

Stem Cell Therapy for Infertility

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Contributor: Sham Kakar

Stem cells are a subtype of cells that remain in undifferentiated form in embryos and in adult tissues and can self-renew and differentiate as and when required. Stem cells in differentiated organs contribute to the restoration of function through organ damage repair. According to their origin, stem cells are classified as embryonic stem cells (ESC), adult stem cells (includes mesenchymal stem cells MSC), induced pluripotent stem cells (iPSC), spermatogonial stem cells (SSCs), and ovarian stem cells. Stem Cells can be applicable for several disorders including infertility both in male and female.

Keywords: infertility ; mesenchymal stem cell ; induced pluripotent stem cell ; spermatogonial stem cell ; assisted reproduction technology

1. Introduction

According to the international glossary, infertility is defined as “A disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person’s capacity to reproduce either as an individual or with his/her partner.” Fertility interventions may be initiated in less than 1 year based on medical, sexual, and reproductive history, age, physical evaluation, and diagnostic testing. In developing countries, 1 in 4 couples suffers from infertility (WHO 2004). To overcome the shortcomings of the current treatment methods and considering the ability of stem cells to replenish damaged tissues via their self-renewal properties and ability to differentiate into multiple lineages, stem cells could be considered as a novel therapeutic measure for infertility ^{[1][2]}.

2. Conventional Treatment

Conventional treatments improve fertilization rates inside the womb. Conventional treatments for male infertility are mainly focused on improving sperm quality, which depends on etiologic factors. Evidence-based medicine revealed a significant improvement in pregnancy rate after treatment with antioestrogens and gonadotropins therapy in cases of idiopathic male infertility ^[3]. Administration of antioxidants such as vitamin E and zinc along with assisted reproduction technology enhanced the rate of live offspring in infertile couples ^{[4][5]}.

Previously, human menopausal gonadotropins, a mixture of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), were used. However, at present, more expensive but purer forms of recombinant gonadotropins are recommended. The risk of multiple pregnancies with injectable gonadotropins is much higher (30%) as compared to orally administered clomiphene citrate or letrozole (7%). After the administration of ovulation-inducing drugs, regular follicular monitoring is carried out using ultrasonography in order to identify the time of formation of the dominant follicle (18–20 mm), which would be followed by ovulation trigger by intramuscular injection of β hCG ^[6].

Intrauterine insemination (IUI) is a conventional treatment used for both male and female infertility. After collection of semen from the male partner, highly motile sperm with normal morphology are isolated. The highest quality isolated sperm are injected within the uterine cavity with the help of a thin malleable catheter bypassing the cervix approximately 36 h after natural ovulation or triggered ovulation ^[6].

3. Implications for Stem Cells in Infertility

Even after recent progress in ART, many couples are unable to parent healthy babies except through gamete donation or adoption. Infertility due to gamete deficiency resulting from genetic defects does not benefit from ART. However, most couples seeking infertility treatment wish to have their own genetically related issues resolved ^[7], which could be less invasive and more cost-effective compared to ART. In this respect, stem cells have shown new hope to overcome the issues related to infertility in the form of cell-based therapies in various experimental preclinical and clinical models ^{[8][9][10][11][12][13][14][15][16]}.

Stem cells are a subtype of cells that remain in undifferentiated form in embryos and in adult tissues and can self-renew and differentiate as and when required. Stem cells in differentiated organs contribute to the restoration of function through organ damage repair. According to their origin, stem cells are classified as embryonic stem cells (ESC), adult stem cells (includes mesenchymal stem cells MSC), induced pluripotent stem cells (iPSC), spermatogonial stem cells (SSCs) [17], and ovarian stem cells [18]. Stem cells collected from various organs explored to treat infertility are listed below:

ESCs play an important role in regenerative medicine because of their indefinite capacity to self-renew, ability to differentiate into all three lineages (ectoderm, endoderm, and mesoderm) and ability to maintain the normal karyotype during growth. It was documented that both mouse and human ESC can differentiate into primordial germ cells in vitro and subsequently undergo meiosis and give rise to male and female gametes [19]. the feasibility of developing functional sperm by using gene repaired ESC isolated from cloned blastocysts that were originated from nuclear transferred somatic cells (ntESC) using gene repair technology [20]. However, because of ethical concerns, even after initial derivation, it is not so commonly used in cell replacement therapy.

