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Application of adult stem cells in obstetrics and gynecology: A scoping review

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ABSTRACT

Background: Advancements in regenerative medicine have led to the applicability of stem cell technology in various diseases. Stem cells that have self-renewable abilities may differentiate into several cell types to provide therapeutic potential. Among different stem cells, adult stem cells are considered as the safest with remarkable potential for therapeutic application. In this review, we provide current available evidence regarding the application of adult stem cells in medicine, especially in the field of obstetrics and gynecology.
Objective: This scoping review aims to map and describe the current research on adult stem cell application in obstetrics and gynecology.
Methods: We performed a systematic search on PubMed, Google Scholar, and Cochrane Library in August 2024 to identify research articles involving adult stem cells in the field of obstetrics and gynecology. We used the Deduplicate website to filter articles based on keywords that met our inclusion and exclusion criteria. The results were presented based on recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.
Results: We found 42 articles that met the inclusion criteria. Some studies were clinical studies, whereas the majority were preclinical studies. We categorized the articles into clinical and preclinical studies to understand their applicability in human subjects.
Conclusions: Adult stem cell therapy is a candidate treatment for several pathologies in obstetrics and gynecology. The promising results of adult stem cell therapy, especially in degenerative gynecologic diseases, may lead to further application of the technology in the near future.

1. Introduction

1.1. Background

Stem cells are considered potential therapeutic modalities in regenerative medicine because of their ability to self-renew. These cells are categorized into 3 types, namely embryonic, adult, and induced pluripotent stem cells. Early embryonic cells have the totipotency to form both embryo and extraembryonic structures that contribute to the development of the entire human body. Four days after conception, embryonic stem cells are derived from the inner cell mass of a pre-implanted human embryo. The cells have significant pluripotency, allowing differentiation into all cell types. However, the application is limited due to ethical issues associated with human embryo derivation. Moreover, artificial generation of induced pluripotency from somatic cells (induced pluripotent stem cells) remains ineffective and leads to heterogeneous cell populations. Therefore, adult stem cells, which provide significant plasticity across various organs, become the primary focus of extensive studies [1].

Adult stem cells are a population of cells in various tissues that are capable of repairing corresponding organs. A certain number of adult stem cell populations in all organs represent their regenerative capacity. Therefore, adult stem cells are considered to maintain the equilibrium or homeostatic state of the organism. The ability to repair tissues has prompted scientists to develop novel therapies using adult stem cells. The first application of adult stem cell therapy started with the

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successful bone marrow transplantation for leukemia and several other immune disorders. The bone marrow is rich in adult stem cells, which are hematopoietic stem cells (HSCs) that have self-renewal and differentiation capabilities. Increasing evidence showed that HSCs can differentiate into various tissues other than blood cells under certain conditions because of their plasticity. On this basis, researchers considered developing adult stem cell technology to be used in regenerative medicine.

The adult stem cell population in other organs, including the skin, digestive system, liver, brain, and muscle, has the capability to replenish certain tissues. The plasticity characteristics of these cells enable them to be used therapeutically. Adult stem cell transplantation is capable of repairing injured tissue as these cells have the ability to migrate and develop into tissue components [1,2]. For example, neuronal adult stem cells may migrate to the brain to repair injured tissues. Moreover, the ability of adult stem cells to secrete certain growth factors may improve the regenerative capacity when transplanted. Tissue-engineered stem cells are another possibility of regenerative technology. Along with the possible therapeutic features of adult stem cells, some issues have been raised regarding their applicability. Well-grown adult stem cells in in vitro systems may not be successfully incorporated into living organisms because of several conditions. Therefore, in this study, we reviewed the applications of adult stem cells in medicine, especially in the field of obstetrics and gynecology.

Adult stem cells may be developed as part of fetal therapy in utero. In addition, the placenta, amniotic fluid, and umbilical cord are abundant in adult stem cells (i.e., mesenchymal stem cells [MSCs]). Thus, the preservation of umbilical cord blood or tissues and placental tissues after birth may be useful in the future. Cryopreservation services are already commercially available in many countries to anticipate serious conditions that require regenerative technology. In the field of gynecology, adult stem cells are expected to repair regenerative disorders, such as menopausal syndrome and pelvic organ prolapses. Primary ovarian failure, Asherman syndrome, chronic salpingitis, and ovarian failure are also other disorders that may be improved by the regenerative effect of adult stem cells. This review aims to understand the current application of adult stem cells in obstetrics and gynecology, as well as the possible harms that follow the treatment. Understanding the applicability may benefit patients with certain diseases in obstetrics and gynecology and lead to further research to improve the applications of regenerative medicine.

2. Methods

A scoping review was conducted to investigate the current application of adult stem cells in obstetrics and gynecology. Several electronic databases, including PubMed, Google Scholar, and the Cochrane Library, were utilized. This review aimed to map the current advances of certain issues and provide evidence-based explanations. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [3] were followed, to provide a standardized body of evidence, specifically in the application of adult stem cells in obstetrics and gynecology. To capture the latest advancement, only articles published between 2019 and 2024 were included. Eligible studies engaged participants who received adult stem cell treatment. The primary outcome assessed was the improvement in these conditions, while any harmful effects were mentioned as a secondary outcome. Additional inclusion criteria required articles to be peer-reviewed, published in English, and provide full-text access. Review articles and reports available only in abstract form were excluded. Table 1

Keywords were initially developed to address the main goal of the review, such as understanding the current applications of adult stem cells in obstetrics and gynecology. PubMed and Google Scholar were selected for comprehensive coverage of scholarly articles in both research and clinical trials. Furthermore, Cochrane Library, a well-known database for clinical trials, was included to enrich the sources in the review. More detailed specific keywords and searching strategies are provided in Table 2. The search strategy was developed to ensure maximum retrieval of relevant articles. Studies discovered with keywords were screened using the Deduplicate website (https://sr-accelerator.com/#/deduplicator). This free and web-based tool provides high-quality screening based on titles and abstracts [4]. Fig. 1

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Focused on the application of adult stem cells in obstetrics and gynecology • Peer-reviewed article • Written in English • Publication between 2019 and 2024	• No available full-text article • Literature reviews (narrative review, scoping, and systematic review) • Proceeding • Letters for editors

During the screening phase, two authors, namely A.K. and M.A.Z., independently assessed articles based on title and abstract to meet inclusion and exclusion criteria. The selection of A.K. and M.A.Z. was then reviewed independently by another author. Any disagreements were resolved through discussion and consensus. When articles passed the initial screening, full-text analysis was conducted comprehensively to extract key information, including study design, types of adult stem cells, subjects, and outcomes. Furthermore, other authors, namely S.S., and A.B.H., conducted a thorough examination to ensure quality and complete data representation from reviewed literature. The risk of bias was formally assessed using Cochrane and ROBINS-I tools for non-randomized interventional studies. Selection bias was evaluated to determine the extent to which participants represented the target population, considering the lack of randomization (D1). Performance bias, mostly arising from insufficient blinding, was assessed for its impact on intervention differences (D2). Attrition bias was examined to account for subject drop-out or missing outcomes in the analysis (D3). Detection bias was evaluated in relation to differences in outcome assessment (D4) while reporting bias was analyzed to identify selective reporting (D5). Visualization of bias assessment is presented in a 'traffic light' plot in Fig. 2, providing a better interpretation of the selected studies. Fig. 3

3. Results

3.1. Overview

We retrieved a total of 299 articles from PubMed, EBSCO, and the Cochrane Library. Based on our inclusion and exclusion criteria, we selected 42 articles for this review. The main objective of this review was to identify current updates in the application of adult stem cells in obstetrics and gynecology. Preclinical and clinical studies were included in this review. Furthermore, we divided the results and reviewed them based on application in obstetric and gynecologic diseases.

