Research Article

AUTOLOGOUS ADIPOSE-DERIVED STEM CELL THERAPY FOR OVARIAN AND ENDOMETRIAL REGENERATION IN INFERTILE PATIENTS: A SINGLE-CENTER PILOT STUDY

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ABSTRACT

Background: Diminished ovarian reserve (DOR) and refractory thin endometrium present major therapeutic challenges in assisted reproductive technology (ART). Conventional treatments frequently yield suboptimal outcomes, prompting growing interest in regenerative strategies such as autologous adipose-derived stem cell (ADSC) transplantation. This study aimed to evaluate the clinical efficacy and safety of autologous ADSC transplantation for ovarian function and endometrial regeneration in infertile women with DOR or refractory endometrium undergoing ART.

Methods: In this retrospective, single-center pilot study conducted between July 2023 and January 2026 at a tertiary reproductive center in Tbilisi, Georgia, 25 infertile women were evaluated. Twenty patients with DOR who met the Bologna criteria received transvaginal ultrasound-guided intraovarian ADSC injection, and 5 patients with refractory thin endometrium (<7 mm) received intrauterine catheter-guided delivery. Patients with elevated malignancy markers (CA-125, HE4, or abnormal ROMA index) were excluded. Interventions involved minimally invasive lipoaspiration followed by enzymatic isolation of stromal vascular fraction (SVF) containing ADSCs. Primary outcomes included changes in antral follicle count (AFC), follicular development, and endometrial thickness (EMT). Secondary outcomes included restoration of trilaminar morphology, clinical pregnancy rates, and adverse events.

Results: The mean (SD) age was 40.0 (5.1) years in the ovarian cohort and 42.8 (5.4) years in the endometrial cohort. Following intraovarian ADSC transplantation, mean (SD) AFC increased significantly from 3.0 (2.6) to 3.9 (2.7) ($P < 0.01$), and mean (SD) dominant follicle count improved from 0.4 (0.6) to 1.6 (0.8) ($P < 0.01$). In the endometrial cohort, mean (SD) EMT increased from 6.1 (1.3) mm to 7.5 (2.2) mm ($P = 0.62$), with trilaminar morphology restored in 3 of 5 patients (60%). One clinical pregnancy was achieved in the endometrial cohort, and one ongoing pregnancy was documented in the ovarian cohort. No major procedural complications or serious adverse events occurred.

Conclusions: Autologous ADSC transplantation was associated with improved ovarian activity and enhanced endometrial development in selected infertile women with DOR or refractory thin

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endometrium. While these preliminary findings suggest ADSC therapy represents a promising adjunctive regenerative strategy in reproductive medicine, larger prospective randomized controlled studies are required to establish efficacy, long-term safety, and reproductive outcomes.

Keywords: adipose-derived stem cells; assisted reproductive technology; diminished ovarian reserve; infertility; in vitro fertilization (IVF); regenerative medicine; thin endometrium.

Introduction

Infertility affects approximately 10% to 15% of reproductive-aged couples worldwide and represents a major public health concern with substantial medical, psychological, and socioeconomic consequences.[1] Despite significant advances in assisted reproductive technology (ART), diminished ovarian reserve (DOR) and refractory thin endometrium remain among the most challenging conditions encountered in reproductive medicine because both are associated with poor ovarian response, implantation failure, and reduced live birth rates.[2,3]

DOR is characterized by reduced quantity and quality of the oocyte pool, resulting in a poor response to controlled ovarian stimulation (COS). Although ovarian reserve decreases physiologically with age, DOR may also occur secondary to genetic abnormalities, previous ovarian surgery, chemotherapy, autoimmune disorders, or idiopathic causes. Women with DOR typically demonstrate reduced serum anti-Mullerian hormone (AMH) concentrations, decreased antral follicle count (AFC), and poor ovarian response during in vitro fertilization (IVF), ultimately resulting in lower pregnancy rates.[2,4] Current therapeutic strategies, including individualized ovarian stimulation protocols, androgen supplementation, dehydroepiandrosterone (DHEA), coenzyme Q10, and platelet-rich plasma (PRP), have shown inconsistent efficacy, and no regenerative treatment has been universally adopted.[5]

