2026 대한 생식면역학회 춘계학술대회

Endometrial Regeneration in Clinical Practice:

Revisiting Stem Cell Therapy

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Contents

The Unresolved Problem: Endometrial Injury & Infertility

2.4%

Prevalence of thin endometrium in IVF

(Thin Endometrium: EMT ≤7 mm)

45.5%

Prevalence of Asherman's syndrome in infertile women

(up to 45.5%)

66%

Intrauterine re-adhesion rate after adhesiolysis

(recurrence risk)

In 22 studies
Systematic review & meta-analysis
260 / 10724 = 2.4%

EMT ≤7 mm
- *Lower ongoing pregnancy rate, live birth rate, clinical pregnancy rate*

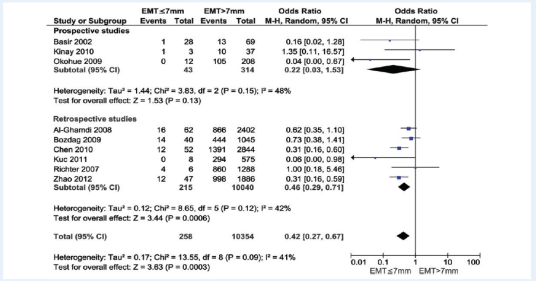
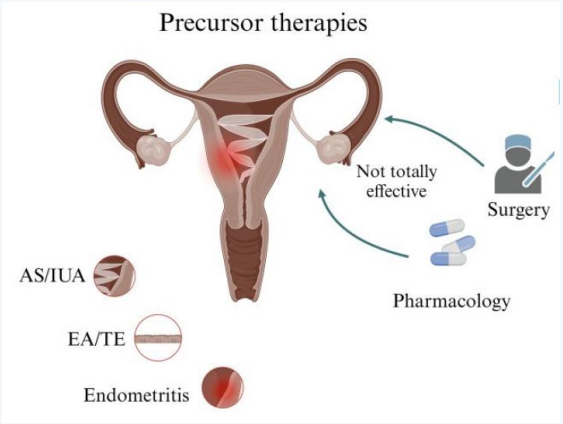


Figure 6 Forest plot of clinical pregnancy for women with EMT ≤ 7 mm and women with EMT > 7 mm. The probability of clinical pregnancy is significantly lower for women with EMT ≤ 7 mm. The I^2 statistic was 41%, indicating that study heterogeneity was low.



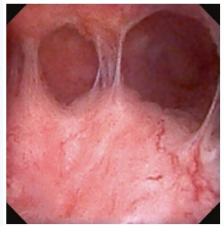


Fig. 5.3 Minimal adhesions after dilation and curettage for endometrial hyperplasia, followed by Megace treatment

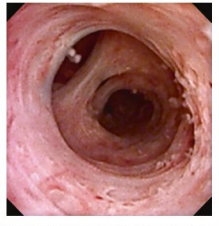


Fig. 5.4 Moderate adhesions after dilation and curettage for first-trimester miscarriage

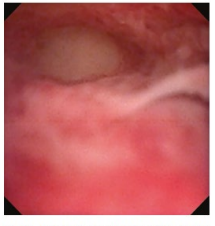


Fig. 5.5 Severe adhesions, with almost complete intracavitary obliteration after dilation and curettage to remove a polyp (rather than directed visualization and resection). Central and fundal location of the hysteroscope was confirmed with concurrent sonography

Ref: Liu K et al. Hum Reprod 2018; Gharibeh N et al. Stem Cell Res Ther 2022; Deans R et al. Hum Reprod 2018; Kasius et al., Hum Reprod 2014, Benor et al. JARG 2020

The Unresolved Problem: Endometrial Injury & Infertility

Pathophysiology of Endometrial Damage

- Injury to the endometrial basalis → stem cell depletion → fibrosis & failed regeneration → implantation failure
- Current treatments (hysteroscopic adhesiolysis + estrogen) fail to adequately restore regenerative capacity
- Analysis of > 40,000 IVF cycles confirms significantly reduced implantation & pregnancy rates with **EMT <7 mm**
- Stem cell-based endometrial regeneration: emerging as a new therapeutic paradigm

