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REVIEW

Cell therapy for the treatment of reproductive diseases and infertility: an overview from the mechanism to the clinic alongside diagnostic methods

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Abstract **Infertility is experienced by 8%–12% of adults in their reproductive period globally and has become a prevalent concern. Besides routine therapeutic methods, stem cells are rapidly being examined as viable alternative therapies in regenerative medicine and translational investigation. Remarkable progress has been made in understanding the biology and purpose of stem cells. The affected pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) are further studied for their possible use in reproductive medicine, particularly for infertility induced by premature ovarian insufficiency and azoospermia. Accordingly, this study discusses current developments in the use of some kinds of MSCs such as adipose-derived stem cells, bone marrow stromal cells, umbilical cord MSCs, and menstrual blood MSCs. These methods have been used to manage ovarian and uterine disorders, and each technique presents a novel method for the therapy of infertility.**

Keywords infertility; stem cell therapy; mesenchymal stem cells; pluripotent stem cells

Introduction

Infertility is characterized by the inability to get pregnant for at least 12 months [1]. Infertility can be classified into three primary classifications, namely, female reasons, male reasons, and combined causes [2]. Female infertility is caused by various circumstances, such as disorders of the reproductive system. In this way, ovulation abnormalities (e.g., polycystic ovary syndrome, hypothalamus instability, and primary ovarian failure), tubal infertility, endometriosis, and uterine and cervical reasons cause female infertility (e.g., polyps, cervical stenosis, and tumors). Hormone replacement therapy can help with infertility in some cases, but previous studies have confirmed that it raises the breast cancer risk [3,4]. Although several reasons linked to increased risks for multiple pregnancies should be examined, ovulation induction, superovulation, or assisted reproductive technologies results showed tendencies toward increasing fertility rates [5] (Fig. 1).

Remarkably, alternative treatments for infertility, including stem cell treatment, have been studied by researchers. Stem cells are undifferentiated cells with the potential to renew themselves for lengthy periods without major modifications in their general features. Under particular physiologic or experimental settings, they can develop into various specialized cells. A significant interest has been observed because of the constraints of employing embryonic and induced pluripotent stem cells in the therapy. One of the most important elements in this type of therapy is the use of mesenchymal stem cells (MSCs). Correspondingly, MSCs are devoid of both ethical problems and the production of teratomas [6]. MSCs, which are commonly known as mesenchymal stromal cells, are a type of pluripotent stem cell that originates in the mesoderm. They can self-renew and differentiate into ectodermic and endodermic cells and mesoderm lineages, including osteocytes, chondrocytes, and adipocytes [7,8]. Considerably, adult tissues, including the umbilical cord (UC), menstrual blood, adipose tissue (AD), placenta, and the bone marrow, can

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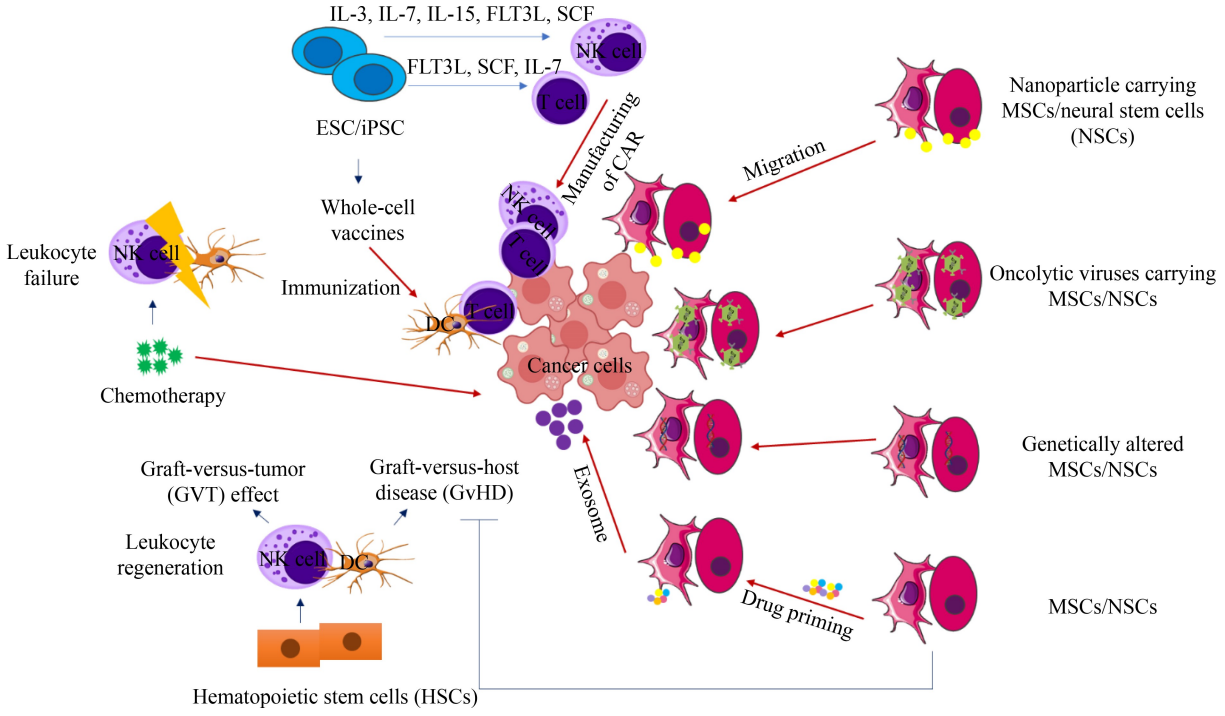

Fig. 1 Different parameters including nanoparticle carrying MSCs, neural stem cells (NSCs), oncolytic viruses carrying MSCs/NSCs, and genetically altered MSCs/NSCs are associated with the treatment of cancer cells in with corporation chemotherapy.

all be used to extract MSCs in the therapy [9,10]. Overall, hormonal imbalance and the physical and mental health are related to the difficulties associated with reproductive diseases and infertility. Correspondingly, assisted reproductive tools can only work out approximately 50% of the patients. Furthermore, it involves significant problems and does not resolve the basic difficulty of infertility. Considering that pluripotent stem cells can differentiate into almost any kind of different cells, they have been extremely associated as an optimal choice in the progress of stem cell-based fertility treatments, which could also regulate genetic disorders and diseases in all offspring. These developments in reproductive technology indicate both oppositions and feasibilities for solving infertility problems caused by different parameters. This paper comprehensively indicates and clarifies all types of infertility diseases and the potential use of stem cells for the treatment of these reproductive disorders.

Current therapeutic of infertility

Although therapeutic intervention has remarkably advanced in recent years, more than 80% of couples experiences infertility [11]. Infertility is a worldwide problem that affects over 15% of all couples, in which male reasons account for roughly 30% of cases, and female factors account for roughly 40% of situations [12]. Infertility is a complicated disease, and therapy varies depending on the age of the patient, the cause of infertility, and other factors. Importantly, therapies must be able to endure financial, temporal, physical, and psychological constraints (Table 1).

Several therapies, including surgery and medicine, may be indicated at roughly the same time based on patient characteristics. Fertility medications are mainly used for promoting ovulation in women with ovulation problems. The ovarian follicles rupture, and the egg is expelled when the levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) suddenly increase. Ovarian malignancy, multiple births, ovarian hyperstimulation syndrome (OHSS), and premature delivery are associated with the usage of fertility medicines [13]. In this account, laparoscopy, hysteroscopy, and fallopian tube operations are considered for restoring female fertility via surgery. IUI and IVF are alternative ARTs for women. Medication therapy, surgery, hormone treatment, and ART are considered for the treatment of male infertility [14]. Sperm can be removed carefully from the testis or epididymis in persons with azoospermia. Accordingly, the varicocele can also frequently be treated with surgery. Furthermore, in certain circumstances, male reproductive problems cannot be cured, and men are unable to father children unless they donate their sperm or give it up for adoption. Considering these limitations, infertility requires improved potential solutions.

Table 1 Clinical trials corresponding stem cell treatment accomplished or underway for modification of infertility

Identifier	Situation	Interventions	Conditions	Trial results	Position	Reference
NCT02240823	Unknown	Adipose-derived stem cells (AdMSCs)	Post-radical prostatectomy erectile dysfunction	Intracavernous injection of AdMSC is a safe process and resulted in the recovery of the erectile role	Odense University Hospital	[252]
NCT02603744	Unknown	Intraovarian injection of adipose-derived stromal cells (ADSCs)	Primary ovarian insufficiency	Intraovarian engrafting of ADSCs is safe and possibly related to a decrease in FSH level	Royan Institute	[253]
NCT02696889	Active	Therapeutic potential of autologous stem cell	Premature ovarian insufficiency (POI), diminished ovarian reserve	A description of two subjects showed considerable progress in clinical characteristics associated with POI. The size and estrogen production increased in the MSC engrafted ovary	The University of Illinois at Chicago	[254]
NCT00429494	Completed	Approach: hematopoietic stem cell transplantation (Hsct) Drug: leuprolide acetate	Amenorrhea primary ovarian insufficiency	Informed that leuprolide could not maintain an ovarian role in HSCT patients	UT MD Anderson Cancer Center, United States	[255]
NCT02313415	Completed	Approach: Umbilical cord MSCs	Infertility with intrauterine adhesions	Demonstrated that transplantation of clinical-grade human UC MSC could enhance the proliferative and differentiation efficiency of the endometrium	Nanjing Drum Tower Hospital, China	[256]
NCT02008799	Recruiting	Intra testicular artery injection of bone marrow stem cell	Azoospermia	None	Man Clinic for Andrology, Male Infertility, and Sexual Dysfunction	
NCT02204358	Unknown	Collagen scaffolds, loaded with human bone marrow-derived stem cells	Endometrial dysplasia, intrauterine adhesion (IUA)	None	Nanjing University Medical School	
NCT03207412	Unknown	Human amniotic epithelial cells (hAECs)	Primary ovarian insufficiency	None	Chongqing Medical University, China	
NCT03592849	Registering by invitation	Collagen scaffolds, loaded with human bone marrow-derived MSC	Infertile women with thin endometrium	None	Nanjing Drum Tower Hospital, China	
NCT02372474	Completed	Biological: stem cell	Primary ovarian insufficiency	None	Al Azhar University, Cairo, Egypt	
NCT04009473	Registering by invitation	SEGOVA method involves stem cell treatment, PPR therapy, and growth factor		None	Multicenter	
NCT02414295	Completed	MSC injection	Klinefelter syndrome (KS)	None	Man Clinic for Andrology and Male Infertility, Cairo, Egypt	
NCT04676269	Recruiting	Amnion bilayer and stem cell combination treatment	Infertile patients with thin endometrium	None	Indonesia University	

(*Continued*)