Similarly, refractory thin endometrium remains an important cause of implantation failure in women undergoing ART. Although implantation depends on multiple factors, an endometrial thickness of less than 7 mm has consistently been associated with reduced implantation and pregnancy rates.[3] Conventional therapies, including prolonged estrogen administration, vasoactive agents (e.g., sildenafil, pentoxifylline), granulocyte colony-stimulating factor (G-CSF), and intrauterine PRP, may improve endometrial development in selected patients; however, a subset of women remain resistant to these treatments and continue to experience repeated implantation failure.[6]

Regenerative medicine has emerged as a promising therapeutic strategy for reproductive disorders. Among mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs) have attracted considerable interest because of their abundance, ease of harvest, high proliferative capacity, and potent paracrine activity.[7,8] Rather than directly replacing damaged tissue, ADSCs exert their regenerative effects primarily through secretion of cytokines, growth factors (including vascular endothelial growth factor [VEGF], transforming growth factor-beta [TGF-β], insulin-like growth factor [IGF]), and extracellular vesicles.[8,9] These signaling molecules stimulate angiogenesis, modulate inflammation, reduce apoptosis, and recruit local progenitor cells to regenerate damaged stromal networks.[9] Experimental studies have demonstrated that ADSCs may enhance ovarian vascularization, activate dormant follicles, improve granulosa cell survival, and promote endometrial regeneration by facilitating stromal remodeling and neovascularization.[10-12]

Early clinical investigations have reported encouraging improvements in ovarian reserve markers, follicular development, endometrial thickness, and pregnancy outcomes following stem-

cell-based therapies in women with DOR, premature ovarian insufficiency, and severe endometrial damage.[10,13-20] However, current evidence remains limited by small sample sizes, heterogeneous patient populations, variable stem cell isolation protocols, and lack of adequately powered randomized controlled trials. Consequently, the efficacy, safety, optimal route of administration, and long-term reproductive outcomes of ADSC therapy have not yet been established.

This single-center retrospective pilot study aimed to evaluate the clinical outcomes of autologous ADSC transplantation in women with diminished ovarian reserve or refractory thin endometrium undergoing ART. We hypothesized that autologous ADSC therapy would be associated with improvements in ovarian function, follicular development, and endometrial regeneration while demonstrating an acceptable short-term safety profile.

Methods

Study Design and Patient Population

This retrospective, observational pilot study evaluated consecutive patients who underwent autologous ADSC transplantation at the Georgian-German Reproduction Center in Tbilisi, Georgia, between July 2023 and January 31, 2026. The study evaluated the clinical outcomes of autologous adipose-derived stem cell (ADSC) transplantation in women with diminished ovarian reserve (DOR) or refractory thin endometrium undergoing assisted reproductive treatment.

The study protocol adhered to the ethical principles of the Declaration of Helsinki. Institutional review was obtained, and all patients provided written informed consent prior to undergoing liposuction and cell transplantation.

Participant Selection and Cohort Allocation

Twenty-five women with infertility who underwent autologous ADSC transplantation during the study period were included.

Patients were allocated into 2 treatment groups according to their clinical indication:

- **Ovarian cohort (n = 20):** Women with DOR who underwent ultrasound-guided bilateral intraovarian ADSC transplantation.
- **Endometrial cohort (n = 5):** Women with refractory thin endometrium who underwent ultrasound-guided intrauterine ADSC catheterization.

Only consecutive patients meeting the predefined eligibility criteria during the study period were included in the analysis.