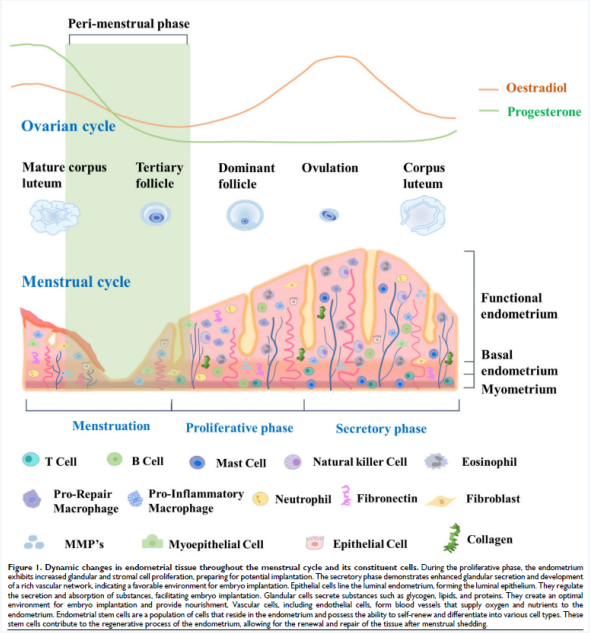


Figure 1. Dynamic changes in endometrial tissue throughout the menstrual cycle and its constituent cells. During the proliferative phase, the endometrium exhibits increased glandular and stromal cell proliferation, preparing for potential implantation. The secretory phase demonstrates enhanced glandular secretion and development of a rich vascular network, indicating a favorable environment for embryo implantation. Epithelial cells line the luminal endometrium, forming the luminal epithelium. They regulate the secretion and absorption of substances, facilitating embryo implantation. Glandular cells secrete substances such as glycogen, lipids, and proteins. They create an optimal environment for embryo implantation and provide nourishment. Vascular cells, including endothelial cells, form blood vessels that supply oxygen and nutrients to the endometrium. Endometrial stem cells are a population of cells that reside in the endometrium and possess the ability to self-renew and differentiate into various cell types. These stem cells contribute to the regenerative process of the endometrium, allowing for the renewal and repair of the tissue after menstrual shedding.

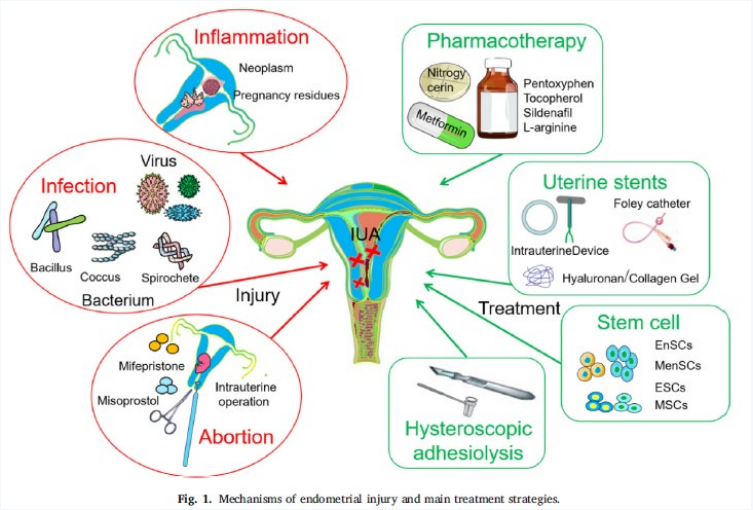


Fig. 1. Mechanisms of endometrial injury and main treatment strategies.

Ref: Cen et al. Materials Today Bio, 2022; Hong. Int. J. Biol. Sci. 2024

Types & Characteristics of Endometrial Stem Cells

Epithelial Stem/ Progenitor Cells (eSPC)

Markers: LGR5, SSEA-1, SOX9, EpCAM

- Replenish functionalis epithelium

Stromal Stem Cells ($CD34^+KLF4^+$)

