertility status, pregnancy outcomes, and neonatal follow-up information. Two specialists

meticulously examined the checklist items, leveraging their expertise in patient complications and fertility outcomes during the assessment. Before the initiation of interviews, informed oral consent was obtained from all participants, who were apprised of the study's objectives, their entitlements, and the voluntary nature of their participation. The confidentiality of the participants was assured, and they were invited to pose inquiries before granting their consent.

Study inquiries

The follow-up protocol encompassing the checklist entailed inquiries regarding the overall survival rates of both mothers and infants, along with newly diagnosed conditions in patients, including but not limited to ovarian cysts, ovarian carcinoma, endometrioma, endometriosis, ovarian torsion, and breast cancer. Furthermore, we solicited information regarding pelvic inflammatory disease, systemic lupus erythematosus, rheumatoid arthritis, other autoimmune disorders, and any subjective health issues that may manifest as potential long-term complications.

In instances where an infant was delivered as a result of this methodology, we sought information concerning the growth and physical health of the infants as well as potential adverse outcomes, which included mortality within the initial year, childhood malignancies (such as leukemia and lymphoma), thyroid dysfunction, congenital anomalies, autism spectrum disorders, and other self-reported health concerns.

To evaluate menstrual health, we probed into the regularity of menstrual cycles and the menopausal status of individuals. To monitor fertility rates and pregnancy outcomes, we inquired about spontaneous pregnancies and pregnancies achieved through Assisted Reproductive Technology (ART).

Statistical analysis

All statistical analyses and graphical representations were performed using the R statistical package. Demographic data, menstrual status, and pregnancy outcomes were summarized using descriptive statistics. Continuous variables were reported as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Associations between categorical variables were evaluated using Pearson's Chi-squared test with Yates' continuity correction. All statistical tests were two-tailed, with a significance level set at $p < 0.05$.

Results

Participant demographics

A total of 105 women who received intraovarian injections of MenSCs due to poor ovarian response were monitored. The average age of these patients was 37.91 years (ranging from 24 to 45) at the time of injection, which increased to 41.98 years during the follow-up period. Of the participants, 70 received a single injection, while 35 received two injections. The average duration of follow-up from the last injection was 3.72 years, with the minimum follow-up being 2.5 years and the maximum extending to 6 years Table 1.

Menstrual status

At the time of the injection, 91 women were experiencing regular menstrual cycles. During the follow-up period, 12 of these women (13.1%) reported irregular menstrual patterns, and 1 woman (1.9%) had entered menopause. Of the 24 women who initially had irregular menstrual cycles, 6 (25%) reported a return to regular cycles at follow-up, while 4 (16%) had undergone menopause Table 1.

Fertility and pregnancy outcomes

Among 105 poor ovarian responders, 38 women (36.19%) became pregnant, with 27 achieving pregnancy spontaneously, 13 through IVF, and 2 through both methods. 27 women (25.7%) with poor ovarian response became pregnant spontaneously after the injection. One woman became pregnant twice, and another became pregnant three times. The median time to spontaneous pregnancy was 3 months post-injection, with a range from 1 to 24 months. Of the 54 women who underwent IVF after their injection, 13 (24%) became pregnant. One case had twin pregnancies. The median time after injection for a successful IVF was 5,5 months, with a range from 2 to 13 months Fig. 1.

Impact of Age on Outcomes: To assess the impact of age on pregnancy outcomes, patients were divided into two groups: under 35 and 35 or older. Among the 23 women under 35, 12 (52.17%) became pregnant. In contrast, among the 82 women aged 35 or older, 26 (31.7%)

Table 1 Demographic Characteristics of women received MenSC injection

Characteristics	Values
Age by First Injection	37.91 ± 4.98
Age by the time of follow-up	41.98 ± 5.00
Follow-Up Duration (Year)	3.14
Menses Before Injection	
Regular	91
Irregular	14
Menses at the time of follow-up	
Regular	84
Irregular	16
Menopause	5