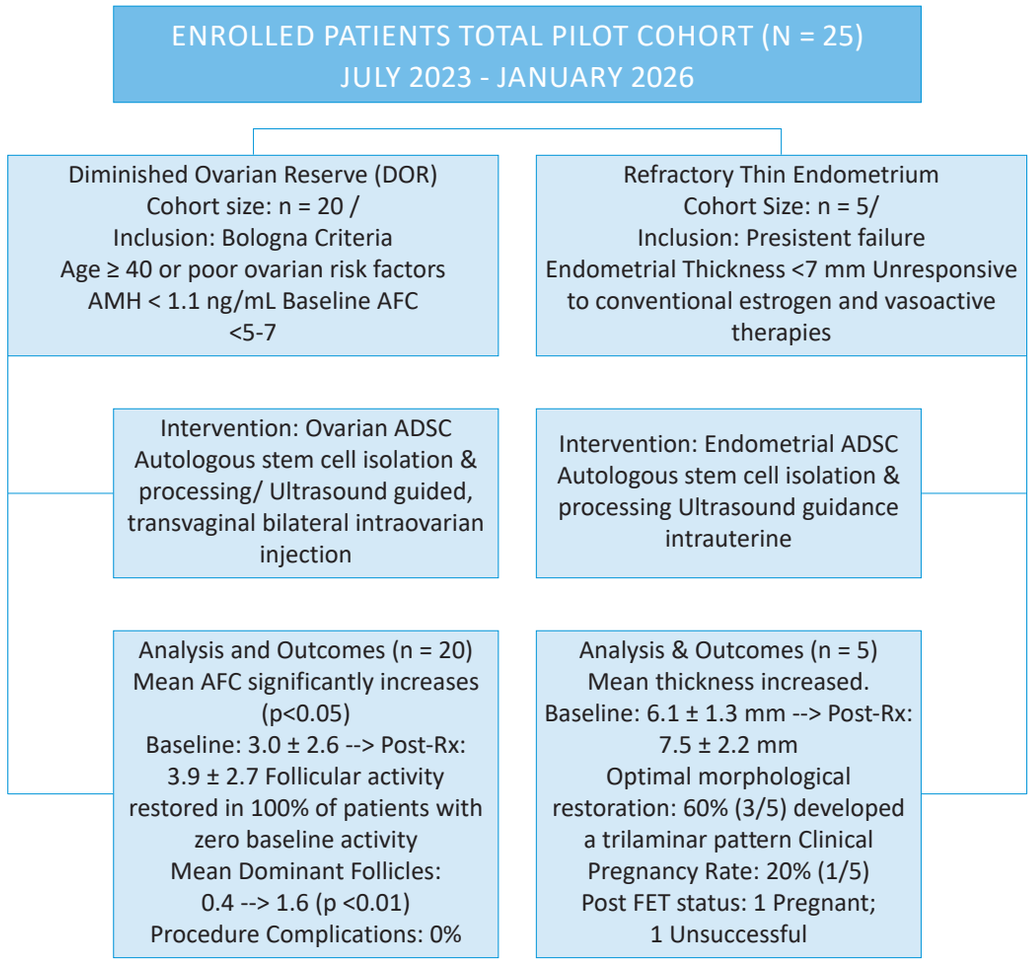

Figure 1. Patient selection and cohort allocation flowchart. A total of 25 patients met the strict selection criteria (Bologna criteria for the diminished ovarian reserve cohort; persistent endometrial thickness <7 mm for the endometrial cohort) and were analyzed for primary and secondary regenerative outcomes following autologous ADSC transplantation.

Inclusion and Exclusion Criteria

Inclusion Criteria (Ovarian Cohort): Must meet at least 2 Bologna criteria for poor ovarian response, including[2:]

- maternal age ≥ 40 years or risk factors for poor ovarian response;
- serum anti-Mullerian hormone concentration <1.1 ng/mL;
- antral follicle count (AFC) <5-7 follicles;
- previous poor ovarian response during controlled ovarian stimulation (≤ 3 oocytes retrieved with conventional stimulation).