Various studies have been conducted for the differentiation of iPSCs to male germ cells in vitro. Next, they harvested the cells in the presence of forskolin, human recombinant leukemia inhibiting factor (LIF), and the CYP26 inhibitor R115866 for 2, 3, and 4 more weeks [21]. They documented that iPSCs transplanted into seminiferous tubules differentiated into germ cell-like cells (GCLCs), whereas cells outside the tubule could not result in GCLCs. They isolated the human PGCs from other cells with the help of markers present on PGCs such as EpCAM

In their studies, at first, they differentiated somatic cells into iPSC by reprogramming and then generated incipient mesoderm-like cells (iMeLCs) in the presence of Activin A and Chiron. These hPGCLCs were mixed with gonadal cells isolated from female mouse embryonic ovaries and cultured for 4 months to obtain oogonia by in vitro gametogenesis. This technique will bring a revolution in reproductive medicine through the generation of oogonia from human pluripotent stem cells. [22], on the other hand, documented the mechanistic explanation of differentiation of human pluripotent stem cells to heterogeneous mesoderm-like cells in the presence of cytokines followed by the generation of PGC-like cells (PGCLCs), and the PGCLCs are committed to developing gametes (sperm or eggs) that were associated with a unique expression of PRDM14 [22].

In spite of promising results obtained from experimental models, the teratogenic potentiality of iPSCs and their derivatives resulting from reprogramming by induction with oncogenes (for example, c-myc) and use of nucleic acid integration procedures restrict their clinical application towards personalized cell-based therapy [23]. Moreover, the persistence of residual epigenetic impressions and gene silencing, as well as genomic instability, might be a potential hurdle that further limits their therapeutic application [24][25].

Although the iPSC technology does not destroy the embryos, the potentiality to exploit the embryo generated from gametes developed after iPSCs reprogramming demand ethical clearance from the institutional review board as well as the collection of informed consent from the cells or tissue donor prior to acquiring any sample for development of iPSC for clinical trials as well as research purpose. In addition, for their application in animal models, approval is required from IACUC.

According to the mesenchymal and tissue stem cell committee of the International Society for Cellular Therapy, MSCs are defined as cells that have plastic-adhesion properties, express CD105, CD73 and CD90 as surface markers, and can differentiate into osteoblasts, adipocytes and chondroblasts [26]. Depending on their origin, MSCs are categorized as bone marrow stromal cells, adipose-derived stem cells, menstrual-blood-derived MSCs and umbilical-cord-derived MSCs [2], amniotic-fluid-derived MSCs, placental-tissue-derived MSCs, salivary-gland-derived MSCs, and dental-pulp-derived MSCs [1]. MSCs travel to the damaged ovary and settle there to restore ovarian function through the release of various cytokines by paracrine mechanisms. Cytokines such as vascular endothelial growth factor, insulin-like growth factor, and hepatocyte growth factor induce the formation of new vessels, prevent apoptosis as well as fibrosis and thus ameliorate ovarian dysfunction.

On the contrary, fetal subpopulations of MSCs exhibit a higher proliferation rate leading to rapid expansion and efficient differentiation to multilineages as well as strong immunomodulatory properties [27]. Augmented telomerase activity might contribute to better performance and prolonged survival of the fetal MSCs (FMSC) compared to adult MSCs [27]. [28] documented that FMSCs could ameliorate ovarian follicular function in a cyclophosphamide-induced mice model via modulation of melatonin membrane receptor 1 and antioxidant enzyme activity. Some of the sources used to derive MSCs used for the treatment of infertility are listed below:

After its initial documentation in 1988 by Owen and Friedenstein [29], the isolation of MSCs from bone marrow was carried out by density gradient centrifugation and then incubated in a growth medium for expansion [30]. These BMSCs are not only differentiated to mesodermal lineages but also committed to the development of endometrial and follicular cells in rat models [31][32].