Identifier	Situation	Interventions	Conditions	Trial results	Position	Reference
NCT01742533	Unknown	Biological: human umbilical cord MSCs and human cord blood mononuclear cells Drug: hormone replacement treatment	Primary ovarian insufficiency	None	Shenzhen People's Hospital, Shenzhen, Guangdong, China	
NCT04706312	Not yet recruiting	Human amniotic epithelial cells (hAECs)	Diminished ovarian reserve (DOR)	None	Nanjing Medical University	
NCT03166189	Completed	Biological: bone marrow–derived MSCs	Asherman syndrome	None	D.O. Ott Research Institute of Obstetrics, Gynecology, Russian Federation	
NCT02151890	Completed	Biological: stem cell	Primary ovarian insufficiency	None	Al Azhar University, Cairo, Egypt	
NCT02041910	Unknown	Derived stem cells	Azoospermia	None	Hesham Saeed Elshaer, El-Rayadh Fertility Centre	
NCT02641769	Recruiting	Intratesticular transplantation of autologous stem cells	Non-obstructive azoospermia	None	Stem Cells of Arabia, Amman, Jordan	
NCT03069209	Active	Biological: stem cell	Primary ovarian insufficiency	None	Stem Cells Arabia, Amman, Jordan	
NCT02713854	Recruiting	Human embryonic stem cell-derived trophoblastic spheroids as a predictive instrument	Subfertility	None	The University of Hong Kong	
NCT02062931	Unknown	Biological: stem cell	Primary ovarian insufficiency	None	Al-Azhar University hospitals, Egypt	
NCT02414308	Unknown	Adipose tissue stem cells (ASCs) injection	Erectile dysfunction (ED)	None	Man Clinic for Andrology, Male Infertility, and Sexual Dysfunction	
NCT02025270	Unknown	Azoospermic patients	Azoospermic patients	Bone marrow-derived MSCs	Al Azhar University, Egypt	

Stem cells express a novel goal in cell treatment

Recent advancements in the *in vitro* propagation of male germ cells from pluripotent stem cells has been considered, in which stem cells can be employed for ovarian regeneration and oocyte production in female infertility [15]. Stem cells are undifferentiated cells that occur in fetuses, adults, and embryos and are responsible for the production of differentiated cells. They are usually composed of adult tissues and early embryogenesis cells. During the post-natal and adult phases of development, tissue-specific stem cells are located in differentiated systems and play a crucial role in organ regeneration. Embryonic stem cells (ESCs), MSCs, spermatogonial stem cells (SSCs), and induced pluripotent stem cells (iPSCs) are the primary kinds of stem cells [16]. Totipotent cells are common undifferentiated cells, which can only be detected in the initial phases of growth. The fertilized egg and the first two dividing cells are totipotent, because they divide into extraembryonic and embryonic tissues that can generate embryos and the placenta. Correspondingly, iPSCs can differentiate into three embryonic stem cell lines, comprising endoderm, mesoderm, ectoderm, and from the mesoderm, tissues and organs grow [17].

Stem cell role has five main forms. The first sample entails the replacement and repair of damaged and dead cells. After being injected into the human body, stem cells self-aggregate in damaged organs and associated parts and develop into cell types that are local to these organs and parts. When SSCs are transplanted into sterile testes, their homing ability drives them to their niches. The transplanted SSCs subsequently attach to the Sertoli cells and form a tight connection with the blood-testicular barrier before migrating into their niche on the basement membrane [18]. Considerably, the activation of dormant and inhibiting cells is another kind. Cell division is the process by which the human body grows and develops. Some cells avoid undergoing regular cell cycles following division as they age and enter a condition of effective dormancy. Stem cells can stimulate dormant and suppressor cells, encouraging them to re-enter the cell cycle and divide to proliferate. This process increases the number of additional cells in the body and either normalizes or reverses the metabolic functions. Preclinical mice studies of chemotherapy-induced premature ovarian failure (POF) have indicated that these transplanted stem cells can reside in ovarian tissues and save the ovarian role. However, these pathways need to be examined further [19]. The third category includes the paracrine production of numerous enzymes, proteins, and cytokines to increase cellular proliferation, suppress efficient cell death, and differentiate existing tissue progenitor cells into tissue cells to repair injured tissue and produce new tissues. Spermatogenesis is a mechanism that is controlled by testosterone, endocrine, and paracrine secretion/autocrine elements such as the IL-1 family [20]. Pro-inflammatory cytokines are elevated, thus adversely affecting spermatogenesis. The development of the testicular paracrine/autocrine component and its control mechanism should be recommended for future male infertility therapeutic approaches [21]. The fourth kind entails the exertion of an immunosuppressive mechanism via cell–cell interaction and the production of soluble substances, thus inhibiting the growth of natural killer cells. The fifth kind includes encouraging intercellular signaling restoration. Impressively, the cell's signal molecule combines with the receptor protein on the cell membrane, resulting in a complex formation in the receptor and the creation of a new signal substance within the cell. This process induces a response, along with an increase in ion permeability, a modification in cell shape, or a modification in another cell process [22].

Stem cells derived from diverse tissues

Induced pluripotent stem cells (iPSC)

Cell-based treatment is improved through the confirmation of pluripotent stem cells from fibroblast cell culture with the aid of different transcriptional regulators, such as Oct4, klf4, sox2, and c-myc. Through this process, the iPSCs produced through reprogramming resemble ESCs in terms of morphology, surface receptors expression, telomerase activity, the ability to differentiate into all three lineages, and the presence of a normal karyotype for development. Meaningly, iPSCs are superior to ESCs in regenerative medicine, because they are derived from adult cells, thus eliminating the ethical concerns associated with the use of embryos; these cells are commonly accessible. Considering that iPSCs are created from patients' somatic cells, the risk of immunological rejection is low [23,24]. Various research has been undertaken to investigate the *in vitro* differentiation of iPSCs to male germ cells. Keratinocytes and cord blood were developed into haploid gamete-like cells. For the first three weeks, retinoic acid (RA) was employed in the culture media to establish differentiation. The cells were then extracted for another 2, 3, and 4 weeks during the administration of forskolin, recombinant leukemia inhibitory factor (LIF), and the CYP26 inhibitor R115866 [25]. Ramathal *et al*. [26] cultivated human skin cells from azoospermic men and fertile men during the addition of BMP4, BMP8, RA, and LIF before using them as xenotransplants into the testes of immune-deficient nude mice created by busulfan therapy. The results show that the iPSCs transplanted into seminiferous

tubules developed into germ cell-like cells (GCLCs), while cells from outside tubules did not. Primordial germ cells (PGCs) results in the production of sperm and ova [26]. Irie *et al*. [27] found that SOX17 is the principal mechanism for human PGCs, although BLIMP1 was repressive based on the characterization. Fragile X male and female patient-derived iPSCs were used in the current research. Human iPSCs might differentiate into hPGCs in the absence of activin A, CHIRON, BMP4, SCF, EGF, and LIF [28]. They separate human PGCs from other cells by using the indicators found on PGCs including EpCAM and integrin 6 [28]. Furthermore, fibroblast-derived iPSCs can be differentiated into spermatogenic cells whether in a standard growth media or an *in vivo* xenotransplantation approach [29]. iPSC differentiation can be employed into oogonia, providing hope to couples with insufficient ovarian function or the inability to generate viable eggs [30]. In these experiments, somatic cells were first reprogrammed into iPSCs, and then incipient mesoderm-like cells (iMeLCs) were developed during the addition of activin A and Chiron. Afterward, human primordial GCLCs (hPGCLCs) were generated by plating iMeLCs in clumps. These hPGCLCs were cultivated for four months with gonadal cells obtained from female mice embryonic ovaries to produce oogonia through *in vitro* gametogenesis. The creation of oogonia from human pluripotent stem cells will usher in a new era in infertility treatment. Sugawa *et al*. [31] recorded the mechanistic explanations for human pluripotent stem cell differentiation to heterogeneous mesoderm-like cells in the form of cytokines accompanied by the transition of PGC-like cells (PGCLCs), and the PGCLCs are dedicated to improving gametes that are affiliated with a unique expression of PRDM14 [18,31–34]. Despite repeated test findings, the teratogenic potential of iPSCs and their derivatives arising from reprogramming by inducing with tumorigenesis and the use of nucleic acid integration techniques limit their therapeutic use to customized cell-based treatment [35]. Furthermore, the persistence of epigenetic imprints and downregulation and the genomic instability may pose a remarkable barrier to their potential therapeutic effects [34,36]. Although the iPSC system does not damage embryos, the possibility of exploiting embryos produced from gametes advanced after iPSC reprogramming necessitates ethical approval from a review committee and the collection of explicit consent from the cells or tissue donation process of obtaining any sample for the advancement of iPSC for clinical purposes. Furthermore, IACUC permission is needed for their use in animal studies [37].

Mesenchymal stem cells

To adequately address the use of MSCs, the International Society for Cellular Therapy's Mesenchymal and Tissue Stem Cell Committee set fundamental criteria for the characterization of human MSCs. MSCs need to be plastic-adherent whenever cultured in conventional circumstances. MSCs should exhibit CD105, CD73, and CD90 but not CD45, CD34, CD14 or CD11b, CD79a or CD19, or HLA-DR surface molecules. Finally, *in vitro*, MSCs have developed into adipocytes, chondroblasts, and osteoblasts [7].

Considerably, the large number of MSCs is grouped according to their source. MSCs are now being used in scientific research and clinical studies, either alone or in combination with other treatments, for possible applications to ovarian malfunction and endometrial problems [38,39]. Treatment agents for various disorders affecting female genitalia are generating a lot of interest. More fundamentally, these findings suggest a promising experimental method for exploring the underlying process of employing MSCs for the treatment of female infertility (Fig. 2).

MSCs can be considered to migrate directly and impulsively to the wounded ovary and survive there under the encouragement of numerous stimuli, facilitating ovarian healing. The quantity of differentiated and functionally integrating MSCs is insufficient to account for the occasions in ovulation. Moreover, it is uncertain whether MSCs develop into oocytes after moving to damaged tissue. The increased ovarian efficiency in these trials could be attributed to paracrine processes. These methods entail the release of cytokines, such as vascular endothelial growth element, insulin-like growth factor, and hepatocyte growth factor, which aid in anti-inflammation, antiapoptotic, angiogenesis, antifibrosis, and immunoregulation, and consequently aid in ovarian repair. Conversely, MSCs increase endometrial reserve, which is primarily determined by homing and paracrine activities. Generally, the paracrine action of MSCs, instead of differentiation, is the most significant in research. The regenerative characteristics of transplanted MSCs can be linked to cell-to-cell contact and the production of bioactive chemicals that enhance tissue regeneration and angiogenesis, regulate inflammation, prevent fibrosis and immunological responses, and activate tissue-specific progenitor cells. MSCs engraft the endometrium in mice and humans. Subsequently, they differentiate into epithelial, stromal, and endothelial cells. Interestingly, MSCs may enhance endometrial regeneration and repair fertility through paracrine factors, although alternative methods are possible. Interestingly, different microRNAs and genes alongside their origination and performance are of great importance (Table 2).