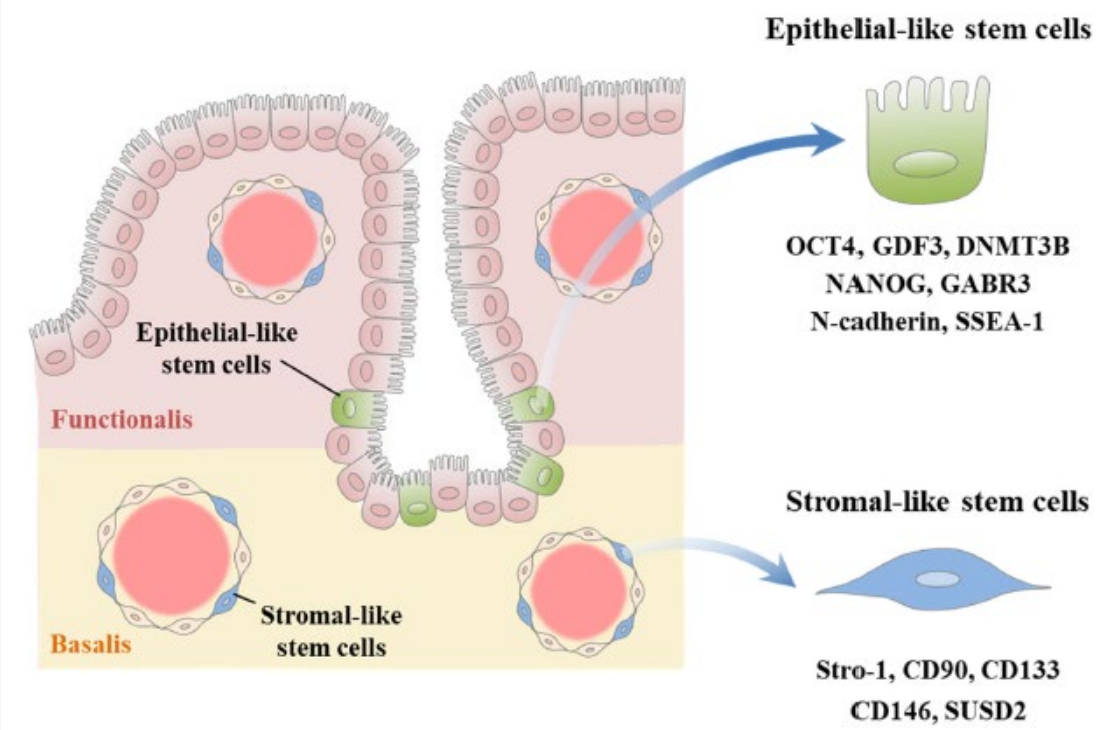
Markers: $SM22\alpha^+$, CD34, KLF4

- Differentiate into decidualized stroma

Endometrial MSC (eMSC / EnSC)

Markers: CD146, PDGFR-β, W5C5

- Multilineage differentiation, immunomodulation



Ref: Hong IS. Int J Biol Sci 2024; Rodríguez-Eguren A et al. Hum Reprod Update 2024

Types & Characteristics of Endometrial Stem Cells

	Source	Markers	Mechanisms in endometrial repair
Bone Marrow MSC (BM-MSC)	Bone marrow	CD90, CD73, CD105, CD29	Ectopic engraftment & paracrine effects
Adipose-Derived MSC (ADMSC / SVF)	Adipose tissues	CD44, CD73, CD90	Angiogenesis promotion, anti-fibrotic
Menstrual Blood MSC (MenSC)	Menstrual blood	CD90, CD44, CD73, CD105	Angiogenesis, anti-fibrotic, Non-invasive, periodic harvest possible
Umbilical Cord MSCs (UC-MSC)	Endometrium	CD90, CD105, CD59, CD146, OCT4, SOX4	Proliferation, anti-fibrosis, angiogenesis
Amniotic MSCs	Amniotic membranes	CD90, CD105, FAP, FSP	Immunomodulation, anti-fibrosis

Ref: Hong IS. Int J Biol Sci 2024; Rodríguez-Eguren A et al. Hum Reprod Update 2024

How MSCs Regenerate the Endometrium

Mechanisms of MSC-Mediated Endometrial Regeneration

① Direct Differentiation

MSCs differentiate into endometrial epithelial/stromal cells, replenishing tissue defects

② Paracrine Signaling

Secrete VEGF, EGF, HGF, IGF-1
→ promote angiogenesis & cell proliferation

③ Immunomodulation

Treg ↑, Th1/Th17 ↓, suppress NK cell activity
→ improve implantation microenvironment

④ Anti-Fibrotic Effect

Inhibit TGF-β/Smad pathway
→ reduce fibroblast activation & matrix remodeling

⑤ Exosome/EV Secretion

miRNA carriers polarize M2 macrophages, activate PI3K/Akt pathway

⑥ Homing Capacity

Migrate to injury site via SDF-1/CXCR4 axis with self-renewal capability

Ref: Marečková et al. Front Bioeng Biotechnol 2025; Hong IS. Int J Biol Sci 2024; Gharibeh N et al. Stem Cell Res Ther 2022