3.2. Application of adult stem cells in obstetrics

We found seven studies that investigated the applications of adult

Table 2
Search strategy.

Database	Searching strategy	Results
Pubmed	(((obstetrics) OR (gynecology)) AND ((adult stem cell) OR (mesenchymal stem cell)) AND ((y_5[Filter]) AND (fft[Filter]))) NOT ("EXACTKEYWORD review" AND ((y_5[Filter]) AND (fft[Filter]))) AND ((y_5[Filter]) AND (fft[Filter]))	1969
Cochrane Library	((mesenchymal stem cell OR adult stem cell)):ti,ab,kw"	934
Google Scholar	stem cell obstetrics gynecology stem OR cell "adult stem cell" -review	162

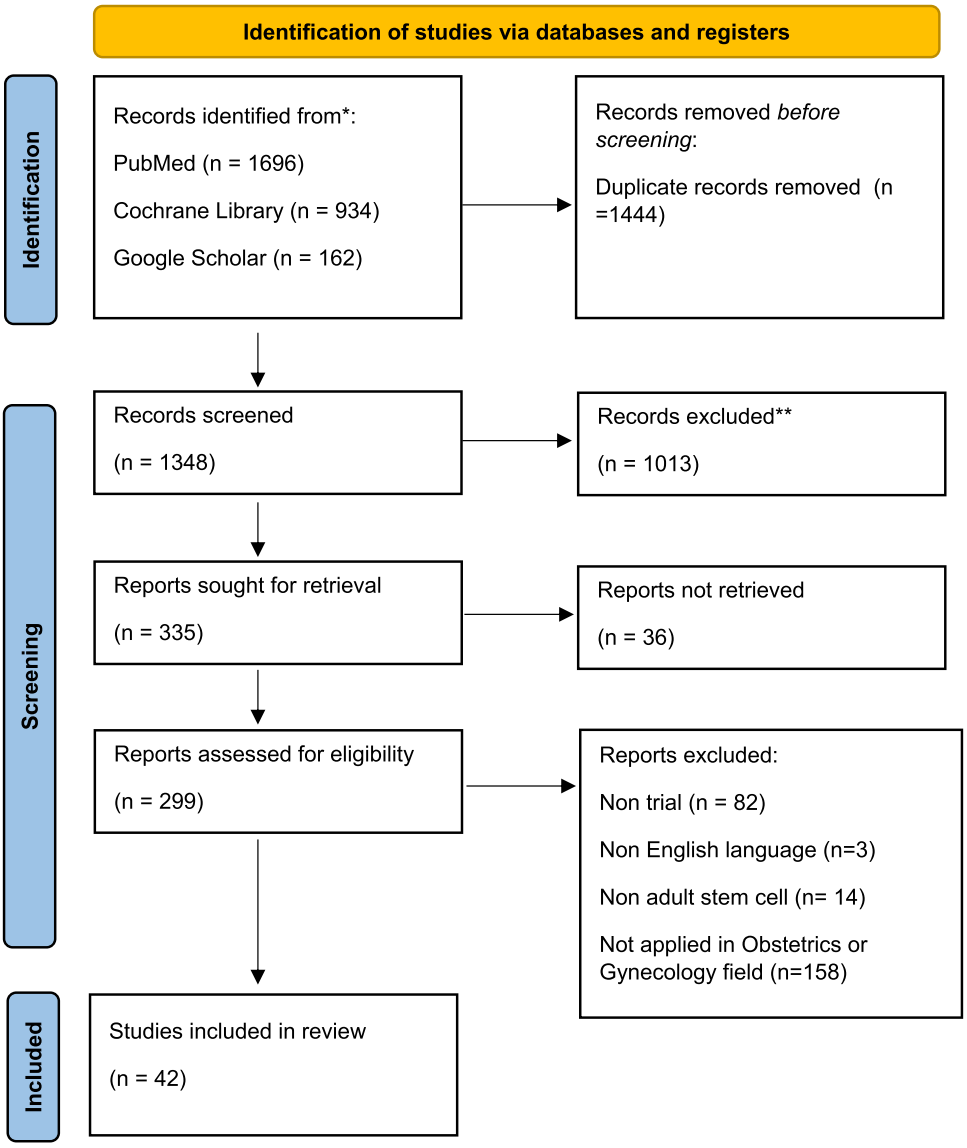

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of search strategy, *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). * *If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

stem cells in obstetrics. One studied used adult stem cells in a clinical trial and investigated the use of endometrial MSCs for recurrent pregnancy loss. Five studies used a preclinical animal model, whereas one in vitro study subcultured placental tissues to study a conditioned medium that was important for placental support [5]. The five animal studies were indicated for recurrent miscarriage, antiphospholipid syndrome, premature rupture of membrane (PPROM), and preeclampsia.

3.3. Applications of adult stem cells in gynecology

Most studies found in the databases were related to applications of adult stem cells in gynecology. We found 35 articles that studied adult stem cell application in several gynecologic diseases. However, only two studies were clinical studies. One clinical study was performed to observe the effects of autologous noninvasively derived stem cell mitochondrial transfer for in vitro fertilization [5,6]. Another clinical study used menstrual endometrial stem cells and supernatant protein to identify endometrial and menstrual abnormalities. Some studies were also conducted with material engineering and technology to improve the applicability of adult stem cells. Three studies used a bioengineered scaffold to improve the homing and regenerative capacity of stem cells [7]. Interestingly, one study used nanoparticles as carriers for stem cells to target organs in a post-chemotherapy ovarian failure model [8]. The other studies were conducted as preclinical studies for gynecologic disease models. Most studies (11 studies) investigated ovarian insufficiency or ovarian failure, whereas others focused on intrauterine adhesions and Asherman's syndrome, tubal occlusion, ovarian cancer, early menopause, in vitro fertilization, pelvic organ prolapse, and urinary incontinence. One study reported the application of adult stem cells for chemotherapeutic drug delivery [8]. Tables 3 and 4

4. Discussion

Stem cells are characterized by their differentiation and self-renewable abilities to various extents. The cellular potency of multipotent stem cells may increase to several cell types in a particular lineage. This multipotent capacity of adult stem cells may be developed for regenerative medicine. Therefore, the application of adult stem cells