Inclusion Criteria (Endometrial Cohort): Persistent EMT < 7 mm on the trigger or progesterone introduction in at least two previous consecutive cycles, despite high-dose oral/vaginal estrogen therapy and ancillary treatments.

Exclusion Criteria

Patients were excluded if any of the following conditions were present:

- elevated ovarian malignancy markers;
- active malignancy;
- untreated endocrine disorders;
- severe endometriosis (stage III-IV);

- uterine structural abnormalities, including submucosal leiomyomas or intrauterine adhesions;
- active pelvic infection;
- contraindication to transvaginal or intrauterine intervention.

Before ADSC transplantation, all patients underwent malignancy risk assessment using serum cancer antigen 125 (CA-125), human epididymis protein 4 (HE4), and the Risk of Ovarian Malignancy Algorithm (ROMA) index. Patients with abnormal findings suggestive of increased ovarian malignancy risk were excluded from treatment.

ADSC Harvesting and Processing

Autologous adipose tissue (50-100 mL) was obtained using minimally invasive syringe lipoaspiration from the abdominal wall or gluteal region under sterile operating-room conditions.

To isolate the unmanipulated stromal vascular fraction (SVF) containing resident adipose-derived stem cells (ADSCs), the harvested lipoaspirate was processed using a standardized, one-step digestion protocol as follows:

- **Washing:** The raw lipoaspirate was washed repeatedly with sterile phosphate-buffered saline (PBS) to remove systemic blood contamination, tumescent fluid, and free lipids.
- **Enzymatic Digestion:** The washed adipose tissue was subjected to enzymatic digestion using sterile collagenase. The mixture was incubated at 37°C for approximately 30-45 minutes with gentle, continuous agitation to break down the extracellular matrix.
- **Separation & Centrifugation:** To neutralize the enzyme, a sterile culture medium or saline solution was added. The digested mixture was then centrifuged to separate the mature, buoyant adipocytes and oil layer from the cellular pellet.
- **Filtration:** The supernatant (containing mature fat cells and liquid) was discarded, and the remaining cellular pellets, representing the heterogeneous stromal vascular fraction (SVF), were resuspended in sterile saline. To ensure safety and remove any remaining tissue fragments, the suspension was passed through a 100-µm mesh filter.
- **Quality Control:** Cell viability and absolute cell count of the final SVF suspension were determined using an automated cell counter via the trypan blue exclusion assay prior to clinical administration. A sterility test aliquot was also processed.

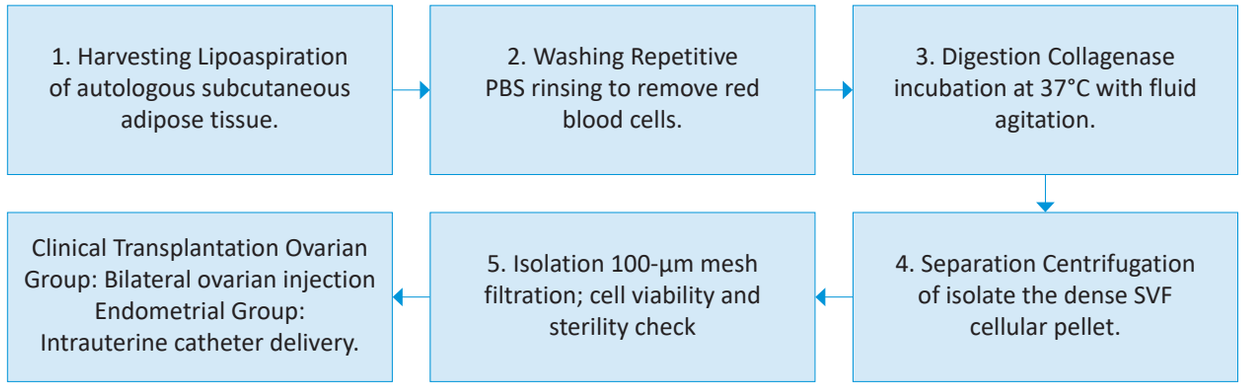

Figure 2. Schematic representation of autologous adipose-derived cell (ADSC) isolation and processing. The workflow illustrates the sequential steps from therapeutic lipoaspiration, mechanical and/or enzymatic processing via collagenase digestion, and gradient centrifugation to yield the cellular stromal vascular fraction (SVF) pellet, through definitive filtration quality control validation, to ultimate clinical autologous transplantation.