Comparison of Stem Cell Sources

Accessibility, Immunogenicity & Evidence Level

Source	Harvesting Method	Accessibility	Immunogenicity	Evidence Level
BM-MSC (Bone Marrow)	Iliac crest aspiration (invasive)	★★★	Low (allogeneic possible)	High — multiple trials
ADMSC / SVF (Adipose)	Liposuction (minimally invasive)	★★★★	Low	Moderate–High
UC-MSC (Umbilical Cord)	Collected at delivery	★★★★★	Very low (allogeneic)	Moderate–High
MenSC (Menstrual Blood)	Menstrual blood (non-invasive)	★★★★★	Low (autologous)	Early clinical
eMSC (Endometrial)	Endometrial biopsy (invasive)	★★	Low (autologous)	Preclinical / Phase I

★ = Accessibility (more stars = easier access)

Ref: Fan Y et al. Front Bioeng Biotechnol 2025; Yamauchi N et al. Clin Exp Reprod Med 2025

SECTION 03

Current Clinical Evidence

MSC-Based Endometrial Regeneration

Systematic Review & Meta-Analysis Summary (2025–2026)

Key Meta-Analysis Findings

Studies included: *Adamyan et al. EJOG 2026*	18 clinical studies, 323 patients
Endometrial thickness:	Significantly increased in **all studies**
Clinical pregnancy rate:	Improved vs. control
Live birth rate:	Improved; miscarriage risk reduced
EV meta-analysis (animal): *Sun Y et al. Reprod Biol Endocrinol 2025*	26 studies, 899 animals
Endometrial gland count:	SMD = 3.78 (95%CI: 2.62–4.93)
Endometrial thickness:	SMD = 2.65 (95%CI: 1.90–3.40)
Fibrosis reduction:	SMD = −3.25 (95%CI: −4.24 to −2.26)

Key Messages

- MSC therapy consistently increases endometrial thickness across diverse stem cell sources
- Trends toward improved pregnancy & live birth rates, reduced miscarriage risk
- No serious adverse events reported — favorable safety profile
- Evidence base still 'nascent' — 18 studies, -323 patients
- Pilot-scale studies dominate → large RCTs urgently needed