Embryonic stem cells (ESC)

ESCs perform a notable function in regenerative medicine. Human embryonic stem cells (hESC) are

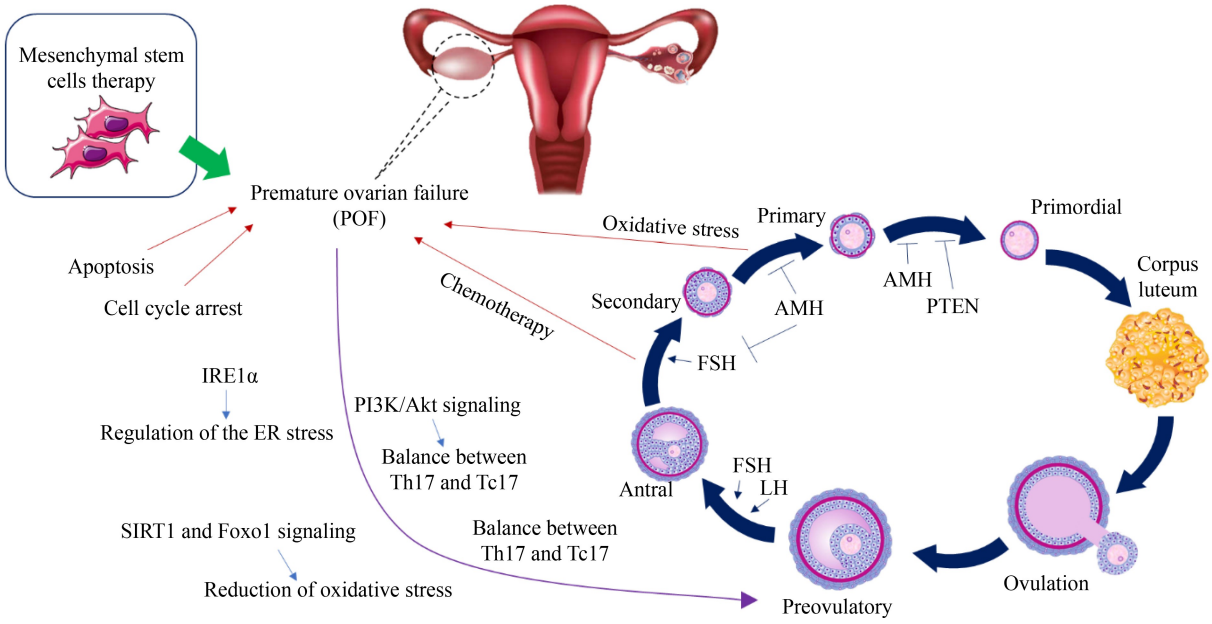

Fig. 2 General view of mesenchymal stem cells therapy and introductions of some cellular and molecular elements in this pathway.

provided from the blastocyst inner cell mass and express the transcription portion Oct 4 [40]. Both mouse and human ESC increase into primordial germ cells *in vitro*, where they undergo meiosis and give birth to male and female gametes [41]. The feasibility of the development of relevant sperm from gene-corrected ESC extracted from cloned blastocysts that are derived from nuclear transferred somatic cells (ntESC) utilizing gene restoration methods has been demonstrated in an egg cell mouse form [42]. As a result, ESCs have emerged as an essential mechanism for cell-based treatment to address infertility concerns. After the first derivation, it has not been widely employed in cell replacement therapy because of ethical issues. Importantly, hESCs participate in endometrial destruction repair and use recovery [43].

Spermatogonial stem cell (SSC)

Through self-renewal and unrestricted differentiation into spermatogonia accompanied by haploid spermatozoa, SSCs serve as a critical role in regulating the highly efficient complicated procedure described as spermatogenesis in the seminiferous tubule [44]. Oocytes are fertilized by such differentiated spermatozoa. The strictly regulated spermatogenesis mechanism in mammals has been divided into three stages, namely, the proliferative phase (mortification of spermatogonia), the meiotic phase (recombination of genetic material), and spermiogenesis (transformation of spermatids into male gametes) [45]. Infertility can occur from any aberration in these regulated stages of spermatogenesis [46]. SSCs are formed from primitive germ cells that move to the gonadal ridge throughout fetal development and eventually lodge into the seminiferous tubules of mature testicles to aid in continuous sperm creation, according to a model system [47,48]. Although SSCs are an excellent tool for the treatment of infertility, they are not widely used during stem cell therapy because of their limited number in the testes and the challenging detection process and effective isolation and cultivation processes [17]. These SSCs might be separated and defined by technological advancements and their species-specific identifying indicators. For instance, in the separation of SSCs from mice [49], stage-specific embryonic antigen-1 (SSEA1), integrins 1 and 6 with rats [50], and SSE4 and G-protein coupled receptor 125 (GPR 125) from humans [51], spermatogonia-specific identifier Stra8 was used.

During spermatogenesis, SSCs can provide viable sperm, suggesting their effective use for the treatment of some instances of male infertility, particularly those caused by chemotherapy. Notably, autologous SSCs have been transplanted into 18 adults and 5 pre-pubertal non-human primates, who had been rendered sterile by chemotherapy. SSCs were found in the ejaculates of approximately 75% of adult animals. Subsequently, by using intracytoplasmic sperm injection, allogenic donated SSCs fertilized rhesus eggs, resulting in different phases of embryogenesis. This process had been an innovative achievement in the field of generative translational medication [52]. For the *in vitro* formation of possible stem cells into germ cells, various biomedical environments have been used, alone or in conjunction with anyone else, such as retinoic acid for correct timing in the onset of meiosis [53], CYP26 inhibitor for the regulation of meiosis across regulation of the STRA8 gene [54], testosterone for the possible release of stem

Table 2 Different microRNAs and genes alongside their stem cell origination and their performance

Origin	Content	Role	Reference
Human UCMSC-EV	miR-21-5p, miR-146a-5p	Improved ovarian role in old mice	[257]
Human UCMSC-EV	miR-147	Repressed M1	[258]
Human ADSC-EV	miR-126, miR-146b, miR-199a, miR-223	Generated M2 polarization	[259]
Human UCMSC-EV	miR-17-5p	Enhanced ovarian role, reducing ROS level	[260]
Human ADSC-EV	miR-323-3p	Anti-apoptosis of CCs	[192]
Human WJMSC-EV	Catalase	Reduced ROS level	[261]
Human UCMSC-EV	TSG-6	Anti-inflammation	[262]
Human AMSC-EV	miR-320a	Reduced ROS level	[182]
Human AFMSC-EV	miR-146a-5p, miR-548e-5p	Anti-inflammation	[263]
Human UCMSC-EV	Let7b	Phenotypic transformation of M1 to M2 inhibited pro-fibrotic genes (TGF-b1/TGFbR1, collagen IVa1)	[264,265]
Human BMSC-EV	EGF, FGF, PDGF, NFκB signaling proteins	Generated angiogenesis	[266]
Human BMSC-EV	STAT3, Wnt3a	Migration, elevated angiogenesis and fibroblast proliferation	[266]
Human BMSC-EV	MFG-E8	Attenuated renal fibrosis partly by interfering with the RhoA/ROCK pathway	[257]
Human ADSC-EV	SCF, MFG-E8, c-kit, ANGPTL1, thrombopoietin	Promoted angiogenesis	[267]
Human BMSC-EV	miR-216a-5p	Promoted M2 polarization	[257]
Human BMSC-EV	IL-10	Anti-inflammation	[268]
Human dental pulp MSC-EVs	Jagged1	Induced angiogenesis	[269]
Human ADSC-EV	miR-30b, miR-125a	Elevated angiogenesis through suppressing DLL4-Notch signaling pathway	[270]
Human UCMSC-EV	Wnt4	Improved angiogenesis by elevating Wnt4/b-catenin signaling	[271]
Human BMSC-EV	KGF	Reduced inflammation and caused M2 polarization	[272]
Human ADSC-EV Mice BMSC-EV	VEGF	Improved neovascularization through elevating VEGF/VEGFR signaling pathway	[268]
Rat BMSC-EV	miR-130a	Advanced angiogenesis	[276]
Rat BMSC-EV	miR-340	Attenuation endometrial fibrosis	[273]
Rat AFMSC-EV	miR-21	Enhanced ovarian role	[179]
Rat BMSC-EV	miR-144-5p		[257]
Mice AFMSC-EV	miR-10a	Enhanced ovarian role and anti-apoptosis of GCs	[176]
Mice BMSC-EV	miR-210	Enhanced angiogenesis, limited fibrosis in ischemic hearts	[270]
Mice BMSC-EV	HGF	Stabilized endothelial barrier role	[270]
Mice BMSC-EV	miR-644-5p	Anti-apoptosis of GCs	[274]
MSC-EV Mice BMSC-EV	miR-210	Elevating angiogenesis via VEGF pathway, ameliorating inflammation through miR-210/serpine1 axis	[270]
Mouse BMSC-EV	miR-182	Generated M2 polarization through targeting TLR4	[275]
Pig ADSC-EV	Angptl4, Ephrin-B2, PDGFC, DOK2, Wnt7b	Elevated angiogenesis	[276]
Pig ADSC-EV	ACVR1, MMP19	Matrix remodeling	[276]
CMPC-MSC-Exo	EMMPRIN	Elevated angiogenesis	[277]
EndMSC-EV Dog WJMSC-EV	TGF-b	Matrix remodeling, prevented $CD4^+$ T cells activation	[278]
MSC-EV	CXCL2, CXCL8, DEFA1, HERC5, IFITM2,CXCL16	Recruited immune cells to proximity of MSC-EVs	[279]
MSC-EV	miR-21, miR-132, miR-222, IL-8	Elevated angiogenesis	[280]
MSC-EV	miR-29	Attenuation renal fibrosis and EMT through targeting PI3K/AKT signaling pathway	[281]
MSC-EV	miR-145	Attenuated EMT by suppressing TGF-b/smad signaling or repressing ZEB2	[281]

cell component to stimulate germ cell differentiation [54], and forskolin for enhanced germ cell proliferation [55]. To confirm the potential of SSCs to establish colonies within the testes while also developing into male gametes via synchronized spermatogenesis, researchers have used both *in vitro* stimulation of stem cell proliferation transplantation into male mice that were made infertile [56]. The primary disadvantage of this cell-based treatment in fertility clinics is that it may disrupt the testes environment, lowering the acceptance of SSC transplantation and leading to therapeutic collapse [57].

Ovarian stem cells (OSC)

The discovery of the frequency of follicular atresia, the mortality of oocytes, and the degradation of ovarian function in mice led to the notion of OSCs. These actively reproducing cells were identified by Johnson *et al*. [58] depending on their ability to integrate 5-bromode-oxyuridine and the development of germ-cell detail related, MVH (mouse vasa homolog). Such mitotically active cells might promote follicle creation in the ovaries of mice in previous investigations [58]. A further study related FACs for the extraction of OSCs from the human ovarian cortex by using the stem-cell-specific marker VASA expression. Results show that after these cells were xenotransplanted into diabetic immunocompromised mice, they were able to improve follicle results [59]. The discovery of these cells defies the convention that only females are capable of prenatal folliculogenesis [60]. However, these cells have remained unidentified for a long time, owing to their small quantity, which accounts for 0.0145% of the total cell population in the mouse ovary, which falls with age. Furthermore, as contrasted to their male counterparts, these cells take a long time to differentiate *in vitro* [61]. According to recent work on the isolation of OSCs from elderly mice and subsequent folliculogenesis after transplantation in young mice [62], the use of OSCs may provide new hope to patients suffering from idiopathic fertility problems.

In age-related infertility and premature ovarian in pediatric trauma survivors during chemotherapy, OSCs restore fertility and give birth to live children [40,63].

MSCs were derived from various sources for the therapy

Endometrial stem cells (EndSCs)

Endometrial stem cells were first identified by Prianishnikov *et al*., through which the isolation of stem cells from endometrial tissues was then performed by Chan *et al*. [64,65]. Subsequently, based on other revealed indicators, they identified and cultivated MSCs from human endometrium and hypothesized the role in endometriosis and endometrial cancer [66]. The expression of CD44, CD73, and CD90 and the lack of CD34 and CD45 phenotypes distinguished stromal cells from epithelial progenitor cells, although SSEA1, N-cadherin, and NTDPase2 activity distinguished epithelial progenitor cells. Endothelial stem cells demonstrated the existence of a typical phenotype such as CD 31 and CD 34 [67–69].