[33] explored whether BMSCs could contribute to endometrial regeneration in the experimental rat model. They transplanted BMSCs through rat tail intravenous injection and observed a significant increase in thickness of endometrium along with enhanced expression of various markers, cytokeratin, vimentin, integrin $\alpha\beta3$, and leukemia inhibitor factor. It was observed that in both cases, BMSCs could effectively heal the endometrial injury, as evidenced by the increase in the number of endometrial glands and decrease in the fibrotic area through upregulation of estrogen and progesterone receptor expression [34]. [10] conducted a prospective, experimental pilot study on patients with Asherman's syndrome/endometrial atrophy and reported that injection of CD133+ BMSCs into the spiral arterioles of recruited patients could improve endometrial thickness, the intensity of matured blood vessels, and the nature of menstruation of infertile patients.

Menstrual-blood-derived MSCs (MB-MSCs) have the potential to proliferate and differentiate into multiple lineages and can self-renew similar to other stem cells. Moreover, the collection of these cells is noninvasive, safe, and easy, without ethical issues and with minimal immune reactions, facilitating their clinical application in reproductive medicine compared to other tissue-derived stem cells.

[35] reported the impact of MB-MSCs on cyclophosphamide-induced premature ovarian failure (POF) in a mouse model. They have shown that MB-MSC treated groups of animals showed an increase in the number of the normal ovarian follicles and restoration of normal ovarian function represented by a higher level of ovarian hormones such as estradiol, antimüllerian hormone and inhibin α/β compared to control. In their studies, they documented that MB-MSC improved ovarian function through localization of MSCs into granulosa cells and by augmentation of the expression of FSH receptors as well as restoration of hormone levels [11]. It was documented that MSC derived from menstrual blood could resume fertility in an animal model of damaged endometrium through induction of angiogenesis and release of anti-inflammatory factors [12].

Moreover, MB-MSCs could improve epirubicin (broad-spectrum anti-cancer drug)-induced ovarian damage and thus promote the multiplication of granulosa cells through upregulation of Cyclin B1 and CDC2 protein expression and downregulation of Gadd45b protein expression [36].

A clinical study conducted by Tan et al. [37] reported on seven patients with resistant Asherman syndrome treated with MB-MSC transplantation followed by hormonal therapy; out of these seven patients, five patients attained endometrial thickness of 7 mm, one out of these five patients achieved pregnancy spontaneously and two conceived after assisted reproduction technology [36]. The role of the OCT-4 transcription factor on differentiation of MSCs documented in animal models was supported by the decreased expression of OCT-4 observed in MB-MSCs isolated from patients with severe intrauterine adhesion [38].

Following the initial introduction of endometrial stem cells by Prianishnikov and his colleagues in 1978 [39], Chan and his colleagues in 2004 [40] isolated stem cells from endometrial tissues and identified the colonization properties of these cells in vitro. The EndSC microenvironment is comprised of stromal cells, epithelial progenitor cells and endothelial cells. However, in the presence of inflammation or damage to the endometrium, these stem cells were directed to the injured site following interaction between chemokines and CXCR4, which is expressed on stem cells, and CXCL12, which is expressed by the epithelium of endometrial tissues [41]. Endometrial stem cells act as the origin of cells that help in replenishing the endometrium, such as mesenchymal stem cells (MSCs), epithelial stem cells, endometrial side population cells (ESP), and endometrial regenerative cells (ERC)

Therapeutic implications of endometrial stem cells have been documented in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced model of Parkinson's Disease [42] to observe if it can restore dopamine release and in a murine model of diabetes mellitus [43]. Mechanistic explanations and roles of endometrial stem cells in the restoration of fertility are summarized in **Figure 1**. Modified from references [44][45].