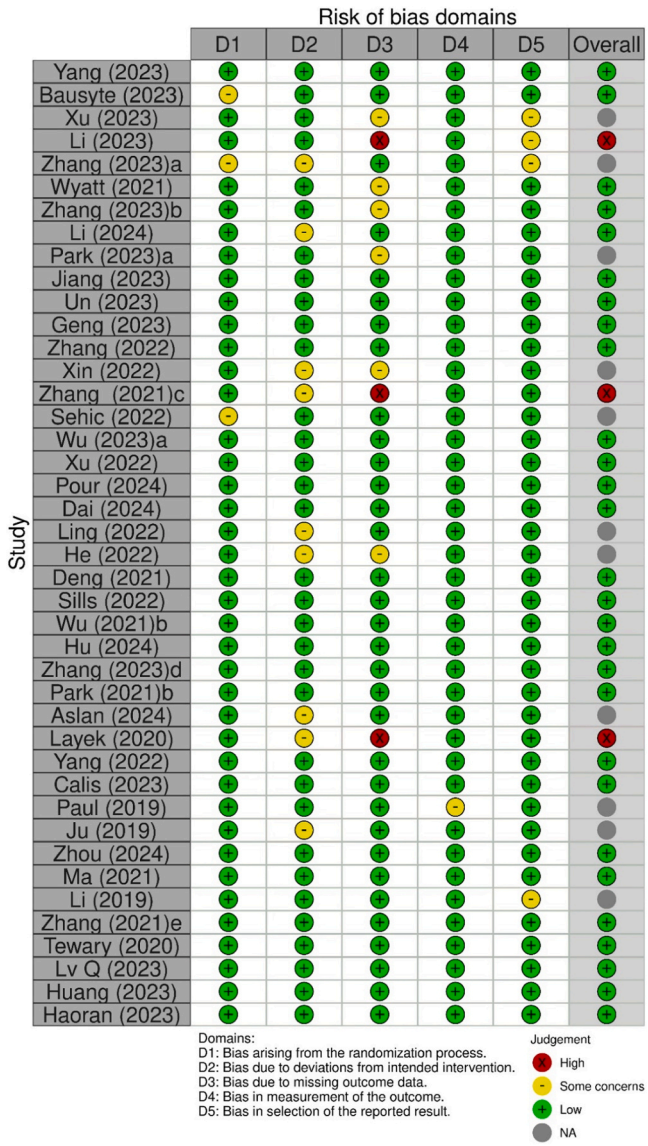

Fig. 2. Traffic light plot.

as a promising therapeutic modality in regenerative medicine has been extensively studied. In this review, we focused on reviewing the current advances in adult stem cell technology in obstetric and gynecological applications.

Ovarian insufficiency or failure is a complex condition that may be caused by various etiologies or sequelae of the disease. Ovarian insufficiency is characterized by sex hormone depletion that is related to infertility and the development of menopausal symptoms. Prolonging ovarian function and preserving fertility may improve the quality of life of patients with ovarian insufficiency. Adult stem cells may serve as potential therapy in patients with premature ovarian insufficiency (POI). MSCs originating from the bone marrow were able to promote ovarian survival and improve folliculogenesis in premature ovarian failure because of chemotherapy. Other sources of adult stem cells for primary ovarian failure included human umbilical cord mesenchymal stem cells (hUCMSCs) [28], human amnion-derived mesenchymal stem cells (hADMSCs) [17], and adipose tissue-derived mesenchymal stem cells (ADMSCs) [26]. These adult stem cells were directly transplanted into the ovary or via intravenous injection [25]. One study used an innovative approach employing low-intensity pulsed ultrasound to promote the migration ability of injected hADMSCs into the target ovarian tissue [26]. This technology also improved chemokine expression, which enhanced the performance of stem cells. To treat POI, the application of the secretome and exosome was also explored in animal studies [46]. The exosomes from human amniotic fluid stem cells may reduce the apoptosis of ovarian granulosa cells via epigenetic regulation [47]. In addition, a study that used MSC-derived exosomes found that apoptosis was inhibited in a mouse model of normal ovarian aging [11]. Therefore, adult stem cells may be further applied to improve ovarian function in aging individuals.

The application of stem cells in restoring fertility remains controversial. However, great advancement was established in a clinical study that used stromal vascular fraction (SVF) from adipose-derived stem cells (ADSCs) to improve the quality of in vitro fertilization (IVF). The application of SVF suspension improves the endometrial thickness and pregnancy outcome of embryo transfer [35]. In a preclinical study, conditioned media of MSCs were rich in important growth factors that increase ovarian maturation, including fibroblast growth factors (FGFs), hepatocyte growth factors, vascular endothelial growth factors, and insulin-like growth factor. The administration of secreted substances from MSCs must be further studied to improve the quality of care for IVF patients.

Severe intrauterine adhesion may lead to female infertility. More importantly, it can cause clinical symptoms, including menstrual disorders and pain, that decrease the quality of life. Severe intrauterine adhesion or Asherman's syndrome was more common after the sharp curettage practice that caused fibrogenesis after endometrial injury. The development of Matrigel containing hUCMSCs could be used to decrease intrauterine adhesion through antifibrotic effects [31]. Another strategy using chitosan bioscaffold insertion was applied in addition to human endometrial stem cells. This bioscaffold was transformed into a long-term organoid structure that regenerates the endometrium [2]. In the future, MSC therapy may be used to treat severe adhesion within the fallopian tubes, particularly caused by chlamydial infection. A study found that MSC injection caused M2 macrophage polarization that presented anti-inflammatory properties to reduce inflammation and infection caused by chlamydia [14]. The improvement of salpingitis in an animal model may be further studied to relieve chlamydial

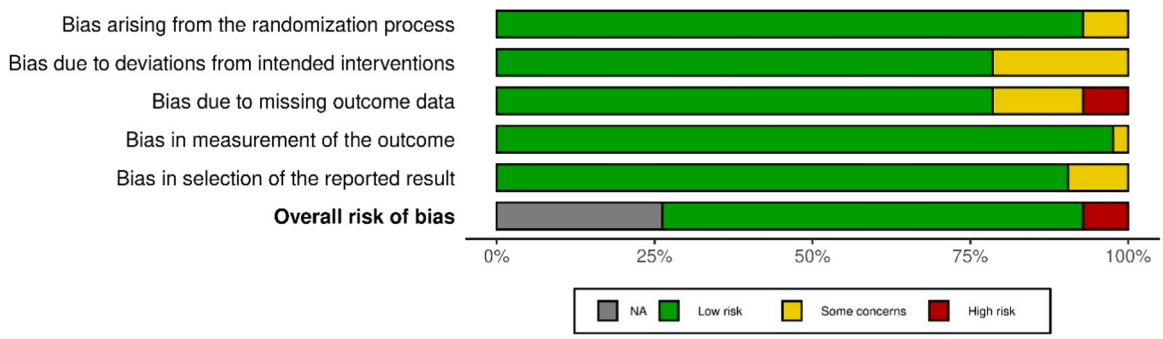

Fig. 3. Overall risk of bias.

Table 3
Study of adult stem cell in gynecology.

Author, Year	Adult stem cell	Study design	Subjects	Intervention	Application	Results
[9]	Mesenchymal stem cell	Preclinical study (material engineering and in vivo animal study)	Stress urinary incontinence mice modeli	Development of injectable and self-healing hydrogel that contains bFGF and SDF−1a to induce homing of intrinsic MSCs	Urinary incontinence	This study developed a novel and innovative self-healing hydrogel that contains bFGF and SDF−1. These soluble factors induce homing of intrinsic MSCs that improve healing in stress incontinence mice model. The released factors promote MSCs homing, matrix deposition and tissue regeneration. The application of secretome technology to regulate intrinsic MSCs may become a useful future clinical application of MSCs to treat incontinence and another degenerative pelvic floor disorders.
[10]	Human endometrium-derived mesenchymal stem cell	preclinical study	Endometrium injured female mice mdoel	Isolated human endometrium-derived mesenchymal stem cells (hEnMSCs)	Endometrial-factor infertility	Endometrial factor of infertility is one of challenging problem that is caused by low receptivity. Isolation of hEnMSCs was followed by injection into endometrium-injured female mice. After treatment, there was improvement of endometrial profiles: fibrosis reduction, lower intensity of inflammatory cells, and decrease apoptotic bodies. These parameters indicate improvement of injured endometria after MSC treatment.
[2]	Multi-lineage human endometrial organoids (MLEO) and endometrial mesenchymal stem cell (eMSCs)	Preclincal study (animal model)	Injury model of endometrium in rats	Seeding eMSCs into biocompatible scaffold as a graft patch that was transplated into injured rats	Asherman's syndrome	Application of scaffold from human acellular amniotic membrane enriched with eMSCs was able to improve endometrial regeneration and pregnancy outcome. This innovative strategy may be used to treat patients with Asherman's syndrome.
[11]	Mesenchymal stem cell-derived exosomes (MSC-Exos)	Preclinical study (*in vitro* and *in vivo*)	Umblical cord mesenchymal stem cell-derived exosome	Exosomes collection from umblical cord mesenchymal stem cells (hUCMSC-Exos)	Normal ovarian aging (NOA)	Limited ovarian reserve and decrease function of the ovary is a natural challenge in fertility management. This study collected exosomes derived from umbilical cord mesenchymal stem cells to improve ovarian function in normal aging. In vitro study showed apoptosis inhibition through targeting PTEN expression. A mice model with normal ovarian aging showed beneficial effect after exosome treatment that the ovarian function was restored. This study may be further investigated in clinical study to improve ovarian function in normal aging women.
[12]	Human umblical cord mesenchymal stem cells (huUCMSCs)	Preclinical study (animal rat model)	Injured endometrium rat model	Injection of hUCMSCs loaded hydrogel	Intrauterine adhesion (IUA)	Oxidized hyaluronic acid hydrogel was loaded with huUCMSCs and injected into injured endometrium rat model. After treatment, rats showed higher expression anti inflammatory cytokines (IL−10) with significant decrease of pro-inflammatory cytokines (IL−6 and IL−1β). In results, endometrial thickness was increased with significant receptivity improvement to achieve live pregnancy in rat model. This is also another study that showed applicability of mesenchymal stem