In the presence of inflammation or endometrial injury, these stem cells were guided to the wounded location via communication among chemokines and CXCR4, which is observed on stem cells, and CXCL12, which is provided by endometrial tissue epithelium [70]. Endometrial stem cells result in the formation of cells such as endometrial regenerative cells (ERCs), epithelial stem cells, MSCs, and endometrial side population cells (ESPs) that support endometrium renewal [71]. ESPs comprise 5% of EndSCs and are mostly seen during the menstrual cycle's proliferative phase [72]. MSCs and other ERCs may differentiate into various tissues, including bones, AD, cartilage, and neural tissue [73]. In comparison with MSCs, they can effectively promote immunological modulation, angiogenesis, and the generation of matrix metalloproteinases. The preservation of several phases of reproduction, such as the growth of the endometrium, needs adequate blood circulation in the uterus [74]. In an animal transplantation system, poor neovascularization causes endometrial decreases, which is likely linked to the decreased discharge of vascular endothelial growth agents [75]. As a result, endometrial stem cells' angiogenic properties might be implicated in reproductive medicine's curative transplantation for endometrial regeneration, and menstrual blood can also be used to create endometrial stem cells (Fig. 3).

Endometrial stem cells have been studied in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced form of Parkinson's disease [76] and animal models of insulin resistance [77] to see if they may restore the release of dopamine [67,71].

Umbilical cord MSCs (UC-MSCs)

CD29, CD44, CD73, CD90, and CD105 expression was found in Wharton's jelly of umbilical-cord-derived MSCs, but CD31, CD45, and HLA-DR85 were not. Correspondingly [78], UC-MSCs have been widely used for cell-based treatment method for restoring fertility because of their low tumorigenicity, rapid self-renewal capability devoted to diverse mesodermal cell types, simple access to regularly-damaged resources, minimal ethical problems, and low immunogenicity [56]. Importantly, UC-MSCs repair ovarian reserve in multiple animal studies of early ovarian dysfunction by

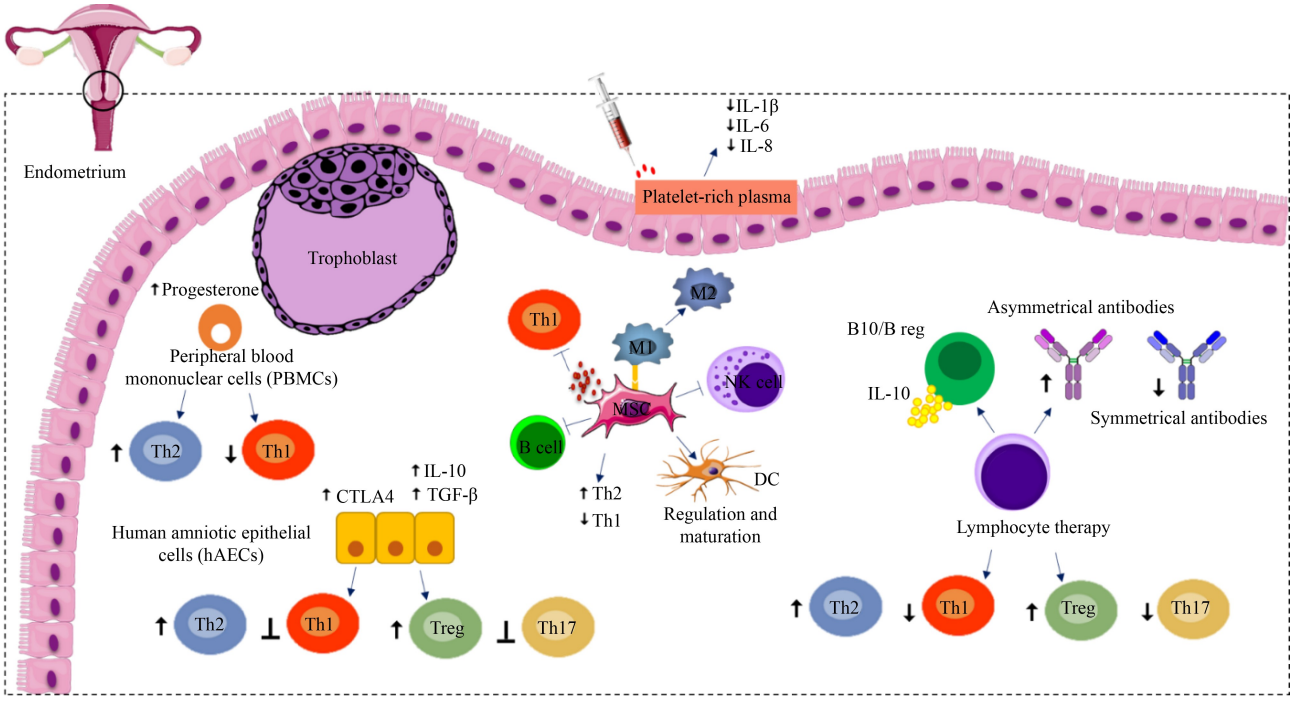

Fig. 3 In this picture, the involvement of peripheral blood mononuclear cells and human amniotic epithelial cells are shown with another cellular.

antiapoptotic action toward granulosa cells and hormone regulation, such as lowering FSH levels while increasing estrogen and progesterone rates [79,80]. By altering ovarian surface epithelium stability, inflecting the expression of cyto keratin 8/18, TGF-β, and proliferating cell nuclear antigen (PCNA), which are significant controls of follicular synthesis and the antiapoptotic activity of UC-MSCs, UC-MSCs could recover ovarian purpose in paclitaxel-induced ovarian dysfunction [81]. UC-MSCs help revive infertility in experimental rats of PCOS produced by dehydroepiandrosterone by inactivating proinflammatory cytokines such as IL-1, tumor necrosis factor-alpha (TNFα), and interferon-gamma (IFN-γ). The favorable effect of UC-MSCs on improving fertility could be associated with various signaling mechanisms. UC-MSCs stimulate the mitogen-activated protein kinase, G protein-coupled receptor, and insulin signaling pathways to inhibit granulosa cell death and increase fertility [82]. Endometrial cells can be formed from UC-MSCs [83]. UC-MSCs increase and decrease vascular and inflammatory markers, respectively, to repair fertility in an experimental animal of injured endometrium [84]. Conversely, in an experimentally induced uterine damage, UC-MSCs transplantation on a collagen scaffold might restore fertility by activating matrix metalloproteinase 9 [85]. The stimulation of primordial follicles via phosphorylation of transcription factors forkhead box protein O3a (FOXO3a) and FOXO1 by UC-MSCs on a collagen scaffold could improve ovarian treatment in patients with premature ovulatory failure (POF), as evidenced by an increase in follicle count [86]. Wharton's jelly-derived MSC could increase the proliferation and reduce the apoptosis of mifepristone-induced destruction in endometrium obtained from women undergoing hysterectomy, according to Yang *et al*. [87], by upregulating VEGF expression and downregulating caspase 3 and 8 [87]. The effectiveness and safety of intramuscular injection of UC-MSCs have been widely studied for the therapies of uterine scars induced by cesarean section in a single-center, prospective, randomly selected double-blind, and placebo-controlled phase II clinical trial.

Amniotic fluid stem cells (AFSCs)

The amniotic fluid, which results in sustenance to the fetus, also provides a source of MSCs. The potential of AFSCs to differentiate into various cell types including adipocytes, osteocytes, and muscle, and their potential systemic immune capabilities make them ideal for regenerative medicine. Therefore, AFSCs have beneficial benefit in muscle and bone problems in various animal investigations [88,89]. AFSCs can help with infertility by restoring ovarian function through the activation of numerous signaling molecules, including VEGF, TGF, EGF, and morphogenic protein (BMP) [82]. AFSCs, particularly those with CD4C/CD105^{+} markers, inhibit follicular atresia, restore viable oocytes, and consequently

preserve ovarian purpose in a mouse model of POF caused by chemotherapy [90,91].

Adipose-tissue-derived stem cells (ADMSC)

ADMSCs are a new form of MSC with biological features that are virtually identical to MSC produced from those other origins, but with greater benefits than BMSCs, since such tissues can be harvested with less invasive techniques and in bigger quantities [92]. As a result, they are frequently employed in reparative therapy for a wide range of clinical diseases. The effect of ADMSCs on ovarian grafts has been studied in a female animal model, and the results show that ADMSCs recovered ovarian use more quickly by increasing VEGF gene expression and encouraging angiogenesis in the transplanted tissue [93]. Across neovascularization and advancement of ovarian follicular proliferation, ADMSCs can recover ovarian function in an animal model of chemotherapy-induced ovarian destruction [94]. Inside an ovarian failure rat model, treatment of ADMSCs on a collagen scaffold resulted in improved ADMSC retention, resulting in a longer recovery of ovarian function and a higher conception rate relative to ADMSC injection [94]. ADMSCs, in mixture with hormonal treatment, succeeded in reducing fibrosis and induced endometrial restoration in an animal experiment of Asherman syndrome [95].

Amnion-derived MSCs (AmDMSCs)

In reproductive medicine, the amnion is a potential resource for cell-based treatment. Numerous investigations [96,97] have established the therapeutic effect of ADMSCs on an ovarian malfunction in chemotherapy-induced animal studies of POF. Considerably, AmDMSCs help preserve ovarian function by reducing apoptosis and enhancing granulosa cell proliferation and neovascularization in the external environment via paracrine processes. Furthermore, AmDMSC therapy works by inactivating the cytokines IL-1, IL-6, and TNF, which suppress inflammation. Human ADMSCs become much more effective in the recovery of ovarian function in a rat model of POF following therapy by using low-intensity pulsed ultrasound, according to Ling *et al*. [110].

Placenta-derived MSCs (PDMSCs)

PDMSCs have beneficial effects on folliculogenesis by modulating cytokines and different hormone production, including AMH, FSH, estradiol, and LH, and their receptors' expression, according to several types of research done on an experimental animal of POF [84,98]. However, Li *et al*. [99] found that PDMSC alleviates ovarian insufficiency by involving the inositol-requiring enzyme 1 (IRE1) signaling pathway. PDMSCs are successful in 3D spheroid formation to achieve their restorative activity in ovariectomized rats, according to Kim *et al*. [100]. PDMSC differentiation may be influenced by the overexpression of miR222 [101].

Menstrual blood MSC (MB-MSC)

MSCs generated from menstrual blood (MB-MSCs) can multiply and differentiate into numerous lineages and self-renew. In addition, unlike other tissue-derived stem cells, the collection of these cells is non-invasive, safe, and simple, with few ethical concerns and minor immunological responses, making them suitable for clinical use in reproductive medicine. In an animal model, Liu *et al*. investigated the effects of MB-MSCs on cyclophosphamide-induced premature ovarian failure (POF). They discovered that when MB-MSC-treated rats were assessed to normal control, the number of regular ovarian follicles and the recovery of normal ovarian function increased as evidenced by the increased levels of ovarian hormones such as estradiol, antimullerian hormone, and inhibin. Researchers tested the busulfan-induced rat model of POF in the same way. They found that MB-MSC enhanced ovarian function by localizing MSCs into granulosa cells and increasing the expression of FSH receptors along with resting the ovary [102]. MSC generated from menstrual blood restored fertility in an animal model of injured endometrium by inducing angiogenesis and releasing anti-inflammatory mediators [103]. During the first period, Zheng *et al*. [104] demonstrated a theoretical foundation for the use of MB-MSCs in intrauterine adhesion therapy. In the laboratory, MB-MSCs could develop into endometrial cells, and the transplantation of these cells into NOD-SCID animals led to endometrium restoration. The inclusion of the OCT-4 transcription factor contributes to the differentiating potential of MB-MSCs. Zhang *et al*. [105] found that MB-MSCs combined with platelet-rich plasma could effectively restore fertility in mechanically injured experimental rats of intrauterine adhesion by significantly modulating the Hippo signaling pathway and its downstream regulators, including CTGF, Wnt5a, and Gdf5 [105].