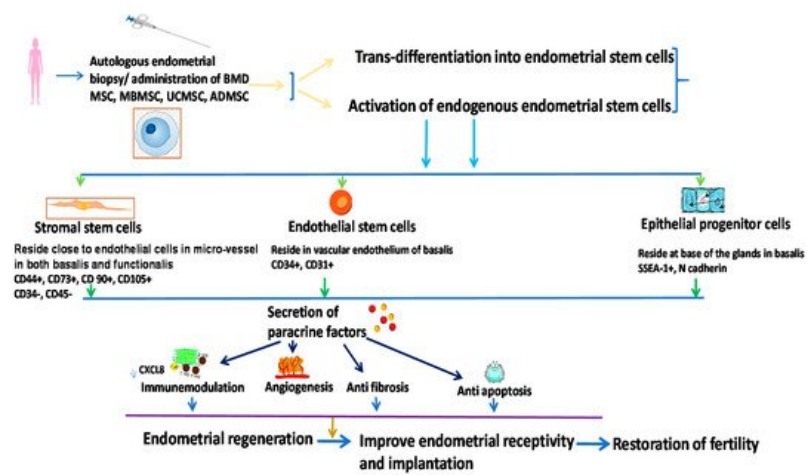


Figure 1. The mechanistic explanation of stem cell therapy for restoration of fertility via endometrial regeneration; BMDMSC: Bone-marrow-derived mesenchymal stem cell; MB MSC: menstrual blood mesenchymal stem cell; UC MSC: umbilical cord mesenchymal stem cell; ADMSC: adipose-tissue-derived mesenchymal stem cell; CXCL: C-X-C motif chemokine ligand; SSEA-1: Stage-specific embryonic antigen-1; CD: Cluster of differentiation. Modified from references [44][41].

Wharton's jelly of umbilical-cord-derived MSCs showed the presence of CD29, CD44, CD73, CD90, and CD105 expression, with the absence of CD31, CD45, and HLA-DR85. Because of low tumorigenicity, rapid self-renewal capacity committed to various mesodermal cell types, easy availability from usually-discarded resources, minimum ethical concerns, and low immunogenicity, UC-MSCs have emerged as a popular cell-based therapeutic approach for restoration of fertility [2].

In various experimental animal models of premature ovarian insufficiency, UC-MSCs restored ovarian function through its antiapoptotic activity against granulosa cells and modulation of hormone levels, for example, reducing FSH levels while augmenting estrogen and progesterone levels [46][47]. UC-MSCs could restore ovarian function in paclitaxel-induced ovarian dysfunction through the provocation of ovarian surface epithelium stability and modulation of the expression of Cyto Keratin 8/18, TGF- β , and proliferating cell nuclear antigen (PCNA), which are critical regulators of follicular synthesis and the antiapoptotic activity of UC-MSCs [48]. UC-MSCs also emerged to be beneficial in the revival of infertility in a mouse model of PCOS induced by dehydroepiandrosterone via inactivation of proinflammatory cytokines, for instance, IL-1 β , tumor necrosis factor alpha (TNF α), and interferon gamma (IFN- γ)

The beneficial effect of UC-MSCs in the improvement of fertility might involve various signaling pathways. UC-MSCs prevent apoptosis of granulosa cells to improve fertility via the activation of mitogen-activated protein kinase signaling pathway, G protein-coupled receptor, and insulin signaling pathways [49]. UC-MSCs restored fertility in an animal model of damaged endometrium through the increase and decrease in vascular and inflammatory factors, respectively [50]. Similarly, transplantation of UC-MSCs on a collagen scaffold in a rat model of uterine injury could rescue fertility via activation of matrix metalloproteinase 9 [51].

Administration of UC-MSCs on a collagen scaffold could restore ovarian function in patients suffering from premature ovulatory failure (POF) as confirmed by the increase in follicle number through activation of primordial follicles via phosphorylation of transcription factor forkhead box protein O3a (FOXO3a) and FOXO1 [52]. Yang et al. [15] documented that Wharton's jelly-derived MSC could improve proliferation and prevent apoptosis of mifepristone-induced damage in endometrium collected from patients undergoing hysterectomy via upregulation of VEGF expression and downregulation of caspase 3 and 8 [15]. [19] conducted a single-center, prospective, randomized, double-blind, placebo-controlled phase II clinical trial and observed the safety and efficacy of intramuscular injection of UC-MSCs for the treatment of uterine scars caused by caesarean section.