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Table 3 (*continued*)

Author, Year	Adult stem cell	Study design	Subjects	Intervention	Application	Results
						cells to treat intrauterine adhesion.
[13]	Menstrual endometrial stem cell and supernatant protein	Clinical study	Non pregnant female	Identification of menstrual endometrial stem cells and supernatant protein to identify patients with menstrual/endometrial abnormality.	Endometrial and menstrual abnormalities	This study included non-pregnant women for collection of menstrual endometrial stem cell and supernatant protein. From flow cytometry, endometrial stem cells showed expression of N-Cadherin (NCAD), SUSD2 and SSEA−1. Repair proteins were also found in the supernatant, indicating the potential application for endometrial regeneration. Interestingly, this study also found that population of menstrual endometrial stem cells and the supernantant proteins were potentially able to identify menstrual and endometrial health status.
[14]	Human umbilical cord mesenchymal stem cell-derived extracellular vesicle (hUCMSC-EV)	Preclinical study (animal model)	Salpingitis mice model (chlamydial infected-mice)	Injection of extracellular vesicles from hUCMSC	Salpingitis	Cell free extracellular vesicles derived from hUCMSC was injected into salpingitis mice model. Previously, mice were infected with chlamydia to develop salpingitis. After treatment, they found macrophage polarization from M1 into M2 to alleviate the inflammation and infection. The immune polarization inti anti-inflammatory profiles was mediated through NF-kB signaling.
[15]	Bone marrow mesenchymal stem cell (BMMSC)	Preclinical study (animal study)	Artificial ovary model (mice model)	Bone marrow mesenchymal stem cell	Premature ovarian failure by radiation or chemotherapy	This study succesfylly reconstitute ovary model with bone marrow mesenchymal stem cell. This ovary model was developed to investigate folliculogenesis and ovarian maturation effect to adult stem cell therapy. They found that the presence of BM-MSC in the ovary model promoted ovarian cells survival and proliferation. This study may be further studied to apply in clinical setting to increase fertility rate in ovarian tissue transplant patients.
[16]	Mesenchymal stem cells and MSC-derived exosomes	Preclinical study (POI mice model)	Chemotherapy-induced POI mice model	Intravenous injection of MSC and MSC-derived exosome in POI mice.	Chemotherapy-induced ovarian failure	Oophorotoxic chemotherapy was used to develop POI mice model. After receiving MSC and MSC-derived exosomes, mouse ovaries reversed the failure and showed improved serum hormone levels that indicate regenerated ovarian function. Eventually, mice that received therapy could achieve pregnancy and restored estrous cycle with pregnancy rate more than 60 %. In other group, MSC-dervied exosomes only treated mice also showed improved ovarian function, eventhough with lower pregnancy rate than MSC-treated mice. These results provide evidence of potential application of MSC and MSC-derived exosome to improve ovarian function after chemotherapy.
[6]	Autologous non-invasively derived stem cell mitochondria transfer	Clinical study	Clinical study (in vitro fertilization with mitochondrial transfer)	Autologous mitochondrial transfer	Female nfertility	Mesenchymal stem cell is a potential high quality donor of mitochondria with low oxidative stress and non-fused spherical morphology. Mitochondrial transfer originated from

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Table 3 (*continued*)

Author, Year	Adult stem cell	Study design	Subjects	Intervention	Application	Results
						mesenchymal stem cells showed improvement in mitochondrial content and activity that improve embryonic development. This technology is a breakthrough innovation to improve pregnancy rate in infertile women.
[17]	Human amnion membrane-derived mesenchymal stem cells conditioned medium (hAMSCs-CM)	Preclinical study	Premature ovarian failure (POF) mice model	Intreavenous injection of hAMSC-CM into POF mice model	Premature ovarian failure	Mesenchymal stem cell conditioned medium was isolated from amniotic membrane. Collection of serum free hAMSC-CM was then continued with injection into mice model. The condition medium improved ovarian function. Serum level of AMH and estradiol were increased significantly after hAMSC-CM administration indicating potential application for POF patients. The improvement of ovarian function was mediated by suppression of apoptosis. In results, number of follicles was increased after condition medium treatment.
Geng, 2022	Human amniotic fluid stem cell-derived exosome (HuAFSC-exosome)	Preclinical study	In vitro and in vivo model of POF	Isolation and administration of exosomes derived from human amniotic fluid stem cells	Premature ovarian failure	Enriched medium with huAFSC-exosomes carried miR−369–3p that reduced apoptosis of ovarian granulosa cells. Exosome from mesenchymal therapy showed useful effect for clinical application in patients with primary ovarian failure.
[18]	Umbilical cord mesenchymal stem cells	Preclinical study	Rat model of primary ovarian insufficiency	Transplantation of UCMSC	Chemotherapy induced-Primary ovarian failure	This study applied in vivo model of Cyclophospamide-induced primary ovarian failure. After UCMSC transplantation, morphology and function of ovary was improved. Restored ovarian function was foundas hormone secretion and ovarian cycle were seen after stem cell therapy. Satisfactory results in rat model may be further investigated for clinical application in chemotherapy induced ovarian failure.
[19]	Bioscaffold for endogenous endometrial mesenchymal stem cells	Preclinical study (material engineering and animal model)	Rat model of endometrial damage	Development of bioscaffold (acellular SDF−1α/E7 modified collagen scaffold)	Severe intrauterine adhesions (IUA)	Acellular bioscaffold that contains stromal derived factor−1α successfully improved endogenous mesenchymal stem cells homing and function. In vivo study of this bioscaffold technology increased regenerative capacity of endogenous adult stem cells. Further, application of bioscaffold enriched with SDF−1α may serve as a clinically available treatment after clinical study.
[20]	Stem cell-derived ovarian regenerative patch	Preclinical study (in vitro and in vivo)	Rat model with POI	Transplantation of regenerative patch containing secretome from MSCs	Primary ovarian insufficiency	Application of bioscaffold that was enriched with MSC-derived secroteme showed fertility restoration in raat model of primary ovarian insufficiency. Sexual hormone secretion, ovarian cycle and follicle development were improved following regenerative patch application. This study may be applied for POI treatment in patients after chemotherapy.
[21]	Bioengineered uterus graft with MSC-recellularized scaffold.	Preclinical study (material engineering and animal model)	Rat model of injured uterus	Decellularized uterus tissue transplantation with MSC-recellularization	Female infertility	Uterine tissue transplantation with bioscaffold graft containing MSCs was conducted in rat model. This technology showed that MSCs