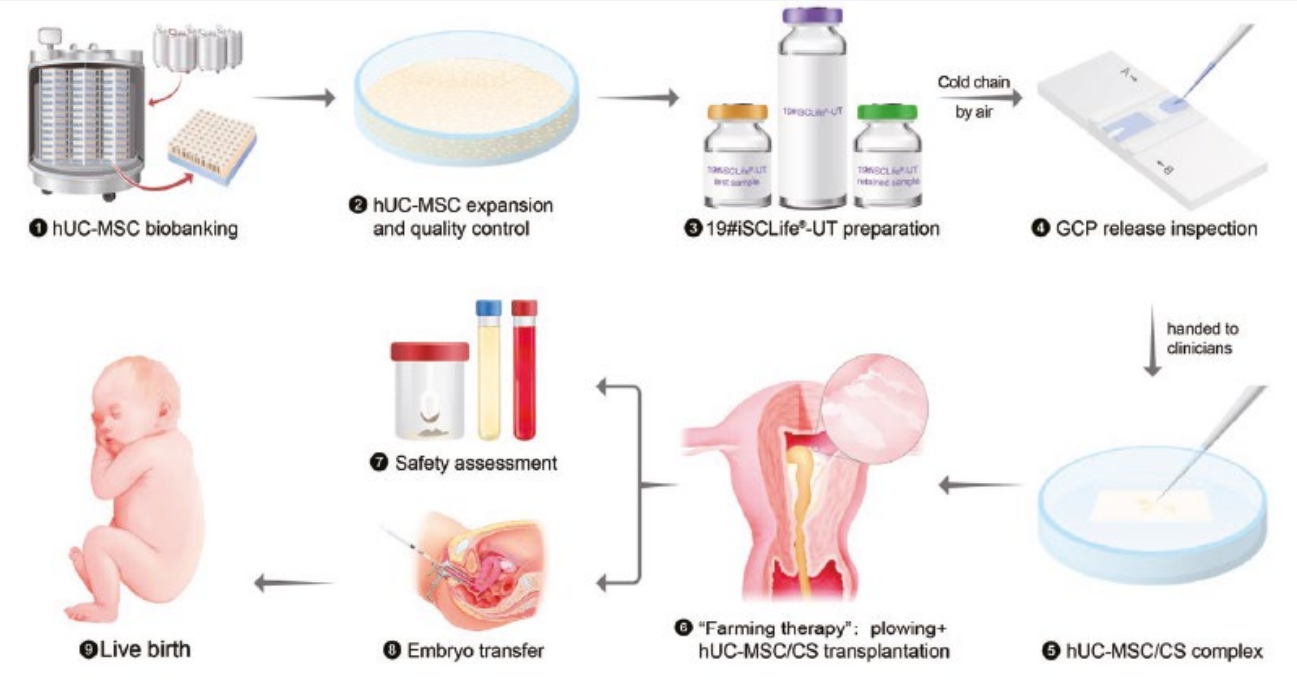
Key Clinical Studies

Hou Z et al. (2025) | Stem Cells Transl Med

Intervention: hUC-MSC-loaded collagen scaffold placed intrauterine

Outcome: Improved cumulative live-birth rate vs. saline/scaffold control

Double-blind RCT n=25
hUC-MSC group n=11
Control group n=13



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Control group n=13

Table 2. Primary, secondary, and safety outcomes.

Outcome	hUC-MSC/CS Group ($n = 11$)	Control Group ($n = 13$)	RR(95% CI)	*P*
Primary outcome				
Cumulative live birth-no.(%)	3 (27.3)	1 (7.7)	3.55 (0.43 to 29.42)	.30
Secondary outcomes				
Cumulative biochemical pregnancy-no.(%)	6 (54.5)	2 (15.4)	3.55 (0.89 to 14.15)	.08
Cumulative clinical pregnancy-no.(%)	5 (45.5)	1 (7.7)	5.91 (0.81 to 43.28)	.06
Implantation rate-no./total no.(%)	5/35 (14.3)	1/22 (4.5)	3.14 (0.39 to 25.15)	.47
Cumulative ongoing pregnancy-no.(%)	3 (27.3)	1 (7.7)	3.55 (0.43 to 29.42)	.30
Early spontaneous abortion-no./total no.(%)	2/5 (40.0)	0/1 (0.0)	NA	NA
Ectopic pregnancy-no./total no.(%)	0/5 (0.0)	0/1 (0.0)	NA	NA

Key Clinical Studies

Hernández-Melcho A et al. (2024) | Am J Transl Res

Intervention: Adipose-derived MSC (SVF) transmyometrial injection — Asherman's syndrome

Outcome: Pregnancy rate 47.6%, implantation rate 66.7%, 10 live births

Retrospective comparative study
n=41
Group 1, n=20
Group 2, n=21

Table 1. Characteristics of study participants

Category	Group 1	Group 2	*p*-value	95% CI
Hysteroscopic adhesiolysis	Yes	Yes	-	-
ADMSC treatment	No	Yes	-	-
Sample size (n)	20	21	-	-
Age (years)	37.9 ± 5.9	40.0 ± 4.7	0.2160	-1.277 to 5.477
BMI (kg/m²)	26.2 ± 3.2	24.8 ± 2.4	0.1135	-3.175 to 0.3520
Infertility duration (years)	4.6 ± 3.2	3.5 ± 3.2	0.2500	-3.152 to 0.8448
Previous IVF cycles with implantation failure (n)[a]	0.6 ± 0.8	0.8 ± 0.9	0.4494	-0.3451 to 0.7642
No. of patients with canceled ET	11	9	-	-
No. of patients with at least one failed cycle	9	12	-	-
AS classification at the time of enrollment				
Removed IUA at the time of ADMSC application	Not applicable	33.3% (7/21)		
Stage I, mild	55.0% (11/20)	42.9% (9/21)		
Stage II, moderate	30.0% (6/20)	14.3% (3/21)		
Stage III, severe	15.0% (3/20)	9.5% (2/21)		

Abbreviations: 95% CI: 95% confidence interval; ADMSC: adipose-derived mesenchymal stem cells; AS: Ash
BMI: Body-Mass Index; IVF: *in vitro* fertilization; ET: embryo transfer; IUA: intrauterine adhesions. Values are
(frequency) or average ± standard deviation. *P*-value was calculated using an unpaired *t*-test. [a]The mean of
with implantation failure is below one as for some patients with poor quality endometrium; their embryo tra
AS classification according to the American Fertility Society 1988 at the time of enrollment [17].

Table 3. Comparison of pregnancy outcomes between no-treatment control and ADMSC treatment

Category	Group 1	Group 2	*p*-value
Hysteroscopic adhesiolysis	Yes	Yes	-
ADMSC treatment	No	Yes	
No. of embryos transferred per cycle	2.5 ± 0.61	2.6 ± 0.77	0.4602[a]
Cycle implantation rate	55.0% (11/20)	66.7% (12/18)	0.7475[b]
Clinical pregnancy rate	65.0% (13/20)	57.1% (12/21)	0.7513[b]
Live birth rate	35.0% (7/20)	47.6% (10/21)	0.5303[b]

Abbreviations: ADMSC: adipose-derived mesenchymal stem cells. Values are percentage (frequency) or average ± standard deviation. [a]*p*-value was calculated using an independent *t*-test. [b]*p*-value was calculated using Fisher's exact test.