Furthermore, by upregulating cyclin B1 and CDC2 protein levels and downregulating Gadd45b protein levels, MB-MSCs might ameliorate epirubicin (broad-spectrum anti-cancer drug)-induced ovarian destruction and thereby boost granulosa cell proliferation [106]. Tan *et al*. [107] noted on patients diagnosed with conferring resistance Asherman syndrome who were managed with MB-MSC transplantation accompanied by hormone treatment; five of these clinical cases resulted in an endometrial thickness of 7 mm, one of these 5 patients thought up spontaneously, and two of these seven patients

construed since assisted reproduction innovation [106]. The downregulated expression of OCT-4 in MB-MSCs derived from individuals with severe intrauterine adhesion [104] supports the involvement of the OCT-4 transcription factor in MSC development found in animals [104].

Bone marrow MSCs (BMSC)

MSCs were isolated from bone marrow by using density gradient separation and then cultured in a growth medium for development since they were first documented in 1988 by Owen and Friedenstein [108]. In experimental rats, these BMSCs are devoted to the formation of endometrial and follicular cells in addition to mesodermal lineages [109,110].

Jing *et al*. used an experimental rat model to determine whether BMSCs may help in endometrial regeneration. They used rat tail intravenous injection to transplant BMSCs and observed a substantial increase in endometrial thickness and the expression of markers, including integrin 3, cytokeratin, leukemia inhibitor factor, and vimentin. The upregulation of anti-inflammatory cytokines such as fibroblast growth factor (bFGF) and interleukin-6 (IL-6) and the downregulation of proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) were likely responsible for BMSCs' beneficial effect [111]. Wang *et al.* [112] later acknowledged the medical applications of BMSCs in endometrial healing in 2016. Intrauterine adhesion was generated by mechanical damage in an experimental model, and BMSCs were administered either by a tail vein or directly into the uterus. Despite the elevation of estrogen and progesterone receptor expression, BMSCs could successfully cure endometrial damage in both situations, as demonstrated by the increase in the size of endometrial glands and the reduction in the fibrotic area [112]. Chemotherapy for cancer patients kills cancer cells and causes the death of granulosa cells, which are responsible for supplying sustenance to eggs through the production of estrogen and other paracrine hormones, resulting in ovarian failure. In a rabbit model of cyclophosphamide-mediated ovarian dysfunction, Abd-Allah *et al*. reported the therapeutic use of BMSCs in 2013 and investigated the underlying principle. They found that intravenous injection of BMSCs restored the shape and role of ovarian follicles by lowering FSH and increasing estrogen and VEGF levels. In 2017, Badawy carried out a comparative research on a white mouse model and found that 21 days after BMSC treatment, hormone levels recovered, and conception was observed in infertile mice. In a potential, experimental pilot testing on patients with Asherman syndrome/endometrial atrophy, Santamaria *et al*. [113] found that injecting $CD133^+$ BMSCs into the spiral arterioles of recruitment of new patients improved endometrial thickness, the intensity of matured blood vessels, and the nature of infertile patients' menstrual period. Furthermore, 10 of the 16 patients conceived naturally or after embryo transfer [113]. Therefore, BMSCs may give fresh chance for biological offspring in situations of ovarian or uterine failure.

Application of stem cell therapy in disease therapy

Azoospermia

Azoospermia, or the lack of mature, morphologically normal, and functioning sperm in the ejaculate, is responsible for approximately 15% of infertility caused exclusively by male causes [114]. Obstructive azoospermia (OA) and non-obstructive azoospermia (NOA) can be distinguished based on the patient's medical history, genetic analysis, extensive thorough physical, and hormone assay. Surgical treatment can be used for the treatment of OA. However, NOA results in testicular failure, which could be caused by pathology primarily in the testis or secondary to the decreased release of gonadotropin from the pituitary. In the case of NOA, the success rate of ART by intracytoplasmic injection is very poor because of the difficulty in retrieving functional sperm. Stem cell therapy can provide the opportunity of having biologically-related offspring to NOA patients [115].

Considering the self-renewal capabilities of spermatogonial stem cells (SSCs), they can develop into haploid spermatids and then mature into spermatozoa, thus boosting spermatogenesis to address this commonality of male infertility [116]. During the first period, Brinster and Zimmerman [117] demonstrated that SSCs could improve fertility in a mouse model [117]. Later, Hermann *et al*. [52] revealed that SSCs injected into the rete testes of pre-pubertal rhesus monkeys grow into mature spermatozoa in tandem with the monkey's maturity; the spermatozoa are detectable in the ejaculate and may fertilize [52]. However, considering the difficulties in identifying SSCs in the testes, the absence of an appropriate culture and maintenance technique for SSCs, and safety issues for patients after transplantation, SSC transplantation could not be repeated in people [115]. In addition to SSCs, embryonic and adult stem cells can develop into germ cells [24] and fertilize in laboratory animals [118,119]. Furthermore, in the case of hESCs, ethical issues and the teratogenicity of iPSCs limit their medicinal utility [24].

Several clinical studies involving the injection of bone-marrow-derived MSCs into the rete testis of azoospermia patients have been conducted or are now underway to

measure the levels of hormones, testicular size, and sexual potency.

Polycystic ovarian syndrome (PCOS)

Rotterdam used two criteria to diagnose PCOS, which is a gynecological illness of reproductive-aged women caused by the following hormonal imbalance, presence of high levels of androgens, and ovulatory failure, or polycystic ovaries. Abnormal hair development on the body, irregular menstruation, infertility/subfertility, and obesity are all symptoms of PCOS [120]. Correspondingly, miR-320 regulates ovarian steroidogenesis by targeting E2F1 and SF-1 [98]. For the recovery of regular menstruation and fertility, hormonal contraceptives and clomiphene citrate are the first-line treatments [120]. The prospective involvement of stem cells for the treatment of PCOS symptoms has been established in various animal settings. MSCs suppress inflammation via the production of anti-inflammatory cytokines, which attenuate DHEA-mediated PCOS in mouse [78] and human theca cells from PCOS patients [121]. In a drug-induced mouse model of PCOS, Igboeli and colleagues [122] demonstrated that hMSCs may reverse and recommence the estrus cycle.

Endometriosis

Endometriosis is an estrogen-dependent complicated illness that affects pregnant women. Accordingly, approximately 10% of females have endometriosis, and roughly 50% of those who have endometriosis have difficulty conceiving [123]. The fertility rate in couples with endometriosis is much lower than that in normal fertile couples based on the Practice Committee of the American Society for Reproductive Medicine [124]. Retrograde menstruation, metastatic spread, coelomic metaplasia modified stem cells, immunology, and genetics are among the leading theories for endometriosis etiology [125]. Endometriosis, with its inflammatory response and elevated cytokine release, may influence fertility by altering ovum formation, gamete transit via tubal obstruction, and endometrial growth via regulation of the Wnt pathway [126].

Remarkably, the treatment of infertile couples with endometriosis with a GnRH agonist accompanied by IVF with or without ICSI improved pregnancy rates considerably [127]. However, later research by Benschop *et al*. [128] observed no clear improvement in infertility when hormone treatment was first administered. Surgical treatment alone or in combination with medical treatment showed different responses. Current scientific findings in both human and animal models have shown that the use of stem-cell-based treatment for the restoration of fertility in endometriosis patients can be effective [125].

Premature ovarian insufficiency (POI)

POI is a medical and biological factor that contributes to infertility. POI is diagnosed by "oligo/amenorrhea for at least 4 months and an increased FSH level > 25 IU/L on two occasions > 4 weeks apart," based on the European Society of Human Reproduction and Embryology (ESHRE) standards [129]. POI affects approximately 1% of women of reproductive age (under 40 years), whereas the frequency is roughly 0.1% in women below the age of 30 years and 0.001% in women below the age of 20 years. Hypoestrogenism can have varying degrees of effect on the affected person's physical and mental health. Nonetheless, in some circumstances, cryopreservation of oocytes before gonadotoxic therapy has been used to restore fertility. Ovarian vitrification is accompanied by *in vitro* activation by stimulation of the AKT pathway, followed by re-transplantation, which can retain fertility in patients with POI [130]. Furthermore, the effective demonstration of ovarian stem cells in both preclinical animal and human models may usher in a change in the possible therapy for infertility repair in POI patients [58]. Therefore, MSC stem cell therapy can be used in female reproductive problems (Table 3).

Asherman syndrome (AS)

In 1950, Joseph Asherman was the first to report a gynecologic condition, in which a women had amenorrhea after a uterine cavity injury. Infertility, repeat abortion, and persistent pelvic discomfort with amenorrhea are all symptoms of Asherman syndrome (AS), which is defined by intrauterine adhesion and partial or full obliteration of the uterine cavity [131]. AS is caused by postpartum curettage in 90% of patients [132]. Three-dimensional ultrasonography, magnetic resonance imaging, hysterosalpingography, and hysteroscopy are some diagnostic options for this condition, and hysteroscopy is the gold standard. Preservation of the uterine cavity with hysteroscopic adhesiolysis and replacement of normal endometrial lining with hormonal treatment are two therapies for infertility caused by AS [133,134]. The surgical excision of AS has already been linked to several obstetric problems, including premature birth [135].

Consequently, the use of stem cell therapy for the treatment of AS has been investigated. In animal models [95] and clinical investigations [151], the use of stem cells obtained from bone marrow [136], autologous menstrual blood [107], and MSCs [137] for endometrial replenishment has been studied. In an animal model of injured endometrium, endometrial MSCs generated from menstrual blood increased fertility [103]. After transplantation of menstrual-blood-derived stem cells, women with AS were able to achieve regular

Table 3 MSC therapy is being used to improve female reproductive problems

MSC kinds		Model	Cause	Therapy	Results	Reference
MB-MSCs	Endometrial disorders	Human	Severe aortic stenosis (AS)	Provide via the cervix to the fundus of the uterus	↑ Endometrial thickness (EMT)	[282]
		Rat	Intrauterine adhesion (IUA) is caused by mechanical injury	Local injection	↑ Pregnancy rate	[79]
	Ovarian failure	Mice	Cisplatin-induced POF	Local injection	↑ Fibroblast growth factor 2 ↑ Ovarian role	[283]
		Mice	CTX-induced POF	Local injection	↓Hormone secretion ↑Ovarian weight	[102]
Bone marrow stromal cells	Endometrial disorders	Human	Refractory aortic stenosis (AS)	Uterine artery injection	Rebuild the endometrium	[113]
		Mice	24-gauge needle-caused	Marked with SPIOs local/tail vein injection	↑Endometrial proliferation	[284]
	Ovarian failure	Mice	CTX-induced ovarian disorders	Local injection	Repair ovarian hormone exposition	[285]
		Rabbit	CTX-induced ovarian disorders	Intravenous injection	↑Ovarian role	[286]
UC-MSCs	Endometrial disorders	Human	Uterine niche	Local intramuscular injection	↑ Uterine scar rebuilds ↓Uterine niche occurrence	[287]
		Rat	95% ethanol-induced endometrial injury	Tail vein injection	↓ Endometrial fibrosis ↑ Fertility and angiogenesis	[84]
	Endometrial disorders	Rat	Perimenopausal ovary	Tail vein injection	↓ Follicle-exciting hormone ↑ Estradiol and follicle number	[288]
		Rat	Paclitaxel-induced POF	Local injection	↓ Follicle-exciting hormone ↑ Estradiol and ovarian role	[81]
		Mice	Busulfan CTX-induced primary ovarian failure	Local injection	↑ Ovarian role and fertility	[79]
		Mice	CTX-induced POF	Tail vein injection	↑Estradiol, weight of the ovaries	[289]
Adipose-derived stem cells	Endometrial disorders	Rat	Trichloroacetic acid-induced aortic stenosis (AS)	Intraperitoneal injection	↑Endometrial proliferation ↓Fibrosis	[290]
	Ovarian failure	Rat	TG-induced ovarian injury	Collagen scaffold	↑Fertility	[291]
		Mice	Cisplatin-cause ovarian disorder	Local injection	↑Ovarian role	[292]

menstruation [138] and endometrial regeneration [107].