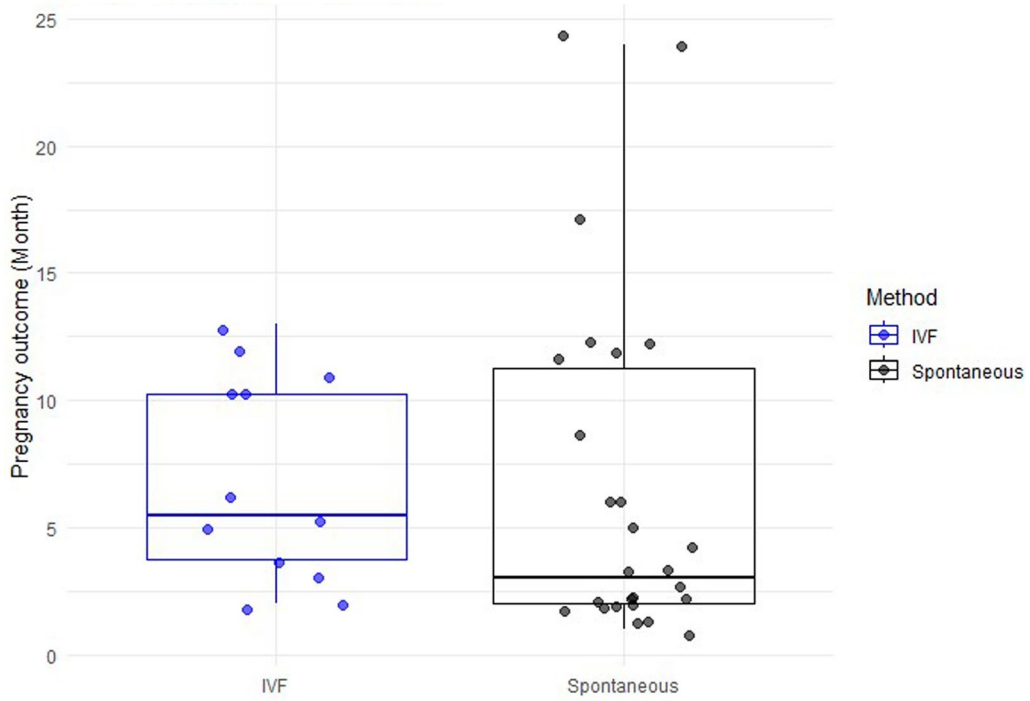

Fig. 1 Pregnancy outcome by method. Distribution of Pregnancy Outcomes by Months After MenSC Injection. The median time to pregnancy after MenSC injection was 3 months for spontaneous pregnancies and approximately 5.5 months for IVF pregnancies

became pregnant. Pearson's Chi-squared test with Yates' continuity correction indicated no significant difference between the two groups (X-squared = 2.4321, df = 1, *p*-value = 0.1189). As shown in Fig. 2, the box plot provides a visual summary of the age distribution among the participants. The median age for pregnancy was 36 years, with the whiskers extending from age 24 to age 42, highlighting the overall age spread Table 2.

Menstrual Status Impact on Outcome The impact of menstrual status on treatment outcomes was assessed by comparing pregnancy rates between women with regular and irregular cycles. It was found that, among the 91 patients with regular cycles at the time of injection, 33 (36.26%) became pregnant. In contrast, pregnancy was achieved by 5 out of 14 women (35.7%) with irregular cycles. No significant difference between the two groups was indicated by Pearson's Chi-squared test with Yates' continuity correction (X-squared = 6.0062e-31, df = 1, *p*-value = 1) Table 2.

Injection Type Distribution 70 women received a single injection, with 29 achieving pregnancy. On the other hand, 35 women received a second injection after the first one, and 9 of them became pregnant. (Table 2).

Complications

Among all the women who were followed up,1 case of an ovarian cyst during pregnancy was reported, which resolved after pregnancy and by the time of follow-up. There were no reports of other complications such as endometriosis, endometrioma, ovarian malignancy, ovarian torsion, pelvic inflammatory disease (PID), ectopic pregnancy (EP), or autoimmune diseases Table 3.

Baby outcome

Of the 105 women who were part of the research, 43 pregnancies were documented, with 38 of them becoming pregnant, some more than once. Out of these pregnancies, 12 resulted in abortion, while 31 pregnancies were successful, leading to live births. Notably, one of these successful pregnancies resulted in twins, bringing the total number of live births to 32. Based on the total number of women, the live birth rates each treatment cycle was determined to be 30.48%, and the live birth rate per pregnancy, which represents the proportion of successful births among all pregnancies, was 74.42%. Despite the possibility of some pregnancy losses, these results show a positive live birth outcome, with most pregnancies ending in live births Table 3.