Their immune regulatory properties, lack of ethical concern, plus ability to differentiate into various cell types such as osteocytes, muscle, and adipocytes make the AFSCs highly useful for regenerative medicine. Various animal studies have documented the therapeutic role of AFSCs in muscular and bone-related disorders [53][54]. Previous studies revealed that AFSCs could ameliorate infertility through the restoration of ovarian function via the activation of various signaling molecules such as VEGF, TGF α and β , epidermal growth factor (EGF), and bone morphogenic protein (BMP) [49]. Various studies on a mouse model of POF induced by chemotherapy documented the role of AFSCs, especially having CD4C/CD105+ markers, on the prevention of follicular atresia, reestablishment of healthy oocytes, and thus preserving ovarian function [55][56].

The restorative effect of ADMSCs on ovarian dysfunction in chemotherapy-mediated animal models of POF has been documented in various studies [57][58]. AmDMSCs restore ovarian function by attenuating apoptosis and improving the multiplication of granulosa cells and neovascularization in the surrounding environment to some extent by paracrine mechanisms. Moreover, AmDMSC treatment accomplished its function via suppression of inflammation by inactivating cytokines IL-1 β , IL-6 and TNF α . [59] documented that surprisingly, human ADMSCs, after treatment with low-intensity pulsed ultrasound, become more efficient in the revival of ovarian function in a rat model of POF.

Various studies conducted on an animal model of POF revealed that PDMSCs produced their beneficial effects on folliculogenesis through modulation of cytokines and various hormone levels such as estradiol, LH, AMH, and FSH and their receptors' expression by activation of PI3K/Akt signaling pathway [60][61]. On the other hand, Li et al. (IRE1) α signaling pathway in PDMSC improved ovarian dysfunction [62]. [63] demonstrated in ovariectomized rats that PDMSCs are more effective in 3D spheroid formation to produce their restorative function [63].

ADMSCs are a novel type of MSCs having almost similar biological properties to MSC derived from other sources but having more advantages compared to BMSC because such tissues can be collected with less invasive procedures and in larger quantity [64]. Therefore, these are widely used for a broad spectrum of clinical conditions in reparative medicine [65][66].

One study observed the impact of ADMSCs on ovarian grafts in a female animal model and revealed that ADMSCs restored ovarian function faster through augmentation of VEGF gene expression and promotion of angiogenesis in the grafted tissue [67]. ADMSCs could restore ovarian function in chemotherapy-mediated ovarian damage in a mouse model through neovascularization and promotion of ovarian follicular proliferation [68]. However, administration of ADMSCs on a collagen scaffold in an ovarian insufficiency rat model revealed better retention of ADMSCs, giving rise to the longer resumption of ovarian function and better pregnancy rate compared to ADMSC injection alone [69]. Hence, ADMSCs could be considered an effective alternative therapeutic tool for the restoration of fertility for infertile couples, depicted in **Figure 1**.

The invention in findings of the rate of follicular atresia along with the death of oocytes and depletion of ovarian reserve in mice brought the concept of the existence of OSCs. Subsequently, they also documented that these cells were able to induce synthesis of follicles after xenotransplantation into diabetic immunocompromised mice [70]. However, these cells remained unidentified for a long time, probably because of their very low number, constituting only 0.0145% of the total cell population in mouse ovary that declines gradually with age. From a previous study on the isolation of OSCs from old mice and subsequent folliculogenesis following transplantation in young mice [71], it could be speculated that these OSCs could show new hope to those with idiopathic premature ovarian failure.

The therapeutic implication of OSCs include restoration of fertility and giving birth to live offspring documented in age-associated infertility and premature ovarian failure in childhood cancer survivors following exposure to chemotherapy [18][72].

SSCs play a crucial role in maintaining the highly productive complex process known as spermatogenesis in the seminiferous tubule through self-renewal and unlimited differentiation into spermatogonia followed by haploid spermatozoa [73]. In an experimental model, it was observed that SSCs are derived from primitive germ cells that travel to the gonadal ridge during embryonic development and then lodge into the seminiferous tubules of adult testicles to help in lifelong sperm generation [74][75]. Various biomedically active factors, either alone or in combination with others, have been used for in vitro induction of potential stem cells into germ cells: retinoic acid for proper timing in the initiation of meiosis, CYP26 inhibitor for control of meiosis through modulation of the STRA8 gene [76], testosterone for the potential release of stem cell factor to induce germ cell differentiation [77], forskolin to promote proliferation of germ cells [78], and leukemia inhibiting factor (LIF) to keep gonocytes alive [79]. Some studies carried out both in vitro induction of stem cells and subsequent transplantation into male mice that were rendered infertile to prove the ability of SSCs to form colonies within the testes as well as to differentiate into male gametes through highly coordinated spermatogenesis [80].