Therapeutic performance of MSC-derived extracellular vesicles in reproductive diseases therapy

Adult stem cells called MSCs can be extracted from various tissues, including endometrial tissue, bone marrow, AD, menstrual blood, and UC [139]. MSCs have emerged as promising candidates for cell therapy in regenerative medicine because of their propensity for self-renewal and differentiation [140,141]. MSCs are effective in a range of illnesses, including diabetes, female reproductive abnormalities, cardiovascular disorders, renal fibrosis, and neurological diseases [142,143], in both preclinical and clinical investigations. Nevertheless, stem cell treatment may cause several drawbacks, such as inconvenient transportation or storage, marketing challenges, transplant rejection, and safety concerns if necessary monitoring tests are not performed [144,145]. EVs are lipid bilayer particles that are released from cells into the milieu and act as messengers by transporting various payloads, including microRNAs, proteins, cytokines, and lipids [146,147]. In comparison with MSCs, MSC generated extracellular vesicles (MSC-EVs) have identical functionalities to the parent cells and have greater biological stability and reduced immunogenicity [148,149]. MSC-EVs have great prospects in the reproductive treatment of different disorders and diseases, including IUA, PCOS, and POI. Remarkably, the therapeutic performances comprise immunomodulation, pro-angiogenesis, anti-oxidative stress, and anti-fibrosis. Accordingly, many studies have acknowledged the efficacy of MSC-EVs in developing female fertility for *in vitro* and *in vivo* cases, like influences before the utilization of MSC-EVs clinically [149].

Extracellular vesicles from MSC

Similar to almost all other cell types, MSCs may produce EVs [150]. Exosomes (50–150 nm), apoptotic bodies (500–5000 nm), and microvesicles (100–1000 nm) are the three kinds of EVs [151]. These subtypes have slightly

different biogenesis mechanisms. Overall, endocytosis and exocytosis report for the biogenesis of most exosomes, initial endosomes can be established in endocytosis of plasma membrane, late endosomes can develop into multivesicular bodies (MVBs) filled with intraluminal vesicles (ILVs) after inward budding of endosomal membrane, and MVBs discharge ILVs upon fusion with the cell membrane, which is influenced by endo [152,153]. The production of MVs is very straightforward; it involves direct budding from the cellular membranes [154]. Exosomes originate from cell membrane protrusions [152,153]. As a result, more research into the process of EV biogenesis is required. Exosomes and MVs have different biogenesis, indicating that their chemical contents and activities also differ [155]. Phinney *et al*. suggested that mitochondria may be delivered to macrophages via MVs rather than exosomes to improve mitochondrial bioenergetics [155]. Consequently, in terms of the therapy of female reproductive problems, the biological components of exosomes and MVs could alter these merits (Fig. 4).

Therapeutic effects of MSC-EVS in reproductive diseases

POI

POI is described as ovarian senescence in women under the age of 40 years, which is defined by amenorrhea or oligomenorrhea for at least 4 months, an increased FSH level (25 IU/L), and fluctuant estradiol (E2) [156,129]. It affects approximately 1% of women under the age of 40 years, resulting in poor infertility results and putting a strain on young couples [156,157]. Aberrant immunity, genetic abnormalities, environmental toxins, and chemotherapy or radiation may cause POI [158,159]. Considering that primordial follicles cannot be produced and the ovarian reservoir is defined at birth, ovarian function can be readily jeopardized by fast activation of primordial follicles, ovarian follicle depletion in the resting pool, and aberrant follicular atresia [160].

The X chromosome and several genes are required for follicle formation and expansion [161,162]. Inactivation of the SMC1B, or REC8 genes, STAG3 involved in meiosis causes oocyte arrest with POI [163,164]. Accordingly, Jaillard *et al*. presented novel candidate POI genes such as NRIP1, XPO1, and MACF1 via whole exome sequencing (WES) study [165]. A single causal component is hard to determine, because numerous genes interact in complex ways during folliculogenesis [160]. Aside from gene mutation, aberrant epigenetic alteration may also participate in atresia follicle growth [166]. As a result, abnormal gene expression or control in women can disrupt folliculogenesis and cause follicular atresia, which might progress to POI.

Signaling pathways including the TGF-β, PI3K/AKT/mTOR, and Hippo pathways play important roles in follicular growth [167,168]. Grosbois *et al*. discovered the synergistic effect of the PI3K/AKT and Hippo signaling pathways, in which primordial follicle recruitment was increased, resulting in fast follicle exhaustion [168]. The overexpression of AKT/mTOR

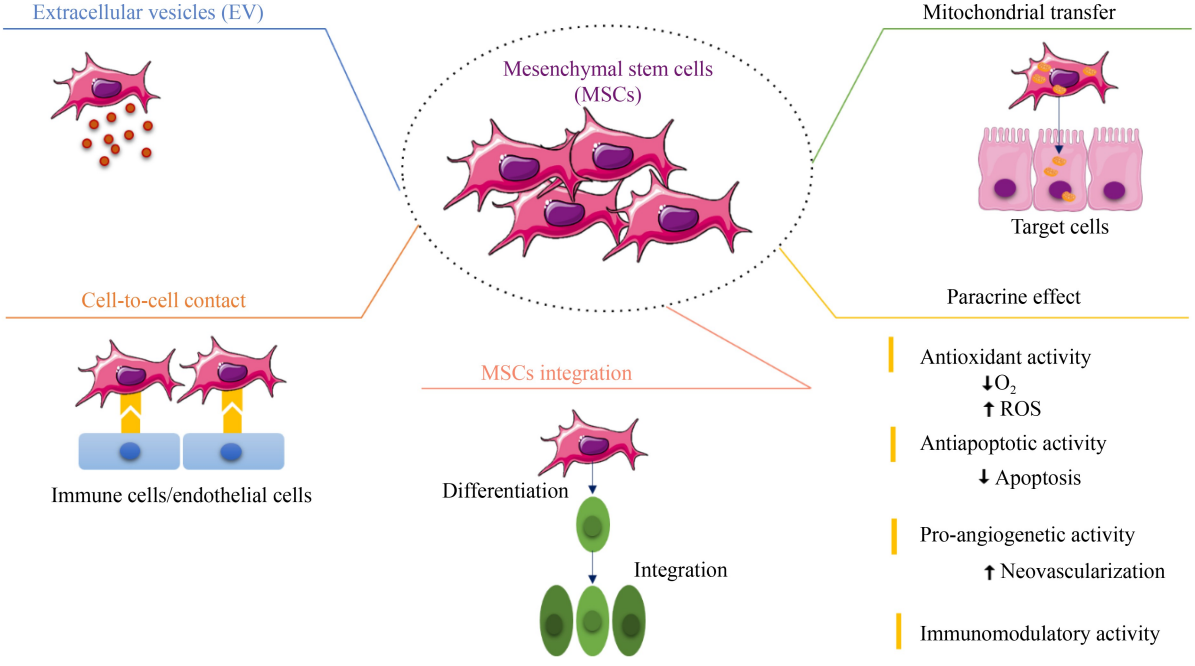

Fig. 4 Associations of extracellular vesicles and mesenchymal transfer in contraction with MSCs.

could be induced by abnormal PI3K pathway activation, whereas the dephosphorylation of YAP/TAZ could be induced by disrupting the Hippo pathway; both processes lead to huge and premature development of primordial follicles [168]. The suppression of the PI3K/AKT pathway by depleting protein kinase Ck2 resulted in large follicular atresia in mice ovaries, demonstrating the need for a balanced PI3K/AKT system. Follicular atresia was also increased by an excessive autoimmune or inflammatory response [156,169]. Follicular atresia, for example, arises when GCs are continuously exposed to proinflammatory cytokines such as IFN-γ [170]. Additional conditions, such as an infinite quantity of certain chemotherapeutics, environmental contaminants, and reactive oxygen species (ROS), may also contribute to follicular atresia or depletion [159,160,171]. The actual cause of decreased ovarian function is unknown, and the convoluted pathological process of the disease makes it difficult to cure. In POI animal models, MSC-EVs can salvage GC viability, decrease ROS levels, and repair follicular count [172–175]. AFMSC-EVs rescue ovarian follicles from chemotherapy-induced gonadotoxicity. In chemotherapeutics-treated mice, miR-10a, a significantly abundant miRNA in AFMSC-EVs, increased the resistance to GC apoptosis or follicular atresia [176]. Sun *et al*. then discovered that UCMSC-EVs decrease cisplatin-induced GC apoptosis *in vitro* [177]. Furthermore, in a mouse study, UCMSC-MVs-treated groups had greater levels of AKT, P-AKT, VEGF, and IGF than non-treated POI groups, indicating that UCMSCMVs may stimulate angiogenesis and activate the PI3K/AKT signaling pathway in the ovaries [174]. Accordingly, PTEN, which negatively regulates the PI3K/AKT pathway, was downregulated in POI rat models following injection of BMSC-EVs or AFMSC-EVs [178,179], indicating that MSC-EVs may reduce GC apoptosis via the PTEN-PI3K pathway. Furthermore, MSCEVs decreased SIRT families and P53 to prevent GC apoptosis, which is triggered by cisplatin or cyclophosphamide (CTX) [86,180,181]. Huang *et al*. discovered that ADSC-Exo controlled the SMAD signaling pathway and saved GCs from apoptosis via mRNA and protein assays [172].

MSC-EVs also enhanced the outcomes of offspring in POI models [182]. In this study, Liu *et al*. discovered that POI mice in the UCMSC-EV transplantation group had better fertility, shorter time to pregnancy, and more offspring than the POI mice. Furthermore, the Y-maze test and new object identification task revealed that their kids had substantially identical cognitive characteristics. MSCEVs boost the fertility of POI mice without adversely affecting their offspring's cognitive functioning [182].

Likewise, the therapeutic use of MSC-EVs in POI women is still in its early stages. The mechanism in which MSC-therapeutic EV affects POI remains unknown, thus requiring additional investigation. The therapeutic properties of MSC-EVs could not be fully extrapolated to human patients based on animal models with abdomen injections. A medical experiment recently indicated that MSCs based on collagen scaffold (CS) were transplanted into the ovaries of POI patients via a retrograde injection approach, implying that CS/MSC-EVs might also be transmitted via intra-ovarian injection [86]. However, the method's safety and effectiveness have not been determined. Remarkably, when murine embryos were exposed to endometrial MSCs (endMSC)-EVs, Blazquez *et al*. found high blastomere count and hatching rate [183,184]. EndMSC-EVs increase the success of *in vitro* fertilization in an elderly mouse model [185]. In POI patients, IVF-embryo transfer (IVF-ET) is commonly used for supported conception [172]. Although the safety of children must be investigated, the combination of IVF-ET with MSC-EVs might be a novel strategy for assisting POI patients in conceiving.