Key Clinical Studies

Ma H et al. (2020) | J Obstet Gynaecol Res

Intervention: Menstrual blood MSC intrauterine transplant

Outcome: Increased EMT and successful pregnancies in patients refractory to prior treatment

Clinical study
autologous MenSC transplant
n=12

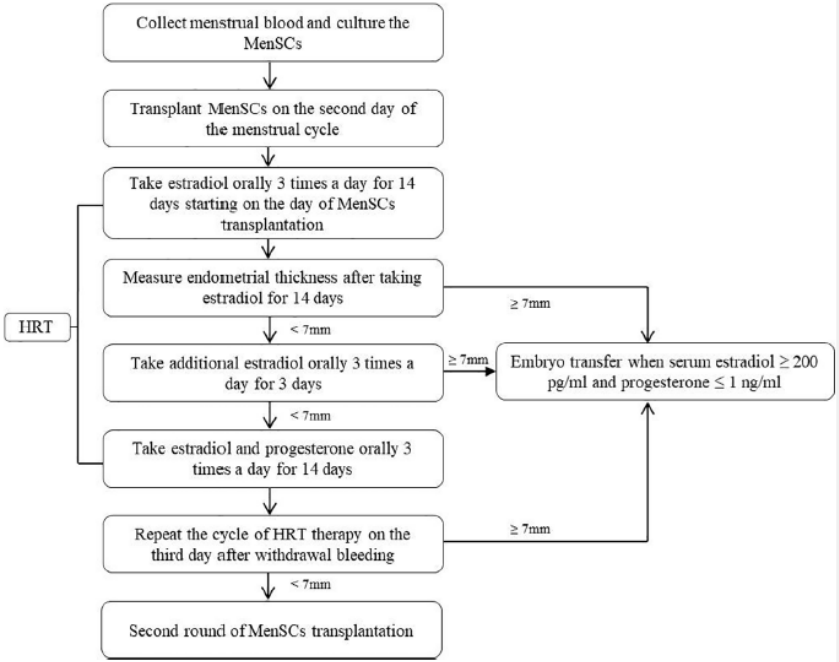


Table 2 Outcomes of patients with IUA

Patient	Menstrual duration (days) before and after MenSCs		Endometrial thickness (mm) before and after MenSCs		Pregnancy outcomes
1	1	5	3.3	7.0	No
2	2	5	3.5	7.5	Singleton
3	3	6	3.3	6.8	Twins
4	3	6	4.6	7.6	Singleton
5	2	5	5	7.2	No
6	2	4	4.0	6.8	No
7	2	5	3.5	7.5	No
8	3	6	4.7	9.0	Singleton
9	3	5	3.1	7.6	Singleton
10	2	5	4.1	7.3	BP (HCG107IU/L)
11	3	6	2.2	8	No
12	3	5	5	7.5	No
Average	2.4	5.3	3.9	7.5	—
SD	0.9	0.6	0.7	0.6	—
P	—	<0.001	—	<0.001	—
CP rate	—	—	—	—	41.7%

IUA, intrauterine adhesion; MenSCs, menstrual blood stem cells; BP, biochemistry pregnancy; HCG, human chorionic gonadotropin; CP, clinical pregnancy; *SD*, standard deviation.

Key Clinical Studies

Scaffold + MSC Meta-analysis | Front Endocrinol 2024

Intervention: Collagen / HA scaffold + BM or UC-MSC combination

Outcome: Improved gland count, angiogenesis, and implantation rate vs. scaffold alone

Systematic review & meta-analysis
N= 13 animal studies

	Std. Mean difference	95% CI	p-value
Endometrial thickness	+1.99	1.54 – 2.44	$p < 0.00001$ $I^2 = 16\%$
Endometrial glands	+1.93	1.45 – 2.41	$p < 0.00001$ $I^2 = 0\%$
Fibrotic area	−2.50	−3.07 −1.93	$p < 0.00001$ $I^2 = 36\%$
Fertility (Embryos)	+3.34	1.58 – 5.09	$p = 0.0002$ $I^2 = 83\%$