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Table 3 (*continued*)

Author, Year	Adult stem cell	Study design	Subjects	Intervention	Application	Results
						increase regenerative capacity of this bioscaffold. Inflammatory profile was decreased that indicates beneficial effect against immune rejection. Moreover, populations of FOXP3 + Tregs and CD163 + M2 macrophages were increased. In conclusion, MSCs in the bioscaffold may be seen as sources of immunotherapeutic cells that promote regeneration and suppress pro-inflammatory tissue rejection.
[22]	Adipose mesenchymal stem cells	Preclinical study (in vitro and in vivo)	Rat model of childbirth injury	Adipose mesenchymal stem cells (ADSCs) enriched hydrogel	Pelvic organ prolapse	Patients with pelvic organ prolapse had higher oxidative stress and inflammatory reaction that caused pelvic floor damage and fibrogenesis. Application of ADSCs could effectively decrease reactive oxygen species (ROS) response and increase cell survival for pelvic floor regeneration.
[23]	Umbilical cord mesenchymal stem cell (UCMSC)	Preclinical study	Three-dimension in vitro model	Hydrogel with UC MSC (Matrigel)	Ovarian-transplant patients	Expression level of neovascularization markers (VEGFA, IGF1 and ANGPT2) were increased after Matrigel treatment. The overexpression lead to increased microvascularization in 3-dimensional in vitro model of ovarian culture. Moreover, follicular function was improved with higher folliculogenesis, lower apoptosis and better microvascularization.
[24]	Mesenchymal stem cell condition medium	Preclinical study (in vitro)	In vitro oocyte maturation	MSC condition medium	In vitro fertilization	Conditioned media of mesenchymal stem cell could improve ovarian quality through bioactive molecules secretion, such as: VEGF, FGF, HGF, FGF and IGF. These growth factors effectively increase ovarian maturation to improve success rate of IVF.
[25]	Human umbilical cord-mesenchymal stem cell exosomes (hUC-MSC exos)	Preclinical study (animal model)	POI rat model	Ultrasound-guided ovarian injection of hUC-MSC exos	Primary ovarian insufficiency	Intraovarian injection of exosomes derived from human umbilical cord mesenchymal stem cells could imrpved ovarian function. Ovarian hormone was significantly improved that restore ovarian function and fertility. Therefore, this innovative direct application to ovary may be further studied in clinical setting.
[26]	Human amnion-derived mesenchumal stem cell (hAD-MSCs)	Preclinical study (in vivo model)	Chemoteherapy-induced POI rat model	Low-intensity pulsed ultrasound (LIPUS) promoted hAD-MSC	Chemotherapy-induced POI	Migration ability and homing of MSC was improved with LIPUS technology. Pretreatment with LIPUS enhanced expression of chemokine receptors (CXCR4 and SDF−1) that promoted migration ability to target tissue.
[27]	Human endometrial epithelial stem cell	Preclinical study (in vitro and in vivo)	Intrauterine adhesion rat model and in vitro culture	In vitro culture and expansion of endometrial stem cell before transplanted with bio scaffold (chitosan)	Intrauterine adhesion (IUA)	Bioscaffold was turned into long-term organoid structure when the endometrial stem cells were applied into chitosan matrix. In addition, the authors found that endometrial epithelial stem cell had better regenerative capacity than endometrial stromal stem cell.
[28]	Human umbilical cord mesenchymal stem cell (UC-MSC) and extracellular vesicles	Preclinical study (animal model)	POF mice model	hUC-MSC transplantation and extracellular vesicles injection	Premature ovarian failure	In POF mice model, UC-MSC and injection of extracellular vesicles were able to improve ovarian function through reducing ovarian injury and apoptosis after

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Table 3 (*continued*)

Author, Year	Adult stem cell	Study design	Subjects	Intervention	Application	Results
						chemotherapy. In addition, they found that MSCs were found only in ovarian interstitium, rather than the follicles, indicating the paracrine regulation of anti-apoptosis.
[29]	Platelet rich plasma	Preclinical study (in vitro and in vivo)	In vitro culture and mice model	Intraovarian injection of PRP to improve undifferentiated oocyte stem precursors	Reproductive aging and early menopause	Injection of platelet rich plasma or condensed cytokines were able to support folliculogenesis and growth differentiation. Some proteins were reported to support this folliculogenesis: GDF9, TGFβ1, PDGF and BMP. Intraovarian PRP injection is also considered to mediate rejuvenation of ovary by cytokine-dependent gene activation.
[30]	Adipose-derived stem cell (ADSC)	Preclinical study	In vitro culture and mice model	Stem cells transplantation and direct injection of growth factor (bFGF)	Pelvic organ prolapse	Reconsitution of pelvic support was necessary for pelvic organ prolapse treatment. Application of regenerative medicine through ADSC could promote fibroblast differentiation that was regulated by bFGF overexpression in ADSC.
[31]	Human umbilical cord-derived mesenchymal stem cell	Preclinical study	Rat endometrial damage model	Minimally invasive delivery of hUCMSC by injectable hydrogel	Intrauterine adhesion	The authors successfully developed a hUCMSC-laden injectable hydrogel for intrauterine adhesion in rat model. This stem cell containing hydrogel had therapeutic efficacy to decrease intrauterine adhesion through anti fibrotic effects. Biocompatibility of the hydrogel may be further studied for clinical application.
[32]	Human umbilical cord mesenchymal stem cells-derived extracellular vesicle (hUCMSC-EV)	Preclinical study	In vitro culture and mice model	Injection of hUCMSC-EV	Chronic salpingitis and tubal occlusion	Chronic inflammation by chlamydia might lead to tubal occlusion and infertility. Extracellular vesicles from hUCMSC regulated the macrophage polarization that might alleviate inflammatory condition.
[33]	Human bone marrow mesenchymal stem cell (hBMMSC)	Preclinical study	POI mice model	Intraovarian engraftment via direct injection of hBMMSC	Primary ovarian insufficiency	Bone marrow is a potential source of MSC for regenerating ovarian failure. This study was addressed to study effectiveness of hBMMSC and toxicity of the application in chemotherapy-induced POI. They found that intraovarin injection of hBMMSC was only detected in ovary, indicating an effective homing. In addition, there was no human DNA was found in the mice fetus indicating safety of potential allogenic transfer.
[34]	Placenta-derived mesenchymal stem cells (PDMSC)	Preclinical study (material engineering and animal model)	Urinary stress incontinence mice model	Developement of biomaterial from polypropylene mesh with PDMSC coating	Urinary stress incontinence	The coating of polypropylene mesh with MSCs decreased tissue inflammation that lead to erosion, pain and failure of mesh implantation. This MSC coculture may be further applied in clinical setting to improve effectiveness of mesh application to treat urinary incontinence.
[8]	Mesenchymal stem cell	Preclinical study (nanoparticle drug development and animal mice model)	Ovarian cancer mice model	Mesenchymal stem cells as vehicles or nanocarriers of cancer drug	Ovarian cancer	Mesenchymal stem cells was used as nanocarriers of chemotherapy that selectively target cancer cells. Stem cells were retained in ovarian tumor to improve biodistribution of the drugs. The paclitaxel-loaded nanoparticles were effectively decreased tumor growth and improved survival in mice model ($p < 0.05$).