PCOS

PCOS is a prevalent reproductive endocrine illness marked by hyperandrogenism, ovulatory failure, polycystic ovarian morphology, overweight, and insulin levels that affect 5%–20% of reproductive-age women [183,186]. The core of PCOS is hyperandrogenism [187,188]. Androgen abundance stimulates tiny antral follicle development and early luteinization, inhibiting dominant follicle selection and thus impairing ovulation [187,188]. For women with PCOS, anovulatory infertility is a severe difficulty, and support and facilitating procedures are considered the last choice for conceiving [189]. *In vitro* maturation procedure focused on heterologous follicular fluid and GCs supernatant (HFF/GC-IVM protocol) was recently discovered to increase the maturity rate of immature denuded oocytes, fertilization rate, and hatched blastocyst level [190]. Conversely, ADSC-EVs prevent apoptosis and boost proliferation in PCOS patients' cumulus cells (CCs), whereas increased expression of miR-323-3p plays a role in exosomes [191]. Even so, a few cases of MSC-EVs are being used for PCOS treatment.

IUA

The destruction of the uterine basalis layer and subsequent obliteration of the endometrium by fibrous structures define IUA, often referred to as Asherman syndrome (AS) [192]. Reduced menstrual flow, repeated fetal death, abnormal placental implantation, and infertility are all symptoms of IUA [193]. Furthermore, the endometrium of individuals with repeated IUA is

frequently thin, resulting in thin endometrial (TE) [194]. Chronic endometritis, retained placenta, artificial abortion, and curettage are possible causes of this syndrome, and they disrupt the uterine environment's balance [195]. Endometrial fibrosis participates in the onset and development of IUA [196]. The damaged endometrium cannot be healed naturally, which can cause immunological activation and inflammation and an overabundance of extracellular matrix (ECM) protein [196,197]. As a result, chronic inflammatory irritation encourages the creation of abnormal avascular fibrotic regions, resulting in tissue hypoxia and obstructing endometrial healing [197].

The amplification of the transforming growth factor-β1 (TGF-β1)/Smad3 signaling pathway has been implicated in the development of IUA in several investigations [198]. Considerably, NF-κB, an inflammatory marker, has been considered a risk factor for IUA [199]. TGF-β and connective tissue growth factor-2 (CTGF/CCN2) expression levels were linked positively to NF-κB pathway activity in the endometrium of IUA subjects, according to Xue *et al*., and TGF-β transcription was reduced after suppressing the NF-κB signaling system [200]. Importantly, an abnormally active Wnt/b-catenin pathway stimulates TGF-β-mediated fibrosis and mediates fibrogenesis in the endometrium [201,202]. FOXF2 protein enhances fibrogenesis in the IUA by activating the Wnt/β-catenin pathway and upregulating collagen type V alpha 2 (COL5A2) transcription in the endometrium [203,204]. As a result, the interaction of several proteins or signaling pathways plays an important role in the pathogenesis of IUA.

Fibroblasts, stromal cells, mast cells, smooth muscle cells, endothelial cells, M1 macrophages, and T cells were identified in the bioinformatic investigation of the uterus [205]. Identifying intercellular connections and cellular transdifferentiation might help researchers truly understand the pathophysiology of IUA and identify new therapy options. For example, a heatmap in this study revealed a significant level of contact between endothelial cells and fibroblasts or stromal cells, indicating that communication may be crucial in the evolution of IUA. Notably, the epithelial-to-mesenchymal transition (EMT) is critical for the evolution of IUA [201]. NUS1 protein overexpression increases EMT by modulating the AKT/NF-κB pathway, which may be inhibited by microRNA (miR)-466, according to research by using IUA rat models [206]. Moreover, miR-1291 increases endometrial fibrosis by inhibiting ArhGAP29 and upregulating the RhoA/ROCK1 pathway, and this process is also involved in EMT [207]. Furthermore, the Hippo/TAZ signaling pathway adversely influences the EMT process to some extend [201]. In this case, the activation of the Hippo pathway results in phosphorylated TAZ, thus inhibiting the EMT process [201]. Zhu *et al*. also discovered that the Hippo system, which would be activated by menstrual blood-derived stem cells (MenSCs), would block TGF-β-mediated stimulation of endometrial stromal cells (ESCs) and myofibroblast phenotypes [208]. Overall, AS needs to be treated by managing the phenotypic alternation in the endometrium, which is implicated in the pathological changes of IUA.

In animal and *in vitro* research, the effects of MSC-EVs on AS have been studied [209–211]. In rat IUA models, Yao *et al*. discovered that BMSC-EVs increase endometrial glands, reduce fibrotic area, and even reverse EMT [212]. The injection of BMSCs-EVs decrease vimentin (VIM) levels while increasing cytokeratin (CK) 19 levels. Similarly, TGF-β1, TGF-β1R, and Smad2 expression were reduced in the intervention group, demonstrating that BMSC-EVs would heal endometrium by suppressing the TGF-β1/Smad2 signaling pathway [122]. Saribas *et al*. found that injecting uterus-derived MSC (uMSC)–EVs into the uterine cavity increased angiogenesis in IUA rats by boosting the expression of vascular markers CD31 and VEGFR1 [213]. UCMSC-EVs boosted rat TE restoration by overexpressing VEGF, Bcl-2 levels, and lowering fibrosis area, accordingly, indicating that MSCEVs might improve endometrial regeneration [214]. MSC-EVs may also stymie IUA progression by suppressing inflammation. UCMSC-EVs suppress the inflammatory factors interleukin (IL)-1b, IL-6, and TNF-α while increasing the anti-inflammatory factor IL-10 [210]. The above research examined the implantation and conception outcomes to fertility reserve. The findings demonstrate that UCMSC-EVs might enhance these two numbers in IUA rats, implying that UCMSC-EVs could be useful in resolving infertility in patients with IUA [210]. Therefore, MSCEVs can be used for the treatment of AS by improving endometrial health, slowing the fibrosis stage, increasing angiogenesis, and acting as an immunomodulator. Generally, the feature of stem cells as a main therapeutic category in infertility is indicated in Table 4.

Role of personalized medicine in reproductive diseases

Personalized medicine was initially coined in the field of genetics more than a decade ago, and it is a desired therapeutic outcome of human genome sequencing. Personalized medicine relates to the capability to design medication based on molecular information to analyze disease patterns and diagnose disease. It also aims to effectively tune prevention and treatment interventions with less side effects. Personalized medicine has numerous definitions in this context. Precision medicine, which is described as the classification of patients with a

Table 4 Stem cell features in infertility therapy

	Nature of cells	Immuno-rejection	Self-renewal capacity	Source of generation	Clinical applications	Ethical concerns
Mesenchymal stem cells	Multipotent	No	Mesodermal-derived tissue, like adipose tissue, muscle, cartilage, bone	Human somatic cells	Widely utilized	No ethical or moral concerns
Embryonic stem cells	Pluripotent	Yes	Differentiate into results of main germ layers	Inner cell mass cells of blastocysts	Limited	Ethical and moral concerns present
Spermatogonial stem cells	Pluripotent	Yes	Differentiate into the results of all primary germ layers	Testicular tissues	Widely utilized	No ethical or moral concerns
Induced pluripotent stem cells	Pluripotent	Yes	Differentiate into the results of all primary germ layers	Adipose tissue, bone marrow, cord blood	Widely utilized	No ethical or moral concerns

specific disease into subpopulations that differ in their response to a given treatment based on phenotypic evidence, including biomarkers or genomes, is sometimes used interchangeably with this phrase. Personalized medicine can apply to the management of individual patients depending on various contextual elements, including therapeutic response, patient preferences, and established phenotypic results. The regulatory process for the commercialization of a novel treatment or a novel purpose for an existing drug necessitates a favorable benefit-risk profile and strong proof of efficacy. The purpose is based on the regulatory approval's eligibility criteria and findings of the clinical trial. In comparison with personalized medicine, which may be focused on a single patient, precision medicine medications are frequently produced with diagnostic techniques that are required for the identification of a subgroup of patients [215,216].

Relatively, this new technology has always been a criterion in every operation in reproductive medicine, involving special analysis, identifying healthy embryos, correct implantation, and etiology-oriented evaluation. An uncharted zone of reproductive medicine will be explored, and the processes underlying the unknown causes of infertility will be described using genetic information and a massive amount of biological data. Precision medicine has become a blueprint for medical advancement, particularly in the field of reproductive health. In many other fields, the increasing availability of clinical and genetic biomarkers has aided clinicians in formulating overall illness predictions and making well-informed treatment decisions. For the treatment of chronic disease, a 4P (predictive, participatory, personalized, and defensive) health care approach has been proposed and is becoming increasingly popular. The expression of HER2 and ER can prognosticate the fate of a patient with breast cancer patient. Prognosis mainly aims to minimize the buildup of stresses and recognize early signs. Existing indicators in infertility treatment such as hormone levels and ultrasound scanning are still at the heart of illness prediction. The next generation of diagnostics, in conjunction with machine learning, will improve the precision with which dysfunctions are identified. The proteome, epigenetic organizations, genome, molecular prognosis, metabolome, and transcriptome can all be merged, and screening and recognition platforms can be built based on this data. The key to protection is to avoid infertility. Some of the reasons for infertility are linked to a sedentary lifestyle. Infertility can be prevented by increasing information about female reproductive health. With a better knowledge of the many reasons for infertility, more customized diagnoses and more accurate therapy can be provided, thus increasing the rate of success of ART. The patient psychological therapy and education need to be improved to solve emotional barriers and avoid dropouts that limit the understanding. Individualization of therapy, preventative treatments, and enhanced data gathering through self-tracking are important. These interventions can be realized by first obtaining as much knowledge of a person's "health literacy." Reproductive medicine will reach its peak as precision medicine continues to be promoted, offering benefits to more patients experiencing infertility [216,217].

Diagnostic genetic tests in reproductive disease

A succession of significant improvements in reproduction and scientific medicine has effectively linked these two professions in the previous few decades. From diagnostic techniques to the selection of the most sophisticated treatment, scientific medicine is essential in all stages of the evolution system.

In reproductive medicine, genetic testing is used for identifying the reasons for infertility, identifying genetic illnesses that are transmissible to kids, and optimizing assisted reproductive technologies.

Accordingly, infertile couples' testing timelines now comprise biochemical and instrumental studies that permit for a prognosis in 65% of instances; genetic testing is used in the remaining 35% of unidentified cases. Considering that approximately 15% of genetic conditions are linked to infertility, and related clinical

symptoms can have both genetic and non-genetic causative factors, an infertility prognosis should be made by using a combination of thorough health information and instrument and laboratory setting assessments, including aimed genetic screening [218]. Genetic assessment can help confirm the diagnostic accuracy, allowing for more specific and focused medical treatment.

Male genetic infertility

All three etiological classes of male fertility (pre-testicular, testicular, and post-testicular) have been linked to genetic variables. Conspicuously, upwards of 200 genetic diseases are associated with male infertility, ranging from the most prevalent clinical manifestations of infertility to the most complicated syndromes with signs and symptoms that go beyond reproductive issues [219]. Infertility is a clinical indication of a complicated disease; nevertheless, in certain hereditary disorders, infertility is the most prominent phenotypic trait. Furthermore, such infertile individuals need to be tracked over time, because they have higher mortality and worse life expectancy than the general public mainly because of the genetic defects that induce male sterility [220].