ADSC Administration Procedure

Ovarian ADSC Transplantation

Under conscious sedation, patients underwent transvaginal ultrasound-guided intraovarian injection of autologous ADSCs. A 17-gauge single-lumen aspiration needle was advanced into the ovarian stroma, and 1 to 2 mL of the prepared SVF suspension was slowly injected into each ovary. All procedures were performed by experienced reproductive medicine specialists using standard transvaginal ultrasound guidance.

Endometrial ADSC Administration

During the mid-proliferative phase of a preparation cycle, 1 to 2 mL of SVF suspension was gently instilled into the uterine cavity using a standard soft embryo transfer catheter under abdominal ultrasound guidance. Patients remained supine for 30 minutes following the procedure.

Outcome Measures

Primary Outcomes

Primary outcome measures included:

- changes in AFC;
- follicular development following ovarian stimulation;
- change in endometrial thickness.

Secondary Outcomes

Secondary outcome measures included:

- restoration of trilaminar endometrial morphology;
- clinical pregnancy following embryo transfer;
- procedure-related complications and adverse events.

Safety Assessment

Patients were monitored clinically following ADSC transplantation for procedure-related complications, including infection, bleeding, ovarian hyperstimulation syndrome, pelvic pain requiring hospitalization, and other adverse events.

No serious adverse events were observed during the study period.

Statistical Analysis

Continuous variables are presented as mean (SD) or median (IQR) based on normality. Pre- and post-treatment comparisons were performed using the paired t test for normally distributed variables and the Wilcoxon signed-rank test for nonnormally distributed variables. Categorical variables were compared using the Fisher exact test where appropriate. Two-sided P values < 0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 25 infertile women underwent autologous ADSC transplantation during the study period and were included in the final analysis. Twenty patients received intraovarian ADSC transplantation for diminished ovarian reserve, and 5 patients underwent intrauterine ADSC administration for refractory thin endometrium. No patients were excluded after treatment.

Baseline demographic and clinical characteristics are summarized in Table 1. The mean (SD) age of the patients in the ovarian cohort was 40.0 (5.1) years (range, 32-47 years), whereas the mean (SD) age in the endometrial cohort was 42.8 (5.4) years (range, 40-52 years). The ovarian cohort demonstrated a mean baseline AMH concentration of 0.21 (0.27) ng/mL and a mean baseline AFC of 3.0 (2.6) follicles. Patients in the endometrial cohort had a mean baseline endometrial thickness of 6.1 (1.3) mm and had experienced multiple previous unsuccessful ART cycles despite conventional treatment.

Ovarian Response Outcomes

Following intraovarian ADSC transplantation, patients showed significant improvements in ovarian reserve parameters and ovarian response during subsequent IVF cycles. The mean (SD) AFC rose from 3.0 (2.6) at baseline to 3.9 (2.7) post-treatment ($P < 0.01$). Furthermore, the mean (SD) number of dominant follicles developed during subsequent controlled ovarian stimulation increased from 0.4 (0.6) to 1.6 (0.8) ($P < 0.01$).

Notably, one patient with complete bilateral absence of detectable follicles before treatment developed multiple follicles during subsequent ovarian stimulation following ADSC transplantation. Similar improvements in follicular recruitment were observed in additional poor responders.

The mean AFC increased following treatment, and the mean number of dominant follicles also increased compared with baseline. These changes were accompanied by improved ovarian responsiveness during controlled ovarian stimulation. One ongoing clinical pregnancy was achieved in the ovarian treatment cohort. Detailed ovarian outcomes are presented in Table 2.