(*continued on next page*)

Table 3 (*continued*)

Author, Year	Adult stem cell	Study design	Subjects	Intervention	Application	Results
[35]	Adipose-derived stem cell in stromal vascular fraction (SVF)	Clinical trial protocol (TRIAL NUMBER: ChiCTR2000035126)	Patients with thin endometrium	Collection of SVF that contains ADSC	Infertility (embryo transfer in IVF technology)	Adipose-derived stem cells in SVF showed high potential for endometrial regeneration in this clincal trial. A single center clinical trial will be conducted to study the application of SVF suspension with intrauterine catheter. After treatment, endometrial thickness, menstrual cycle and pregnancy outcome will be longitudinally assessed.
[36]	Adipose-derived mesenchymal stem cells (ADMSC)	Preclinical study (animal model)	POI rat model	Intravenous injection of ADMSC	Primary ovarian insufficiency	Application of ADMSC via intravenous injection was studied in this porspective study. After treatment, number of follicles was significantly increased that represents improved folliculogenesis.
[37]	Endometrial stem cell	Preclinical study (material engineering and animal model)	Pelvic organ prolapse Mice model	3D-printed poly caprolactone (PCL) mesh was used as bioscaffold with endometrial stem cell	Pelvic organ prolapse	Endometrial stem cell was bioprinted into polycaprolactone (PCL) bioscaffold to enhance pelvic regeneration in pelvic floor prolapse mice model. The bioprinted EMSC was able to increase anti-inflammatory M2 macrophagethat boost up the repair process.
[38]	Adipose-derived mesenchymal stem cell (ADSC)	Preclinical study (in vitro and animal model)	PCOS mice model	Combined use of ADSC and thrombospondin 1 (TSP1)	Polycystic ovarian syndrome	Thrombospondin 1 in combination with ADSC decreased abnormal vessel formation and inflammation in PCOS. As results, the apoptosis of ovarian cells was decreased while the number and hormone production was restored in the follicles. Moreover, ADSC and TSP1 showed synergistic effect to obtain these outcomes.
[39]	Exosomes from bone marrow mesenchymal stem cells (BMMSC)	Preclinical study (in vitro and animal model)	Pelvic floor dysfunction (PFD) rats	Tumor necrosis factor-α was used to enhance exosomes production by BMMSC	Pelvic floor dysfunction	Exosomes was applied to increase regeneration in pelvic floor. When added with TNF-α, BMMSC produced more amount of proteins for tissue regeneration: Elastin, Collagen I, collagen III and MMP2. When the exosomes were administered into mice, the leak point pressure and peak bladder pressure were decreased in PFD mice.

salpingitis, which is considered one of the important causes of tubal occlusion infertility.

Adult stem cells were also extensively studied in urogynecological diseases, as many of the diseases were related to degeneration. An innovative self-healing hydrogel that contains bFGF and SDF1 from MSCs promoted pelvic floor regeneration in a stress urinary incontinence mouse model [9]. This technology was also applied to other degenerative pelvic floor disorders. Patients with pelvic organ prolapse tend to have higher oxidative stress and inflammatory reactions. Adipose-derived MSCs could effectively decrease the reactive oxygen species response to improve pelvic floor regeneration. Regeneration by ADSCs was mediated by bFGF overexpression [9].

Although relatively less studied, adult stem cell application in obstetric disorders was also found. One study even conducted a clinical trial. The injection of sitagliptin could increase the number of intrinsic endometrial MSCs to address recurrent pregnancy loss. Sitagliptin significantly increased the number of endometrial mesenchymal stem cells [42]. The application of adoptive MSCs was also studied for recurrent miscarriage. Embryo rejection was relieved through the paracrine effect by cell-to-cell contact between MSCs and proinflammatory cytokines [40]. In placental-factor miscarriage, placenta-derived MSCs and conditioned medium played important roles in the angiogenesis and proliferation of primary placental cells. This is mediated by the secretion of several growth factors that support angiogenesis, including CXCL5, IL-6, and IL-8 [5].

Neonatal death is one of the major health problems related to prematurity. The preterm premature rupture of the membrane is one of the causal mechanisms of prematurity that needs to be solved. Fetal membrane inflammation may lead to PPROM that causes prematurity and poor fetal outcome. A study found that the application of exosomes from umbilical cord MSCs could suppress intrauterine inflammation [44]. After exosome treatment, the inflammation profile and production of membrane degradation enzymes (MMP2 and MMP9) were decreased [44]. The current advances of research on adult stem cell application must be further studied in clinical trials to ensure the efficacy and safety of treatment. The wide applicability of adult stem cells is mediated by their multipotency.

5. Limitations

This review has limitations due to the small number of studies identified in the databases and the lack of clinical investigations.

Table 4
Study of adult stem cell in obstetrics.

[5]	Placenta-derived mesenchymal stem cell and conditioned medium	Preclinical study (in vitro)	Sub-cultured placenta tissue	Isolation of primary hPDMSC and collected conditioned medium	Recurrent miscaarriage	Placental support is necessary for pregnancy. This study found that hPDMSC played important role in angiogenesis and proliferation of primary placental cells. In addition, conditioned medium of PDMSC showed high level of growth factors that support placental angiogenesis, such as: IL-8, CXCL5, MCP1, GRO and IL6. Therefore, application of PDMSC conditioned medium may be helpful to support until full term pregnancy.
[40]	Mesenchymal stem cell	Pre-clinical study (disease model)	Abortion model	Adoptive transfer of MSC	Recurrent miscarriage	Application of adoptive MSC may relief rejection of embryo through paracrine effect by cell-to-cell contact between MSCs and proinflammatory cytokines. Immune tolerance was also mediated by inhibition of CD4 + T-cell proliferation and decidual macrophages switch to anti-inflammatory M2. This study found the potential future application of MSCs to relieve immune rejection in recurrent miscarriage patients.
[41]	Mesenchymal stem cells	Preclinical study (animal study)	Female mice abortion model	Adoptive MSC transfer	Recurrent spontaneous abortion (RSA)	Adoptive MSC transfer could enhance decidual expansion of FOXP3 + T cells with anti-inflammatory cytokines. Regulation of maternal-fetal immune tolerance was improved after MSC adoptive transfer that may be used to solve recurrent miscarriage.
[42]	Endometrial mesenchymal stem cells	Clinical study	Patients with history of 3 or more miscarriages	Injection of sitagliptin to increase endometrial mesenchymal stem cells	Recurrent pregnancy loss (RPL)	Recurrent pregnancy loss is associated with decreased number of endometrial mesenchymal stem cells. Therefore, any strategies to increase the number and improve the function of EMSC may be indicated to solve RPL. This RCT was conducted to study the EMSC profiles after sitagliptin treatment. They found that Sitagliptin increased colony forming units of EMSC (RR: 1.52, 95 %CI: 1.32–1.75, $p < 0.01$).
[43]	Human umbilical cord mesenchymal stem cell-derived exosomes (hucMSC-exos)	Preclinical study	Mice model with antiphospolipid syndrome.	Intravenous injection of hucMSC-exos	Obstetrics antiphospolipid syndrome	Injection of exosomes originated form huc-MSCs could improve placental injury and impaired function of trophoblast in antiphospolipid syndrome. This effect was mediated by delivery of exosomal miR−146–5p that suppressed pro inflammatory cytokines (IL−1β) and tumor necrosis factor via TRAF6 inhibition. This study was a promising study that may be applied for Obstetrics patients with antiphospolipid syndrome.
[44]	Exosomes from umbilical crod mesenchymal stem cells (UCMSC)	Preclinical study (in vivo)	Pregnant mice model	Injection of exosomes from UCMSC and FPR2 agonist LXA4	Preterm premature rupture of membrane (PPROM)	Fetal membrane inflammation may lead to PPROM that is related to prematurity and poor fetal outcome. This study applied exosomes from UCMSC that was also enriched with lipoxin A4 (LXA4) to activate FPR2 and suppress inflammation. After treatment with exosomes, inflammation profile and production of membrane degradation enzymes (MMP2 and MMP9) were decreased. In addition, neovascularization was promoted via MAPK/NFkB signaling pathway to increase membrane tissue regeneration. This study may be clinically evaluated for patients with PPROM to decrease inflammation process and increase tissue remodelling.
[45]	Placental mesenchymal stem cells	Preclinical study	In vitro study	Hypoxic conditioning of placental mesenchymal stem cells	Preeclampsia	Hypoxic conditioning of placental mesenchymal stem cells increased cell viability and migration ability via overexpression of DANCR and HIF−1α. this study showed that hypoxia conditioning could increase viability and migration ability of PMSC to restore normal placenta formation that improve preeclampsia condition.