The existence of abnormalities in the stereogram is now the primary indication for genetic testing, especially in cases of severe oligospermia [221]. The number of genes indisputably connected to the more frequent phenotypes of oligozoospermia or azoospermia remains restricted (50%); the other half are genes implicated in terato-zoospermia, despite the monomorphic variants of terato-zoospermia being exceedingly rare [222].

Full chromosomal abnormalities (structural or numerical), partial chromosomal aberrations, and monogenic illnesses are all genetic disorders that are linked to male infertility. Importantly, sex chromosomal defects have a strong influence on spermatogenesis, whereas autosomal mutations are associated with teratozoospermia, or hypogonadism, and familial types of obstructive azoospermia.

The karyotype, the research of chromosome Y microdeletions, and the examination of the CFTR gene are the most popular genetic tests used for the diagnosis of male infertility. Although various mutations have been linked to male infertility, the underlying genetic etiology in 40% of all instances of male infertility is unclear [223]. Notably, the function of *de novo* mutations should be examined further, particularly in the wake of what occurs with Klinefelter syndrome and AZF alterations, which are virtually entirely caused by *de novo* mutations [222]. As a result, the entire diagnostic–therapeutic pathway of male infertility can be optimized and customized using genetic testing for the detection of particular clinical pictures, after suitable genetic testing: (1) for medical testing, (2) during medical decision to determine the most appropriate ART strategy.

Whole chromosomal aberrations

The frequency of chromosomal abnormalities ranges from 1.05% to 17% (depending on the study group) but is 0.84% in infants [224]. In terms of numerical abnormalities, structural chromosomal inversions are more prevalent; however, this does not relate to sex chromosomes, in which abnormalities, which account for approximately 4.2% of all chromosomal aberrations, are indicated by sex chromosome aneuploidies in 84% of the cases and structural rearrangements of chromosome Y in the remaining 16% of cases. The much more common kind of sex chromosomal aneuploidy discovered in infertile males is Klinefelter syndrome (karyotype 47, XXY); the second most common gonosomal abnormality is double Y syndrome or Jacobs syndrome, which is defined by the existence of the Y chromosome disomy [225,226]. In terms of providing a lower reproduction rate, people with chromosomal abnormalities are likely to have an abortion or have a kid with an abnormal karyotype.

Partial chromosomal aberrations

Microdeletions in the AZF (azoospermia factor) section of the Y chromosome (Yq) have indeed been discovered in 8%–12% of azoospermic males and 3%–7% of oligozoospermic males [222], leading to the most prevalent molecular gene responsible for male infertility [225]. Considering that the AZF area contains three sets of genes (AZFa, AZFb, and AZFc) that are involved in spermatogenesis, partial or full reductions in this domain may reduce reproductive potential. Interestingly, the sperm count (5106 spermatozoa/mL) linked with primary vestibulopathy indicates AZF deficiency detection, and ICSI is required to overcome infertility [227].

Considering that male children will inherit the same or worse Yq microdeletions as their fathers, genetic counseling is required [228]. Turner's syndrome (45, X0) and other phenotypic malformations linked with sex chromosomal mosaicism [229] are risks that parents should be informed. Approximately 60% of all Yq microdeletions are caused by a reorganization of the AZFc zone [230]. The 3.5 Mb AZFc region includes multiple copies of five repetitions (b1, b2, b3, b4, and gr), whose familiarity and huge size predispose an individual to *de novo* deletions by homologous recombination [231]. The deletion of the entire b2/b4 area, which contains the DAZ family, is the most prevalent and causes spermatogenesis to deteriorate [231,232].

Although millions of genes are implicated in male infertility, only a few genetic illnesses (e.g., cystic

fibrosis) have been studied [233]. The methods for identifying a single causal gene are ineffective considering that the testis just expresses over 2300 genes, many of which regulate reproductive activities and potentially contribute to male infertility. Single or several genetic abnormalities account for roughly half of all infertility cases, and 20% of patients have unidentified genetic reasons [218]. Additionally, considering that methods such as next-generation sequencing become more widely used for both diagnostic reasons, we will be able to quickly extend our understanding in this sector [234]. The clinical features and the primary genetic problems that may interfere with healthy reproduction need to be examined to enhance the focused genetic test in the presence of particular clinical images.

Female genetic infertility

Unlike male infertility, the genetic causes of female infertility are poorly understood. As a result, infertile females undergo fewer diagnostic tests to evaluate the existence of chromosomal diseases or single-gene problems linked to their clinical characteristics. Female infertility is more usually caused by syndromic disorders than by isolated infertility owing to hereditary factors. Genetic testing is now confined to chromosomal abnormalities and FMR1 premutation in patients with POI. Remarkably, more details have been reported about the primary chromosomal and genetic variations that could interact with healthy reproduction, and the primary phenotype extraction and laboratory tests that can be obtained in pre- and postnatal durations have been mentioned.

Whole chromosomal aberrations for female genetic infertility

Considering that chromosomal problems remarkably influence fertility and the chance of miscarriage, a karyotype study is typically recommended [235]. Robertsonian reciprocal translocations are abnormalities personally accountable for blocks of meiosis and structural modifications of the X chromosome, which are the most clinically meaningful structural abnormalities in infertile females. Infertility is considerably elevated in patients with reciprocal translocations, especially hypogonadotropic hypogonadism with primary or secondary amenorrhea or oligomenorrhea. The balanced conformational changes do not induce health concerns for their carriers, because they do not induce genetic information loss or duplication, but these conditions may result in gametes with imbalanced genetic data and possibly cause infertility or numerous miscarriages. Some chromosomal anomalies, including the XXX karyotype, are not strongly linked to infertility. Serious mistakes throughout crossing-over and/or meiotic nondisjunction in women with a normal karyotype generate a variable number of oocytes with chromosomal anomalies [236,237]. 45X, trisomy, and polyploidy are the three basic types of disorders. These occurrences increase with maternal age [224]. PGT allows for the analysis of gametes or embryos while undergoing ART. While checking for aneuploid embryos and exclusively transferring euploid embryos, the technique's effectiveness is improved [238].

Fragile X syndrome

The existence of over 200 repeats of the CGG triplet pattern in the fragile X mental retardation 1 gene or a loss impacting the fragile X mental retardation 2 gene causes fragile X syndrome, which is an autosomal dominant genetic condition. Accordingly, menstrual instability reduces ovarian reserve, and early ovarian insufficiency is a symptom of female FMR1 premutation or FMR2 microdeletion [239,240]. In contrast to the family background, a molecular test should be discussed in the case of women with similar clinical signs. X-chromosome-linked abnormalities are the most prevalent genetic donors to POI. These conditions may be caused by a change in an autosomal chromosome [241]. Mutations should be identified immediately to manage reproductive choices and, if required, a preimplantation genetic diagnostic program should be selected to determine the particular clinical scenarios, in which a focused genetic test could help lead to a tailored diagnostic–treatment strategy.

Detection of hereditary illnesses that are transmissible to progeny by using molecular techniques

Perinatal mortality is caused by inherited chromosomal or genetic abnormalities in 20%–25% of instances [242]. Preconception carrier detection has been increasingly popular in recent decades as a result of increased medical understanding. The ability to identify couples at risk of passing on a certain hereditary illness to their children allows future parents to make educated reproductive decisions. If one of the reproductive partners has a gene mutation that causes one of the hereditary diseases, the pregnancy might result in a kid with that disease.

More than 2000 genetic abnormalities can be tested, including major disorders such as cystic fibrosis, spinal muscular atrophy, and sickle cell anemia and more complicated ailments such as mental retardation and congenital heart disease. In this setting, genetic counseling is critical for identifying genetic risk, correctly assigning patients, and alerting patients about genetic concerns that affect decision-making [243].

Preconception carrier examination provides genetic data in various illnesses, allowing all carrier couples to make reproductive options depending on their findings. The personalized genetic test is an important tool for women and their newborns to enhance short- and long-term results [244,245].

Therefore, in the involvement of carrier or afflicted spouses, various tests are available to determine a transmissible condition to the children during the prenatal period. Any one of these treatments can only be used during a certain point in pregnancy or at various stages of the IVF process.

Investigative PND is often conducted on DNA recovered from fetal cells acquired by chorionic villus sampling (CVS) or amniocytes, and the results are available in 7 to 15 days [246]. The molecular diagnosis for monogenic illness is carried out by direct mutation analysis when the parental mutations are recognized or by linkage analysis when the parental mutations are unclear [246,247]. In terms of the specified analytic steps, paternity verification and contamination analysis are always conducted [247].

The non-invasive prenatal diagnosis (NIPD) of monogenic illness, which can identify fetal genetic changes in maternal blood at an initial gestational age, has gained wide attention. NIPD remains a difficulty, although non-invasive prenatal testing (NIPT) by using cell-free fetal DNA (cfDNA) for the screening of chromosomes 21, 18, 13, X, and Y has been clinically used [248]. Under sex-related diseases and RHD, NIPD has just lately been adopted for therapeutic usage [249]. NIPD has been studied in several monogenic illnesses, including Duchenne, congenital adrenal hyperplasia, thalassemia, and Becker muscular dystrophy [250,251]. The prospect of adopting NIPD in clinical instances is being driven by the disruptive technology of NGS combined with the haplotyping technique.

Considerably, PGT has the same diagnosis and treatment motivation as traditional PND, with the added benefit of diagnosing at an earlier stage in the embryo. Curative abortion can be prevented by delivering only disease-free embryos to the mother. PGT appears to require the use of IVF methods, including the collection of gametes from both partners, fertilization of the oocyte by intracytoplasmic sperm injection (ICSI), embryo transfer, embryo biopsy that allows one or more cells from the blastomere or trophectoderm to be taken 3 or 5 days post-fertilization, and molecular analysis.

Conclusions

Stem cell treatment can now be used for the treatment of degenerative disorders, prevention of aggressive malignancies, and healing of damaged tissue. However, many areas of stem cell treatment are currently unclear, leaving the huge unrealized potential for use in managing disorders such as infertility. Based on the findings, once the correct technique is discovered, research will be suitable for the treatment of infertility. Ovarian-derived stem cells have a wide range of therapeutic applications. The therapeutic use of stem cells needs to be following ethical criteria, such as informed optional approval and other clinical investigation ethics guidelines. Whether a normal offspring can be created from gametes obtained from pluripotent stem cells is unknown. At the moment, stem cell-derived gametes can be utilized as an *in vitro* system to assess medication benefits. Generally, stem cell analysis has yielded significant new advances in the medicine of infertility. We shall keep on trying to disentangle the intricate web of ethical considerations surrounding this treatment. In certain circumstances, stem cell treatment may provide promise to people who would like to have their own genetically linked children. Embryonic stem cell transplantation has fallen out of favor because of ethical concerns and immunologic interference, pushing infertility doctors to look into additional stem cell treatments. Moreover, significant analysis is being done on induced pluripotent stem cells (iPSCs), which has few-to-no ethical problems and can produce person-specific haploid gametes. MSCs, which are produced from widely accessible resources such as AD, bone marrow, amniotic fluid, placenta, amnion, and menstrual blood and have few ethical problems, are gaining favor for use in fertility clinics. Several animal and human investigations have confirmed the importance of MB-MSCs in endometrial regeneration and ovarian performance recovery. Knowing the role of microRNAs in stem cell differentiation will provide a thorough understanding of stem cell modes of action for fertility restoration. Nonetheless, further large-scale clinical trials are required to demonstrate the safety and effectiveness of stem cell-based treatment in reproduction.

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Compliance with ethics guidelines

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