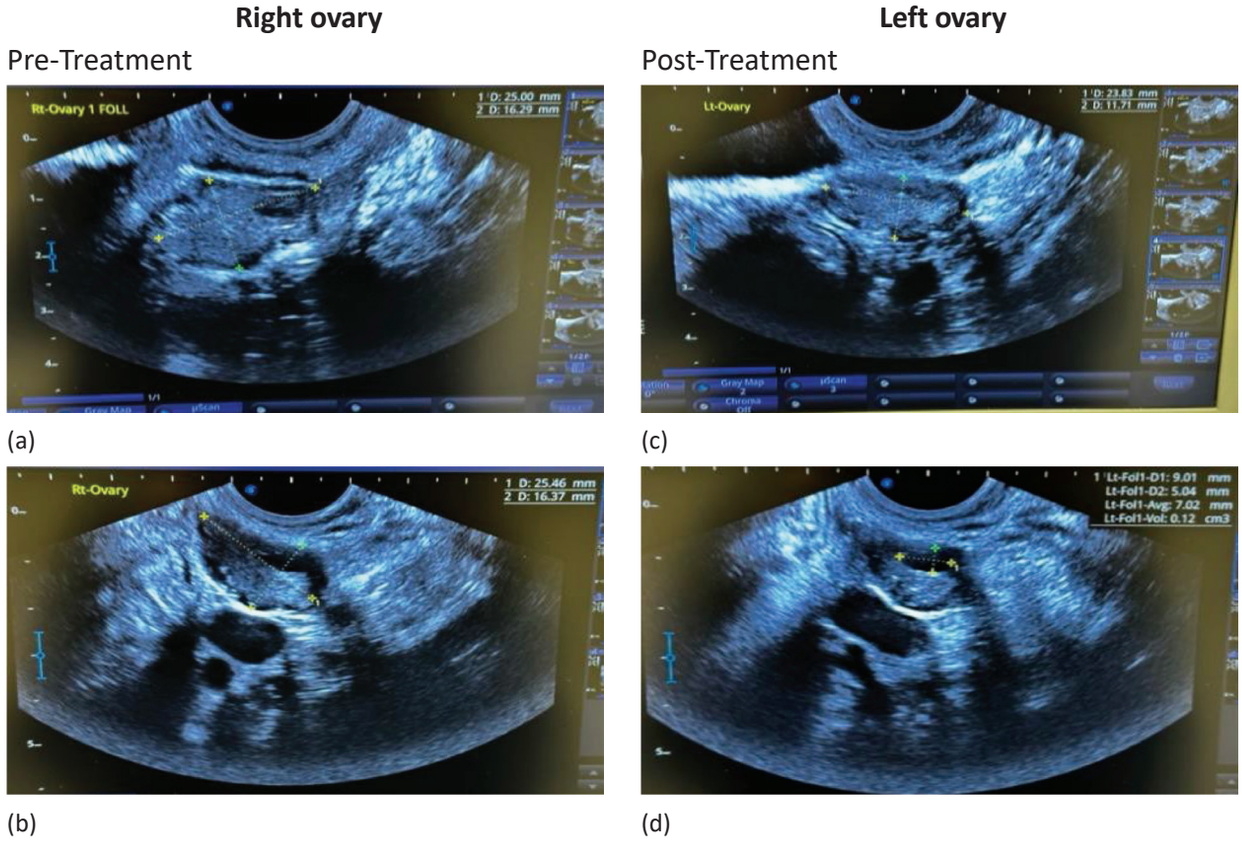

Figure 3. Transvaginal ultrasound monitoring of bilateral ovarian architecture pre- and post-autologous ADSC transplantation. (a) Baseline pre-treatment scan of the right ovary showing reduced follicular activity with a single small, restricted antral follicle. (b) Post-treatment evaluation of the right ovary showing persistence of the follicle with increased follicular size.

and maturation. (c) Baseline pre-treatment scan of the left ovary confirming absence of visible follicles with an absolute absence (0) of visible antral follicles. (d) Post-treatment evaluation of the left ovary documenting improved ovarian morphology with the appearance of a new antral follicle.