Administration Routes & Delivery Strategies

Intrauterine Infusion

- ◆ Simple procedure, outpatient setting
- ◆ Low engraftment rate, cell survival issues

Evidence: Most widely used in clinical studies

Transmyometrial Injection

- ◆ Accurate delivery to target zone
- ◆ Invasive, requires specialist technique

Evidence: Used in ADMSC/SVF clinical studies

Scaffold-Based Delivery

- ◆ Enhanced cell engraftment & survival; 3D support
- ◆ Complex manufacturing; GMP production challenging

Evidence: Collagen/HA scaffold RCT ongoing (Hou Z 2025)

Systemic IV Infusion

- ◆ Simple to administer
- ◆ Risk of off-target distribution; pulmonary embolism concern

Evidence: Superior in preclinical; limited clinical evidence

Ref: Fan Y et al. Front Bioeng Biotechnol 2025; Ferreira et al. EJOG 2026; PMC 2020 — stem cell therapy for Asherman

SECTION 04

Next-Generation Strategies

The Rise of Exosomes, Scaffolds & Cell-Free Therapy

Exosome & Extracellular Vesicle (EV) Therapy

Why EVs? (vs. Cell Therapy)

- ✓ No risk of tumorigenesis
- ✓ Low immunogenicity
- ✓ Cross biological barriers
- ✓ Long-term storage & standardizable
- ✓ GMP-compatible production
- ✓ Overcomes key limits of cell therapy

Key Mechanisms & Preclinical Evidence

M2 Macrophage Polarization

miRNA (e.g., miR-146a-5p) suppresses TRAF6 → anti-inflammatory shift

Anti-Fibrotic Effect

TGF-β1/Smad inhibition → reduced α-SMA and Col-1 expression

Pro-Angiogenic

Upregulates VEGF, activates PI3K/Akt signaling cascade

Endometrial Receptivity Restoration

Increases ER-α, PR, integrin-β3, LIF expression in rat IUA models

Meta-analysis (animal, 26 studies):
Gland count SMD=3.78, EMT SMD=2.65, Fibrosis SMD=–3.25
— all statistically significant

Ref: Xu Y et al. Reprod Biol Endocrinol 2025; Xin L et al. Acta Biomaterialia 2020; Zhao S et al. Reprod Sci 2020

Biomaterials & Scaffold-Based Delivery

Natural Polymer-Based

Collagen

UC-MSC loading → promotes implantation & angiogenesis

RCT: Hou Z et al. Stem Cells Transl Med 2025

Hyaluronic Acid (HA)

Auto-crosslinked HA gel → prevents re-adhesion + enhances MSC engraftment

CFDA-approved medical device (China)

GelMA (Gelatin Methacrylate)

3D-printable scaffold, supports cell proliferation

Preclinical stage

Silk Fibroin

ADMSC loading → reduced fibrosis, restored endometrial structure

Preclinical stage

Synthetic Polymer-Based

PCL Nanofibers (Electrospun)

Excellent mechanical properties; supports cell adhesion & proliferation

Composite systems in development

PLA / PLGA

Biodegradable; enables sustained drug release

Experimental stage

HA-CHO + Gel-ADH Hydrogel

Dynamic covalent crosslinking → injectable hydrogel system

Preclinical / early clinical

❖ Scaffold + stem cell combinations outperform cell injection alone — enhanced engraftment is the key mechanism

Ref: Fan Y et al. Front Bioeng Biotechnol 2025; Theranostics 2026; Front Endocrinol 2024

Menstrual Blood MSC (MenSC): A Promising Clinical Source

Non-invasive · Periodic harvest · Autologous → Ethical & immunological advantages

Clinical Study Outcomes

- 7 IUA patients — 5 achieved EMT 7–8 mm, 2 clinical pregnancies after MenSC transplant (Tan et al.)
- 12 refractory IUA patients — increased EMT, successful pregnancies reported (Ma et al.)
- Two autologous trials (n=19): MenSC isolation feasible; pregnancies achieved after intrauterine transplant
- No tumorigenesis or ectopic distribution at 6-month follow-up

Current Limitations

- Severe IUA → reduced menstrual volume → uncertain MenSC yield
- eMSC senescence observed in vivo in AS patients
- Bacterial/fungal contamination risk from menstrual blood — GMP culture challenging
- Predominantly small case series — no large RCTs yet

◆ MenSC-EVs (exosomes): Confirmed ovarian function restoration + endometrial cell proliferation & VEGF secretion (animal models) — evolving toward cell-free therapy