Discussion

This study explored the outcomes of intraovarian injections of MenSCs in 105 women with poor ovarian response, with a focus on pregnancy, live birth rates, and potential complications. Notably, no significant

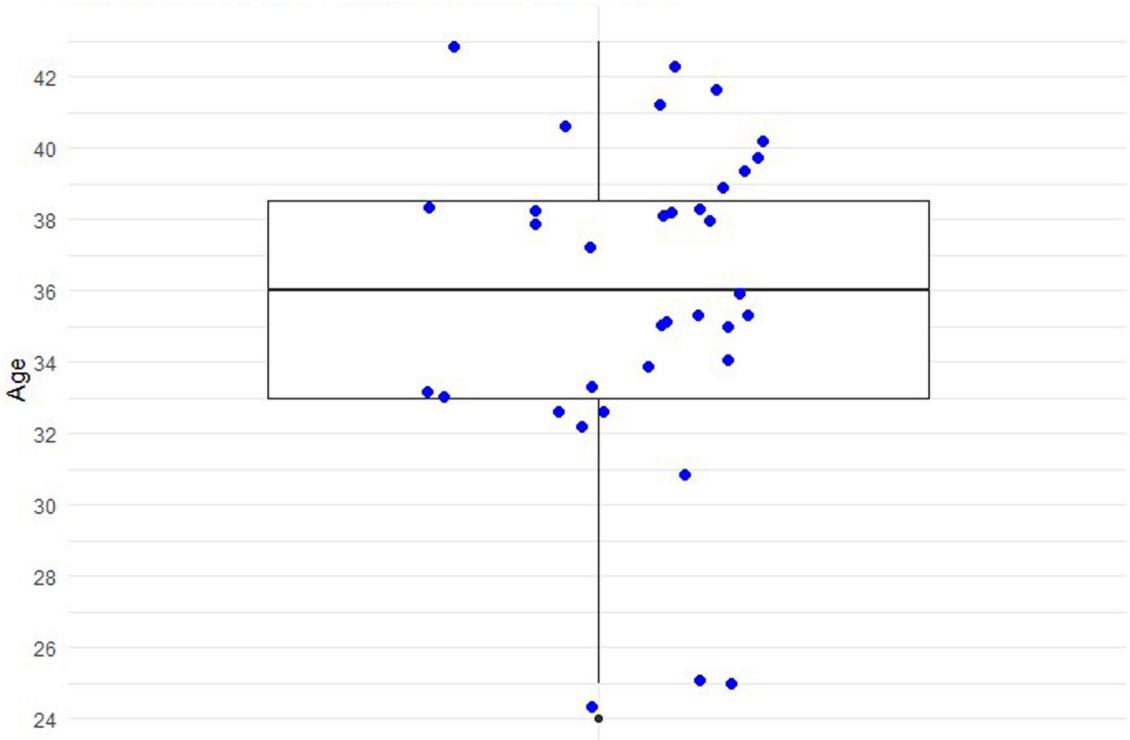

Fig. 2 Age Distribution of Women with POR. Age Distribution of Women Who Got Pregnant Following MenSC Injection. The ages of women who became pregnant after MenSC injection ranged from 24 to 43 years, with a median age of 36 years

Table 2 The impact of different factors on stem cell treatment outcome

Factor	Pregnancy/Total	Percentage	Chi-squared Value	*p*-value
Pregnant Women	38/105	36.19		
Impact of Age				
< 35 years	12/23	52.17		
≥ 35 years	26/82	31.7	2.4321	**0.11***
Impact of Menstrual Status				
Regular Menses	33/91	36.2		
Irregular Menses	5/14	35.7	6.0062e−31	**1****
Injection Type				
Single Injection	29/70	41.4		
Double Injection	9/35	25.71		

pregnancy outcomes based on various factors. *The difference between pregnancy rates for women over 35 years and those under 35 years was not significant (p-value = 0.11). **Menstrual status prior to injection does not significantly impact

long-term problems were noted over an average follow-up time of 3.72 years. Only one case of an ovarian cyst during pregnancy was documented, which resolved without intervention. There were no instances of endometriosis, ovarian malignancies, torsion, pelvic inflammatory disease, ectopic pregnancies, or autoimmune disorders. These findings suggest that intraovarian injections of MenSCs are a safe, long-term treatment option for women with poor ovarian response, with a low complication profile even years after treatment.