The main drawback of this cell-based therapy in reproductive medicine is that this procedure may disturb the environment of the testes, resulting in a decline in acceptability of SSC transplantation, giving rise to treatment failure [81].

4. Stem Cell Therapy in Some Known Syndromes

Syndromes leading to infertility are shown in **Figure 2** and discussed below:

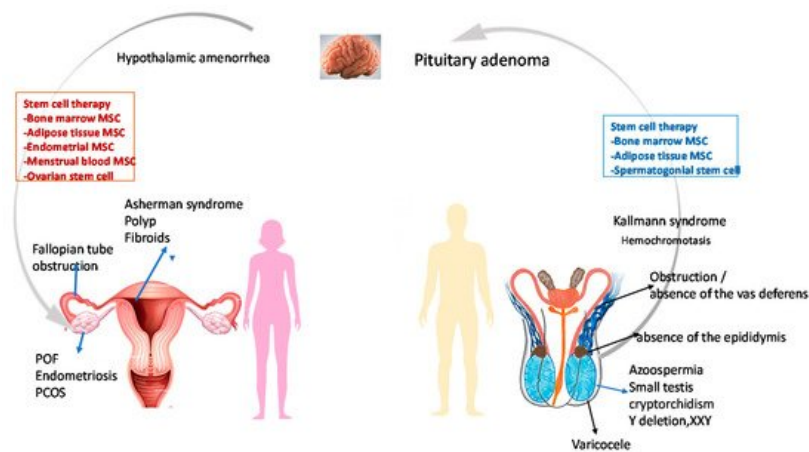


Figure 2. Some probable causes of infertility in male and female POF: premature ovarian failure, PCOS: Polycystic ovarian syndrome, XXY: Klinefelter syndrome, MSC: Mesenchymal stem cell. Modified from references Lindsay and Virtikas [2] and Zhao et al. [82].

Various diagnostic approaches are available to diagnose this syndrome, including hysterosalpingography (HSG), 3D ultrasonography, hysteroscopy, and magnetic resonance imaging (MRI), with hysteroscopy being the gold standard. Common treatments of infertility resulting from AS include restoration of the uterine cavity through hysteroscopic adhesiolysis and replenishment of normal endometrial lining with hormonal therapy [83][84]. Surgical treatment of AS has been found to be associated with various obstetric complications such as preterm delivery [85]. Hence, the use of stem cell therapy to treat AS has been evaluated.

The use of stem cells derived from bone marrow [86], autologous menstrual blood [37], as well as mesenchymal stem cells [87] for the replenishment of endometrium, has been worked out in various animal models [88] as well as clinical studies [89]. It was observed that endometrial MSCs derived from menstrual blood could improve fertility in an animal model of damaged endometrium [12]. Various studies reported that women with AS attained regular menstruation [90] and endometrial regeneration following transplantation of menstrual-blood-derived stem cells [37].

With the increase in cancer survivors, the incidence of POI is also increased proportionately. However, in these cases, restoration of fertility has been tried by cryopreservation of oocytes prior to gonadotoxic treatment (Ethics Committee of American Society for Reproductive Medicine, 2013). Several studies have documented that fertility could be preserved in POI cases by ovarian vitrification followed by in vitro activation by stimulation of the AKT pathway followed by re-transplantation [91][92][93]. However, the successful demonstration of ovarian stem cells both in experimental animal and human models might bring revolution in the potential therapy for restoration of infertility in patients with POI [94].