Endometrial Outcomes

Intrauterine ADSC therapy resulted in a mean (SD) EMT increase from 6.1 (1.3) mm before treatment to 7.5 (2.2) mm after treatment. Although this represented a clinically meaningful change that allowed embryo transfer to proceed, the increase did not reach statistical significance in this pilot sample (P = 0.62).

Crucially, a favorable trilaminar pattern was restored in 3 of the 5 patients (60%), who previously lacked it. Following frozen embryo transfer (FET), one patient achieved a confirmed clinical pregnancy. One patient had a negative pregnancy test, and the remaining three patients were awaiting FET at the time of this analysis. Detailed endometrial outcomes are summarized in Table 3.

Table 3. Endometrial Outcomes Following ADSC Therapy.

Parameter	Pre-Treatment	Post-Treatment	p-value
Mean (SD) endometrial thickness, mm	6.1 (1.3)	7.5 (2.2)	0.62
Trilaminar Pattern Present, No. (%)	0/5 (0)	3/5 (60.0)	0.08
Clinical Pregnancies, No.	0	1	-

Safety and Adverse Events

No serious adverse events were reported following autologous ADSC transplantation. Specifically, no cases of pelvic infection, clinically significant bleeding, ovarian hyperstimulation syndrome (OHSS), or procedure-related complications were observed during the study period. Furthermore, no patients required hospital admission because of treatment-related adverse events. Safety outcomes are summarized in Table 4.

Table 4. Adverse Events and Safety Outcomes.

Complications	Frequency
Infection	0
Bleeding	0
Ovarian Hyperstimulation	0
Procedure-related complications	0

Discussion

This pilot study demonstrated that autologous ADSC transplantation is associated with improved ovarian activity and enhanced endometrial development in patients with severe DOR or refractory thin endometrium.[10,13,14] The findings show a significant increase in AFC and dominant follicle recruitment, alongside improvements in late proliferative EMT and endometrial trilaminar morphology.

The therapeutic efficacy of ADSCs is likely mediated by their strong secretory profile rather than direct cellular differentiation.[8,9] ADSCs release high concentrations of key cytokines and growth factors, including VEGF, TGF-β, basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF).[8,9] In the ovary, these paracrine mediators promote angiogenesis, reduce stromal apoptosis, and may rescue dormant primordial follicles.[10,11] In the endometrium, these factors facilitate cellular proliferation, downregulate inflammatory pathways, and stimulate tissue remodeling, thereby resolving chronic fibrosis.[14,19]

Our clinical findings align with early animal and human studies. Herraiz et al.[10] demonstrated that mobilizing and transplanting bone marrow-derived stem cells could improve ovarian function in poor responders. Similarly, clinical trials by Tan et al.[14] and other groups[16,20] demonstrated that mesenchymal stem cell transplantation could repair damaged endometria and support successful clinical pregnancies. Our work extends these observations by utilizing ADSCs, which offer a more accessible cell source while maintaining strong therapeutic safety.

A key limitation of this study is its retrospective, noncontrolled design. Additionally, while the endometrial cohort showed a clinically meaningful increase in mean EMT from 6.1 mm to 7.5 mm, this did not reach statistical significance (P = 0.62) due to the small sample size (n = 5). Larger, prospective randomized controlled trials are required to confirm these findings, evaluate long-term live birth rates, and establish standardized processing and administration guidelines.

Conclusion

Autologous ADSC therapy may improve ovarian function and enhance endometrial receptivity in selected infertile patients with diminished ovarian reserve or refractory thin endometrium. These preliminary findings support the potential role of regenerative medicine approaches in assisted reproduction. Larger prospective randomized studies are required to confirm efficacy and establish standardized treatment protocols.