In terms of fertility outcomes, 36.19% of women became pregnant, with a live birth rate of 30.48% per treatment cycle and 74.42% per pregnancy. The data also highlight that age was a key determinant of success, with women under 35 showing significantly higher odds of pregnancy. In contrast, menstrual status (regular

Table 3 Women, Fetal, and Neonatal Complications Following MenSC Injection

Women's Complications	N = 105	Fetus/ Neonatal Complications	N = 43
Ovarian Cyst	1	Abortion	12
Ovarian Torsion	0	Died within the First Year	0
Endometrioma	0	Leukemia	0
Endometriosis	0	Autism	0
Ovarian Malignancy	0	Childhood Cancer	0
Pelvic Inflammatory Disease	0	Thyroid Disorder	0
Ectopic Pregnancy	0	Congenital Anomalies	0
Autoimmune Diseases	0	Other	0

vs. irregular) did not significantly impact pregnancy outcomes.

When exploring new methods for treating poor ovarian response, it's essential to consider factors such as efficacy, safety, accessibility, and cost-effectiveness. Stem cell therapy has demonstrated promise in treating infertility. [17] The remarkable ability of Menstrual Stem Cells (MenSCs) to undergo proliferation and differentiation makes them an excellent choice for enhancing ovarian function in the long term. These cells can differentiate into various cell types, including follicular cells and even oocyte-like cells, which positions them as a valuable option for addressing diminished ovarian reserve. [18, 19]

Our study followed 105 women who underwent intraovarian injection of MenSCs due to poor ovarian response. While a meta-analysis by Máté Éliás et al. (2023) indicated a spontaneous pregnancy rate of 7% following intra-ovarian injection of platelet-rich plasma (PRP) in poor ovarian responders, our study found a significantly higher spontaneous pregnancy rate of 25.7% following intraovarian injection of MenSCs. [20] Another meta-analysis by Vahabi Dastjerdi et al. on the effect of intraovarian PRP injection showed a 5% rate of spontaneous pregnancy in poor ovarian responders. [21] This difference could be attributed to the fact that, Unlike MenSCs, which can proliferate and differentiate, PRP primarily works by releasing growth factors that can temporarily enhance ovarian function. [22, 23] The pregnancy rate achieved through IVF after injection of MenSCs was 24%, with a live birth rate of 16.6%. In comparison, a study by Cakiroglu et al. that included 510 women with poor ovarian response who were treated with intraovarian injection of autologous PRP reported a pregnancy rate of 17% and a live birth rate of 11.4%. [24] A systematic review of 10 studies on women with POR treated with intraovarian PRP injection showed a clinical pregnancy rate of 25.4% and a live birth rate of 16.6%. [8] In our study, we achieved higher rates, with a 36.15% pregnancy rate and a 30.48% live birth rate. These findings suggest that the intraovarian injection of menstrual blood-derived mesenchymal stromal cells (MenSCs) may be more effective than PRP treatment for women with POR.

In this study, it was observed that women who received a single injection had a higher pregnancy rate (41.4%, 29 out of 70) compared to those who received a double injection (25.71%, 9 out of 35). While this suggests that a single injection may be associated with a higher likelihood of pregnancy, it is important to note that the second injection was typically administered to women who did not achieve pregnancy after the first injection, often following their insistence. These women's chances of becoming pregnant may have been affected by their initial worse prognosis. Therefore, the lower pregnancy rate in the double injection group does not necessarily indicate that two injections were less effective. On the contrary, the fact that some women did conceive after the second injection suggests that it had a positive impact on pregnancy outcomes for those who initially had a poor response. This highlights the potential value of a second injection as a supplementary option for women who do not respond to the initial treatment.

Our analysis showed that menstrual status did not significantly impact pregnancy outcomes. Among women with regular cycles, 36.26% became pregnant, compared to 35.7% of those with irregular cycles ($p=1$). Even women with irregular cycles had comparable pregnancy rates, indicating that treatment may be effective regardless of cycle regularity. This highlights the need for further research to identify other factors that may play a more critical role in fertility outcomes.