However, current advancements in the studies contribute to a better understanding of the regenerative mechanism. Preclinical studies offer valuable insight into the origins, obtainment, cultivation, and processing methods of adult stem cells, facilitating their translation into clinical trials. Therefore, future clinical trials focusing on the safety and efficacy of adult stem cell applications should be conducted more efficiently. In addition, some concerns may arise from methodological biases in the included studies. Eventhough overall risk of bias assessment showed low risk, some studies had concerns regarding intended intervention bias, lack of randomization bias and bias in the selection of reported results. Information of bias assessment in Fig. 2 provides a better interpretation of the selected studies.

6. Conclusions

In conclusion, in the last 5 years, 3 clinical studies have incorporated adult stem cells in obstetrics and gynecology. One clinical study performed sitagliptin treatment to enhance endometrial stem cells for recurrent pregnancy loss. The others had focused on gynecologic disorders, specifically infertility and endometrial conditions. Several studies also integrated bioengineering to improve the applicability of adult stem cell technology. The application of a bioengineered scaffold improved the regenerative capacity of the cells in three studies. This review emphasized the potential of adult stem cells, specifically in the treatment of degenerative diseases and the preservation of fertility. The current advances in the investigations should be further evaluated in clinical trials to provide strong evidence of the effectiveness and safety of adult stem cell treatment.

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Kurniadi Andi: Writing – original draft, Resources, Data curation. **Suardi Dodi:** Conceptualization, Supervision, Validation. **Adipurnawan Winarno Gatot Nyarumenteng:** Supervision, Validation. **Kusumanto Ardhanu:** Validation, Supervision. **Mantilidewi Kemala Isnainiasih:** Data curation. **Harsono Ali Budi:** Validation, Supervision. **Salima Siti:** Validation, Investigation, Formal analysis. **Zucha Muhammad Ary:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used English language editing service by Enago, an editing brand of Crimson Interactive. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Erceg Ivkošić I, et al. Unlocking the potential of mesenchymal stem cells in gynecology: where are we now? Multidisciplinary Digital Publishing Institute (MDPI); 2023. https://doi.org/10.3390/jpm13081253.
[2] Xu Y, et al. Multi-lineage human endometrial organoids on acellular amniotic membrane for endometrium regeneration. Cell Transpl 2023;32. https://doi.org/10.1177/09636897231218408.
[3] Tricco AC, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Am Coll Physicians 2018. https://doi.org/10.7326/M18-0850.
[4] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev Dec. 2016;5(1). https://doi.org/10.1186/s13643-016-0384-4.
[5] Ma H, et al. Conditioned medium from primary cytotrophoblasts, primary placenta-derived mesenchymal stem cells, or sub-cultured placental tissue promoted HUVEC angiogenesis in vitro. Stem Cell Res Ther Dec. 2021;12(1). https://doi.org/10.1186/s13287-021-02192-1.
[6] Jiang Z, et al. Autologous non-invasively derived stem cells mitochondria transfer shows therapeutic advantages in human embryo quality rescue. Biol Res Dec. 2023;56(1). https://doi.org/10.1186/s40659-023-00470-1.
[7] Zhang Y, et al. Unresponsive thin endometrium caused by Asherman syndrome treated with umbilical cord mesenchymal stem cells on collagen scaffolds: a pilot study. Stem Cell Res Ther Dec. 2021;12(1). https://doi.org/10.1186/s13287-021-02499-z.
[8] Layek B, Shetty M, Nethi SK, Sehgal D, Starr TK, Prabha S. Mesenchymal stem cells as guideposts for nanoparticle-mediated targeted drug delivery in ovarian cancer. Cancers Apr. 2020;12(4). https://doi.org/10.3390/cancers12040965.
[9] Yang L, et al. Chitin-based hydrogel loaded with bFGF and SDF-1 for inducing endogenous mesenchymal stem cells homing to improve stress urinary incontinence. Carbohydr Polym Nov. 2023;319. https://doi.org/10.1016/j.carbpol.2023.121144.
[10] Bausyte R, et al. Human endometrium-derived mesenchymal stem/stromal cells application in endometrial-factor induced infertility. Front Cell Dev Biol 2023;11. https://doi.org/10.3389/fcell.2023.1227487.
[11] Li Z, et al. Human umbilical cord mesenchymal stem cell-derived exosomes improve ovarian function in natural aging by inhibiting apoptosis. Int J Mol Med Oct. 2023;52(4). https://doi.org/10.3892/ijmm.2023.5297.
[12] Zhang D, et al. Functionalized human umbilical cord mesenchymal stem cells and injectable HA/Gel hydrogel synergy in endometrial repair and fertility recovery. Acta Biomater Sep. 2023;167:205–18. https://doi.org/10.1016/j.actbio.2023.06.013.
[13] Wyatt KA, Filby CE, Davies-Tuck ML, Suke SG, Evans J, Gargett CE. Menstrual fluid endometrial stem/ progenitor cell and supernatant protein content: cyclical variation and indicative range. Hum Reprod Aug. 2021;36(8):2215–29. https://doi.org/10.1093/humrep/deab156.
[14] Zhang C, et al. Human umbilical cord mesenchymal stem cells derived extracellular vesicles alleviate salpingitis by promoting M1–to–M2 transformation. Front Physiol 2023;14. https://doi.org/10.3389/fphys.2023.1131701.
[15] Li J, et al. Mesenchymal stem cells promote ovarian reconstruction in mice. Stem Cell Res Ther Dec. 2024;15(1). https://doi.org/10.1186/s13287-024-03718-z.
[16] soo Park H, et al. Comparison of the therapeutic effects between stem cells and exosomes in primary ovarian insufficiency: as promising as cells but different persistency and dosage. Stem Cell Res Ther 2023;14(1). https://doi.org/10.1186/s13287-023-03397-2.
[17] Un B, Cetinkaya-Un B, Akpolat M, Andic F, Yazir Y. The effects of human amnion membrane-derived mesenchymal stem cells conditioned medium on ionizing radiation-induced premature ovarian failure and endoplasmic reticulum stress-related apoptosis mechanism. Eur J Obstet Gynecol Reprod Biol Sep. 2023;288:191–7. https://doi.org/10.1016/j.ejogrb.2023.08.001.
[18] Zhang M, et al. Umbilical cord mesenchymal stem cells ameliorate premature ovarian insufficiency in rats. *Evid-Based Complement Altern Med*, Vol 2022;2022. https://doi.org/10.1155/2022/9228456.
[19] Xin L, et al. An acellular scaffold facilitates endometrial regeneration and fertility restoration via recruiting endogenous mesenchymal stem cells. Adv Health Mater Nov. 2022;11(21). https://doi.org/10.1002/adhm.202201680.
[20] Zhang S, et al. A stem cell-derived ovarian regenerative patch restores ovarian function and rescues fertility in rats with primary ovarian insufficiency. Theranostics 2021;11(18):8894–908. https://doi.org/10.7150/thno.61690.
[21] Sehic E, Thorén E, Gudmundsdottir I, Oltean M, Brännström M, Hellström M. Mesenchymal stem cells establish a pro-regenerative immune milieu after decellularized rat uterus tissue transplantation. J Tissue Eng 2022;13. https://doi.org/10.1177/20417314221118858.
[22] Wu X, et al. The mechanism of adipose mesenchymal stem cells to stabilize the immune microenvironment of pelvic floor injury by regulating pyroptosis and promoting tissue repair. Mater Today Bio Feb. 2024;24. https://doi.org/10.1016/j.mtbio.2023.100910.
[23] Xu W, et al. UC-MSCs promote frozen-thawed ovaries angiogenesis via activation of the Wnt/β-catenin pathway in vitro ovarian culture system. Stem Cell Res Ther Dec. 2022;13(1). https://doi.org/10.1186/s13287-022-02989-8.
[24] Pour FK, Dari MAG, Ramazii M, Keivan M, Farzaneh M. Mesenchymal stem cells-conditioned medium; an effective cell-free therapeutic option for in vitro maturation of oocytes. Bentham Sci Publ 2024. https://doi.org/10.2174/1574888X18666221219163753.
[25] Dai F, et al. Model construction and drug therapy of primary ovarian insufficiency by ultrasound-guided injection. Stem Cell Res Ther Dec. 2024;15(1). https://doi.org/10.1186/s13287-024-03646-y.