PCOS, a gynecological disorder of reproductive-aged women resulting from hormonal imbalance, was initially diagnosed by Rotterdam using two criteria: "(1) presence of high levels of androgens, and (2) ovulatory dysfunction, or polycystic ovaries". Patients with PCOS commonly present with irregular menstruation, obesity, abnormal hair growth on the body and infertility/subfertility [95]. Hormonal contraceptives and clomiphene citrate are the first-line therapy for restoration of normal menstruation and fertility, respectively [95]. MSCs could attenuate DHEA-mediated PCOS in mouse [96] and human theca cells from PCOS patients [97] by suppression of inflammation via the release of anti-inflammatory cytokines.

Endometriosis is an estrogen-dependent complex disorder affecting women of reproductive age; approximately 10% of women suffer from endometriosis, and approximately 50% of those women with endometriosis have trouble achieving pregnancy [98]. According to The Practice Committee of the American Society for Reproductive Medicine, 2012, the fecundity rate is significantly decreased in couples with endometriosis compared to normal fertile couples [99]. The principal speculations related to the pathogenesis of endometriosis include retrograde menstruation, coelomic metaplasia and metastatic spread, altered immunity, stem cells, and genetics [100]. Endometriosis with its inflammatory response and increased release of cytokines could affect fertility via alteration of ovum formation, gamete transport through impairment of tubal movement, and endometrial development through modulation of the Wnt pathway [101].

A previous study revealed that initial treatment with GnRH agonist followed by IVF with or without ICSI could significantly improve pregnancy rates in infertile couples with endometriosis [102]. [103] did not find significant improvement in fertility with the initial administration of hormonal therapy [103]. Surgical treatment alone or in combination with medical treatment showed different responses. However, recent experimental evidence in both animal and human models has documented promising results of stem-cell-based therapy for the restoration of fertility in patients with endometriosis [100].

Azoospermia, characterized by the absence of mature morphologically normal and functional sperm in the ejaculate, contributes approximately 15% of infertility solely related to male factors [104]. Based on history, detailed physical examination, hormonal assay and genetic testing, azoospermia can be divided into two subtypes: obstructive (OA) and nonobstructive (NOA) azoospermia. However, NOA results in testicular failure, which could be due to pathology primarily in the testis or secondary due to 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.

Spermatogonial stem cells (SSCs), having self-renewal properties, can differentiate into haploid spermatids and finally undergo maturation to spermatozoa and thus might play an important role in promoting sperm production to solve this prevalent cause of male factor infertility [105]. [106] demonstrated that SSCs injected into the rete testes of pre-pubertal rhesus monkeys undergo a transformation into mature spermatozoa along with the maturation of the monkey; the spermatozoa present in the ejaculate and have fertilization capability [106]. However, SSC transplantation could not be replicated in humans because of challenges associated with the identification of SSCs in the testes, lack of proper culture and preservation protocol for SSCs, and safety concerns for the recipients following transplantation [107]. Other than SSCs, embryonic and adult stem cells were demonstrated to have the ability to be differentiated to germ cells [108] and have the ability to fertilize in animal models [109][110].

Various clinical trials (NCT02025270, NCT02641769, NCT02414295) have been performed or are underway on injection of bone-marrow-derived MSCs to the rete testis of azoospermia patients to assess hormonal levels as well as testicular size along with sexual potency (see **Table 1**).

Table 1. Clinical trials related stem cell therapy performed or underway for improvement of infertility.

Trial Identifier	Est. # of Subjects	Status	Site	Conditions	Interventions	Outcome of Trial
NCT04706312	12	Not yet recruiting	Nanjing Medical University	Diminished Ovarian Response	Human Amniotic Mesenchymal Stem Cells (HamsCs) Transplantation	No results posted
NCT04676269	40	Recruiting	Indonesia University	Thin Endometrium Infertile Patients	Amnion Bilayer and Stem Cell Combination Therapy	No results posted
NCT03207412	20	Unknown	Chongqing Medical University, China	Premature Ovarian Failure	Human Amniotic Epithelial Cells	No results posted
NCT02696889	3	Active	University of Illinois at Chicago	Primary Ovarian Insufficiency, Low Ovarian Reserve	Autologous Stem Cell Therapy	Report of 2 cases revealed a significant improvement in clinical features related to POI. There was an increase in size as well as estrogen production in the MSC engrafted ovary [111]
NCT02713854	240	Recruiting	The University of Hong Kong	Subfertility	Human Embryonic Stem-Cell-Derived Trophoblastic Spheroid (Bap-Eb) as a Predictive Tool	No results posted
NCT03592849	50	Enrolling by invitation	Nanjing Drum Tower Hospital, China	Infertile Women with Thin Endometrium or Endometrial Scarring	Procedure: Collagen Scaffold Loaded with Umbilical-Cord-Derived Mesenchymal Stem Cells Therapy	No results posted