The median time to spontaneous pregnancy after MenSCs injection was observed to be 3 months, and the median time to pregnancy through IVF was 5 months, aligning with most studies on PRP injections that report effects within 1 to 6 months. [8, 25–27]

Interestingly, a large proportion of spontaneous pregnancies occurred within the first 3 months following the MenSCs injection. It could be wise to wait at least

three months before starting IVF therapy in light of this tendency. This finding implies that MenSCs' beneficial effects on ovarian function may start to show around this period. Starting IVF too early may overlook the potential for spontaneous pregnancy, as ovarian responsiveness could improve naturally within this window. Therefore, a 3-month waiting period post-injection before considering IVF may optimize the treatment's impact on fertility outcomes, allowing for the possibility of natural conception while still leaving IVF as a subsequent option for those who do not conceive spontaneously.

The lack of long-term follow-up studies on PRP injections makes it challenging to compare the long-term efficacy of these treatments. However, our findings show that several cases of MenSCs injections resulted in pregnancies even after one year, with two cases achieving pregnancy after two years. This suggests that MenSCs may have a prolonged effect on ovarian function compared to PRP. Future research should focus on extended follow-up periods to better understand the sustained impact of both PRP and MenSCs injections on fertility outcomes in poor ovarian responders. [20, 28]

Complications

MenSCs exhibit impressive differentiation capabilities, including the potential to become adipocytes, chondrocytes, osteogenic cells, fibroblasts, endometrial cells, and germ cell-like structures. [29, 30] Retrograde menstruation, a widely accepted pathophysiological mechanism of endometriosis, involves the backward flow of shed endometrial cells. [31] Hypotheses suggest that mesenchymal stromal stem cells from menstrual blood, carried by retrograde menstruation, play a role in endometriosis development by differentiating outside the uterus. [32, 33] Contrary to initial expectations, our findings suggest that injecting these cells into the ovaries does not increase the risk of endometrioma and endometriosis for the patient. Recent research highlights endometriosis as a systemic disease influenced by various factors. [34] These include immune system dysregulation, disrupted signaling pathways, and hormonal imbalances. [35–37] Notably, MenSCs exhibit distinct characteristics between women with and without endometriosis, including differences in gene expression, morphology, cluster of differentiation (CD) markers, and immunomodulatory molecules. [38–40] This suggests that injecting MenSCs derived from women with endometriosis could potentially cause endometriosis. [41] Consequently, cautious utilization of MenSCs in patients with endometriosis is crucial, and further comprehensive studies are warranted.

Fibrosis is a potential complication and adverse effect of stem cell injection, with reports indicating liver, cardiac, and renal interstitial fibrosis due to the potential differentiation of stem cells into fibroblast cells. [42, 43] A study by Gu et al. reported that ovarian fibrosis, which can manifest as decreased ovarian function, is caused by the excessive proliferation of fibroblasts and their activity in producing transforming growth factor beta (TGF-β) and extracellular matrix (ECM). [44] In our study, we observed that a noteworthy portion of women with initially irregular menstrual cycles reported regular cycles at follow-up, suggesting a positive impact of the injection on menstrual regularity and ovarian function. However, the development of irregular cycles or menopause in some women with initially regular cycles highlights the natural progression of ovarian aging and the variability in individual responses. [45, 46] In our follow-up to identify any long-term complications, there were no reports of issues as a probable consequence of intra-ovarian MenSCs injection, except for a case of an ovarian cyst during pregnancy, which resolved on its own. Studies indicate that ovarian cysts are common during pregnancy, and the majority of these cysts are benign and resolve spontaneously. [47–49]

Our findings suggest that MenSCs treatment does not carry the same increased risk of infant complications observed with other treatment methods. This underscores the potential safety of MenSCs therapy not only for the mothers but also for the infants born through this method.

A comprehensive study conducted in Sweden revealed that babies conceived through ART have a 45% increased risk of mortality within the first year of life, depending on the specific type of ART, when compared to naturally conceived infants. [50] Our study found that none of the babies born, whether through spontaneous pregnancy or IVF, died within the first year.

Additionally, research indicates that infants conceived through ART have a slightly elevated risk of nonchromosomal birth defects compared to naturally conceived babies. [51] Major congenital anomalies are generally recognized at birth, while minor ones might go unnoticed initially, with most significant congenital anomalies typically identified during the first year of life. [52] In our study, there were no reports of congenital anomalies, defects, or other problems.