[26] Ling L, Hou J, Wang Y, Shu H, Huang Y. Effects of low-intensity pulsed ultrasound on the migration and homing of human amnion–derived mesenchymal stem cells to ovaries in rats with premature ovarian insufficiency. Cell Transpl 2022;31. https://doi.org/10.1177/09636897221129171.
[27] He W, et al. Long-term maintenance of human endometrial epithelial stem cells and their therapeutic effects on intrauterine adhesion. Cell Biosci Dec. 2022;12(1). https://doi.org/10.1186/s13578-022-00905-4.
[28] Deng T, et al. Human umbilical cord mesenchymal stem cells improve ovarian function in chemotherapy-induced premature ovarian failure mice through inhibiting apoptosis and inflammation via a paracrine mechanism. Reprod Sci Jun. 2021;28(6):1718–32. https://doi.org/10.1007/s43032-021-00499-1.
[29] Growth factors, gene activation and cell recruitment: From intraovarian condensed platelet cytokines to de novo oocyte development. J Clin Transl Res 2022. https://doi.org/10.18053/jctres.08.202201.008.
[30] Wu X, Jia Y, Sun X, Wang J. Acceleration of pelvic tissue generation by overexpression of basic fibroblast growth factor in stem cells. Connect Tissue Res 2022;63(3):256–68. https://doi.org/10.1080/03008207.2021.1895130.
[31] Hu S, et al. Minimally invasive delivery of human umbilical cord-derived mesenchymal stem cells by an injectable hydrogel via Diels–Alder click reaction for the treatment of intrauterine adhesions. Acta Biomater Mar. 2024;177:77–90. https://doi.org/10.1016/j.actbio.2024.02.001.
[32] Zhang C, et al. Human umbilical cord mesenchymal stem cells derived extracellular vesicles alleviate salpingitis by promoting M1–to–M2 transformation. Front Physiol 2023;14. https://doi.org/10.3389/fphys.2023.1131701.
[33] Park HS, et al. Safety of intraovarian injection of human mesenchymal stem cells in a premature ovarian insufficiency mouse model. Cell Transpl 2021;30. https://doi.org/10.1177/0963689720988502.
[34] Aslan E, Maytalman E, Nemutlu Samur D, Köle E, Günizi ÖC. An in vitro pilot study investigating placenta-derived mesenchymal stem cell coating on polypropylene mesh materials. Int Urogynecol J Mar. 2024;35(3):553–9. https://doi.org/10.1007/s00192-023-05687-y.
[35] Yang S, Liu FT, Peng TL, Yu Y, Rong L. Efficacy and safety of autologous adipose tissue-derived stromal vascular fraction in patients with thin endometrium: a protocol for a single-centre, longitudinal, prospective self-control study. BMJ Open Mar. 2022;12(3):e057122. https://doi.org/10.1136/bmjopen-2021-057122.
[36] Calis P, et al. A new technology for the treatment of premature ovarian insufficiency: cell sheet. Cell Tissue Res Jan. 2024;395(1):117–31. https://doi.org/10.1007/s00441-023-03848-5.
[37] Paul K, et al. 3D bioprinted endometrial stem cells on melt electrospun poly ε-caprolactone mesh for pelvic floor application promote anti-inflammatory responses in mice. Acta Biomater Oct. 2019;97:162–76. https://doi.org/10.1016/j.actbio.2019.08.003.
[38] Ju M, et al. Improvement of inflammation and abnormal vascularization by TSP1 treatment combined with ADSCs transplantation in mice with induced polycystic ovary syndrome. Adv Biol Feb. 2024;8(2). https://doi.org/10.1002/adbi.202300451.
[39] Zhou C, et al. Exosomes isolated from TNF-α-treated bone marrow mesenchymal stem cells ameliorate pelvic floor dysfunction in rats. J Cell Mol Med Jun. 2024;28(12). https://doi.org/10.1111/jcmm.18451.
[40] Li Y, et al. Cell–cell contact with proinflammatory macrophages enhances the immunotherapeutic effect of mesenchymal stem cells in two abortion models. Cell Mol Immunol Dec. 2019;16(12):908–20. https://doi.org/10.1038/s41423-019-0204-6.
[41] Zhang D, Lin Y, Li Y, Zhao D, Du M. Mesenchymal stem cells enhance Treg immunosuppressive function at the fetal-maternal interface. J Reprod Immunol Nov. 2021;148. https://doi.org/10.1016/j.jri.2021.103366.
[42] Tewary S, et al. Impact of sitagliptin on endometrial mesenchymal stem-like progenitor cells: a randomised, double-blind placebo-controlled feasibility trial. EBioMedicine Jan. 2020;51. https://doi.org/10.1016/j.ebiom.2019.102597.
[43] Lv Q, et al. Exosomal miR-146a-5p derived from human umbilical cord mesenchymal stem cells can alleviate antiphospholipid antibody-induced trophoblast injury and placental dysfunction by regulating the TRAF6/NF-κB axis. J Nanobiotechnol Dec. 2023;21(1). https://doi.org/10.1186/s12951-023-02179-5.
[44] Huang X, et al. Combined application of exosomes and FPR2 agonist LXA4 in controlling fetal membrane inflammation and promoting fetal membrane tissue repair. Reprod Sci Jun. 2023;30(6):1979–93. https://doi.org/10.1007/s43032-022-01148-x.
[45] Haoran S, et al. Hypoxic preconditioning enhances cellular viability and migratory ability: role of DANCR/miR-656-3p/HIF-1α axis in placental mesenchymal stem cells. Stem Cells Sep. 2023;41(9):877–91. https://doi.org/10.1093/stmcls/sxad048.
[46] soo Park H, et al. Comparison of the therapeutic effects between stem cells and exosomes in primary ovarian insufficiency: as promising as cells but different persistency and dosage. Stem Cell Res Ther Dec. 2023;14(1). https://doi.org/10.1186/s13287-023-03397-2.
[47] Geng Z, et al. Human amniotic fluid mesenchymal stem cell-derived exosomes inhibit apoptosis in ovarian granulosa cell via miR-369-3p/YAF2/PDCD5/p53 pathway. Oxid Med Cell Longev 2022;2022. https://doi.org/10.1155/2022/3695848.