Ref: Ma H et al., J Obstet Gynaecol Res2020 ; Front Bioeng Biotechnol 2025 (MenSC-EVs); Front Endocrinol 2023

SECTION 05

Limitations & Future Directions

Regulatory, Safety & Standardization Challenges — Prerequisites for Clinical Adoption

Current Limitations & Challenges

Quality of Evidence

- Predominantly small pilot studies (most, n<50)
- Many studies lack control arms — placebo effect cannot be excluded
- Short follow-up periods — long-term safety unconfirmed

Lack of Standardization

- Inconsistent cell source, dose, timing & frequency across studies
- Many studies lack rigorous MSC quality & surface marker verification
- Heterogeneous outcome measures (clinical pregnancy vs. live birth)

Safety Concerns

- Risk of ectopic differentiation & tumorigenesis (no long-term data)
- Immune rejection risk with allogeneic cell products
- EVs: batch-to-batch variability; standardized GMP production difficult

Regulatory & Feasibility

- High cost & infrastructure required for GMP cell manufacturing
- Korea: complex approval process under Advanced Regenerative Medicine Act
- Insurance coverage & accessibility remain unresolved

Future Directions: Toward Clinical Translation

◆ Large-Scale Multicenter RCTs

Well-powered randomized controlled trials with standardized protocols are urgently needed

◆ EV Standardization

Establish manufacturing, characterization & dosing guidelines (MISEV criteria)

◆ AI + Organoid Integration

Endometrium-on-chip + AI analytics for personalized implantation prediction platforms

◆ Combination Therapy

Synergize MSC/EV with PRP, G-CSF, or estrogen for maximal regenerative effect

◆ Regulatory Framework

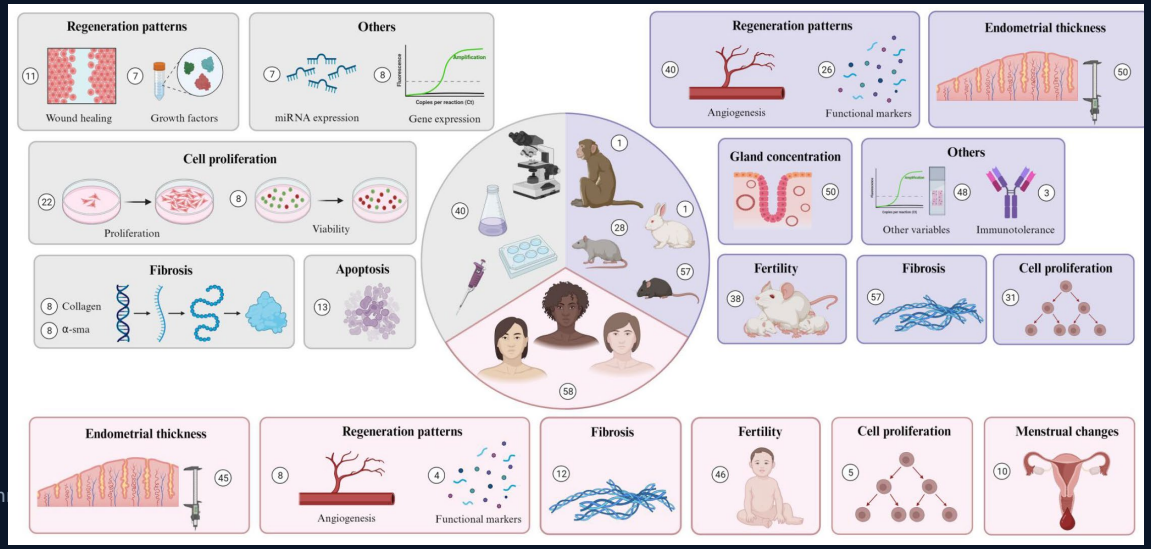
Clarify clinical approval pathways; establish GMP-certified cell banking infrastructure

◆ Korea Context: Low Birth Rate

Link with national fertility policy — expand regenerative medicine trials for IVF failure patients

Conclusions

- MSC-based endometrial regeneration - a promising approach
  - Reporting increased EMT and successful pregnancies in patients refractory to conventional therapy
- Multiple sources (UC-MSC, ADMSC, MenSC)
- Delivery modes (scaffold, injection) have confirmed safety at Phase I–II level
- EVs/exosomes represent the next-generation strategy
  - Strong preclinical meta-analytic evidence overcoming limitations of cell therapy
- Large-scale RCTs, standardization, and long-term safety data are prerequisite conditions for clinical adoption



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