Declarations

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Conflict of Interest: The authors declare no competing interests.

References:

1. World Health Organization. Infertility prevalence estimates, 1990-2021. World Health Organization; 2023.
2. Ferraretti AP, La Marca A, Fauser BCJM, et al; ESHRE Working Group on Poor Ovarian Response Definition. ESHRE consensus on the definition of poor ovarian response to ovarian stimulation: the Bologna criteria. Hum Reprod. 2011;26(7):1616-1624. doi:10.1093/humrep/der092.
3. Kasius A, Smit JG, Torrance HL, et al. Endometrial thickness and pregnancy rates in in vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update. 2014;20(4):530-541. doi:10.1093/humupd/dmu011
4. Broekmans FJ, Kwee J, Hendriks DJ, Mol BWJ, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update. 2006;12(6):685-718. doi:10.1093/humupd/dml034.

5. Chang EM, Han JE, Kim YS, Lyu SW, Lee WS, Yoon TK. Use of platelet-rich plasma in reproductive medicine. Clin Exp Reprod Med. 2021;48(3):208-217. doi:10.5653/cerm.2020.04302.
6. Wang Y, Tang Z, Teng X. Recent advances in therapeutic strategies for thin endometrium. Front Endocrinol (Lausanne). 2024;15:1269382.
7. Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng. 2001;7(2):211-228.
8. Gimble JM, Katz AJ, Bunnell BA. Adipose-derived stem cells for regenerative medicine. Circ Res. 2007;100(9):1249-1260.
9. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J Cell Biochem. 2006;98(5):1076-1084.
10. Herraiz S, Romeu M, Buigues A, et al. Autologous stem cell ovarian transplantation to increase reproductive potential in patients with poor ovarian response. Fertil Steril. 2018;110(3):496-505.
11. Ding L, Yan G, Wang B, et al. Transplantation of adipose-derived stem cells on collagen scaffold improves ovarian function in a premature ovarian insufficiency rat model. Stem Cell Res Ther. 2018;9(1):2.
12. Cakiroglu Y, Saltik A, Yuceturk A, et al. Effects of intraovarian injection of autologous platelet-rich plasma on ovarian reserve indicators and IVF outcomes. Aging (Albany NY). 2020;12(11):10211-10222..
13. Saad-Naguib MH, et al. Mesenchymal stem cell therapy for refractory thin endometrium: a systematic review. Front Endocrinol (Lausanne). 2024;14:1268990.
14. Tan J, Li P, Wang Q, et al. Autologous menstrual blood-derived stromal cells transplantation for severe Asherman's syndrome. Hum Reprod. 2016;31(12):2723-2729.
15. Singh N, Mohanty S, Seth T, Shankar M, Devi SG, Albert V. Autologous bone marrow-derived stem cell therapy for endometrial atrophy. J Hum Reprod Sci. 2014;7(2):93-98.
16. Chen K, Wang H, Zhao X, et al. Clinical application of mesenchymal stem cells in endometrial repair. Reprod Sci. 2024;31(6):1662-1673.
17. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev. 2004;25(4):581-611. doi:10.1210/er.2003-0027.
18. Gargett CE, Schwab KE, Deane JA. Endometrial stem/progenitor cells: the first 12 years. Hum Reprod Update. 2016;22(2):137-163. doi:10.1093/humupd/dmv051.
19. Li T, Chan RWS, Li RHW, Ng EHY, Zhang S, Yeung WSB. Endometrial mesenchymal stromal/stem cells improve regeneration of injured endometrium in mice. Biol Res. 2024;57(1):6. doi:10.1186/s40659-024-00484-3.
20. Huang QY, Zheng HD, Shi QY, Xu JH. Validity of stem cell-loaded scaffolds to facilitate endometrial regeneration and restore fertility: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2024;15:1397783. doi:10.3389/fendo.2024.1397783.