Strengths and limitations

This study has several strengths that support the conclusion of the safety and long-term efficacy of intraovarian MenSCs injection. The number of participants who underwent the procedure, along with the extensive follow-up period, provided robust data to assess both short-term and long-term outcomes. All potential complications, based on the differentiation capabilities of MenSCs, were thoroughly considered and investigated.

Additionally, all babies conceived through this method were closely monitored to ensure there were no negative outcomes associated with the intervention for the babies.

However, this study also has some limitations. One significant limitation is the lack of long-term pregnancy outcome data for the control group from previous studies, which could have provided a more comprehensive comparison. Another limitation of this study was the inability to invite all participants to our center for direct, in-person evaluation of long-term complications. Many of the women were residing in various cities, and access to the center was limited. As a result, we relied on medical follow-up sessions conducted over the years through their local healthcare providers and supplemented this with self-reported telephone interviews. While this approach allowed us to maintain contact with participants and collect necessary data, it may not have been as precise or comprehensive as regular in-person assessments conducted at our center. Future studies would benefit from more consistent and standardized follow-up methods, such as in-person visits, to ensure a more accurate evaluation of long-term outcomes.

Conclusion

The use of MenSCs represents a safe and promising avenue for improving pregnancy outcomes in women with poor ovarian response. However robust evidence is needed to validate its efficacy and safety. Rigorous studies and clinical trials are essential to establish MenSC therapy's effectiveness. We encourage researchers to consider some suggestions including:

- *Cell Differentiation* Exploring MenSC differentiation into specific cell types (e.g., follicular structures or fibroblasts) before injection may enhance therapeutic outcomes.
- *Co-Administration of Factors* Co-administering cytokines or growth factors alongside MenSCs could optimize tissue repair.
- *Adjunct Therapies* Beyond intra-ovarian injection, adjunct therapies should be explored.
- *Personalized Approach* Tailoring therapy based on individual patient profiles may maximize success.

Abbreviations

POR	Poor ovarian response
MenSCs	Menstrual blood-derived stromal cells
IVF	In vitro fertilization
ORT	Ovarian reserve tests
AMH	Anti-Müllerian hormone
AFC	Antral follicular count
MSC	Mesenchymal stem cell
ART	Assisted reproductive technology
PID	Pelvic inflammatory disease
EP	Ectopic pregnancy
PRP	Platelet-rich plasma
CD	Cluster of differentiation
ECM	Extracellular matrix
TGF-β	Transforming growth factor beta
ECM	Extracellular matrix

Supplementary Information

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Additional file 1.

Additional file 2.

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Author contributions

SZ: Designed the study, supervised the project, and critically reviewed the manuscript for important intellectual content. HD: Contributed to the conception and design of the study, performed data collection, analysis, and interpretation, and drafted the manuscript. MGG: Provided clinical expertise, contributed to patient recruitment, and reviewed the manuscript. MT: Involved in statistical analysis and interpretation of the data, and helped in drafting the manuscript. SA: Contributed to the design of the study and supervised the project. SA: Involved in the interpretation of the data, and helped in drafting the manuscript. MFK: Assisted in the literature review, contributed to writing sections of the manuscript, and reviewed the final draft.

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Availability of data and materials

All of the data generated and analyzed during this study are included in the manuscript.

Declarations

Ethics approval and Consent to participate

The study was started after providing complete information to patients and obtaining signed written consent. This clinical study was conducted with the permission of the Ethics Committee for Biomedical Research of the Academic Center for Education, Culture, and Research (ACECR, Tehran, Iran) (IR.ACECR.REC.1397.002, 2018–05-06 and IR.ACECR.REC.1399.002, 2020–05-31) under the title "Evaluation of the safety and feasibility of intra-ovarian injection of menstrual blood stem cells in women with poor ovarian responders (POR)". All procedures observed were under the Declaration of Helsinki, Good Clinical Practice (GCP), and GMP guidelines. Furthermore, this study was registered with the Iranian Clinical Trials Registry (IRCT20180619040147N2) and ClinicalTrials.gov (NCT05703308). The cell manufacturing was performed by STERCO (Tehran, Iran) in a GMP clean room authorized by Iran Food and Drug Administration authorities.

Consent for publication

Not relevant.

Competing of interests

The authors declare that they have no competing interests.

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