Trial Identifier	Est. # of Subjects	Status	Site	Conditions	Interventions	Outcome of Trial
NCT03166189	46	Completed	D.O. Ott Research Institute of Obstetrics, Gynecology, Russian Federation	Infertility of Uterine Origin Asherman Syndrome	Biological: Bone Marrow-Derived Msc and Hrt Other: Hormonal Replacement Therapy	No Results Posted
NCT02313415	26	Completed	Nanjing Drum Tower Hospital, China	Infertility with Intrauterine Adhesions	Procedure: Umbilical Cord Mesenchymal Stem Cells	Phase 1 trial revealed that transplantation of clinical grade human UC MSC could improve the proliferative and differentiation efficiency of endometrium ^[112]
NCT02025270	100	Unknown	Al Azhar University, Egypt	Azoospermic Patients	Bone-Marrow-Derived Mesenchymal Stem Cells	No results posted
NCT02641769	50	Recruiting	Stem Cells of Arabia, Amman, Jordan	Non-obstructive Azoospermia	Intratesticular Transplantation of Autologous Stem Cells	No results posted
NCT02414295	1	Completed	Man Clinic for Andrology and male infertility, Cairo, Egypt	Klinefelter Syndrome Azoospermia	Mesenchymal Stem Cell Injection	No Results Posted
NCT02062931	60	Unknown	Al-Azhar University hospitals, Egypt	Premature Ovarian Failure	Biological: Stem Cell Preparation and Injection	No results posted
NCT02603744	9	Unknown	Royan Institute	Premature Ovarian Failure	Intraovarian Injection of Adipose-Derived Stromal Cells (Adscs)	Intraovarian engrafting of ADSCs were found to be safe and feasible and linked to reduction in FSH level ^[113]
NCT02204358	30	Unknown	Nanjing University Medical School	Intrauterine Adhesions, Endometrial Dysplasia	Collagen Scaffold Loaded with Autologous Bone Marrow Stem Cells Testicular Injection of Autologous Human Bone Marrow	No results posted
NCT02041910	60	Unknown	Hesham Saeed Elshaer, El-Rayadh Fertility Centre	Azoospermia	Derived Stem Cells	No results posted
NCT02151890	10	Completed	Al Azhar University, Cairo, Egypt	Premature Ovarian Failure	Biological: Stem Cell	No results posted
NCT02372474	112	Completed	Al Azhar University, Cairo, Egypt	Premature Ovarian Failure	Biological: Stem Cell	No results posted

Trial Identifier	Est. # of Subjects	Status	Site	Conditions	Interventions	Outcome of Trial
NCT01742533	40	Unknown	Shenzhen People's Hospital, Shenzhen, Guangdong, China	Premature Ovarian Failure	Biological: Human Umbilical Cord Mesenchymal Stem Cells and Human Cord Blood Mononuclear Cells Drug: Hormone Replacement Therapy	No results posted
NCT03069209	50	Active, not recruiting	Stem Cells Arabia, Amman, Jordan	Premature Ovarian Failure	Biological: Stem Cells	No results posted
NCT00429494	60	Completed	UT MD Anderson Cancer Center, United States	Amenorrhea Premature Ovarian Failure	Procedure: Hematopoietic Stem Cell Transplantation (Hsct) Drug: Leuprolide Acetate	Phase II trial revealed that Leuprolide could not preserve ovarian function in HSCT patients ^[114]
NCT04009473	100	Enrolling by invitation	Multicenter	Ovarian Failure Premature Ovarian Failure	Combination Product: SEGOVA Procedure Includes Stem Cell Therapy, Growth Factor, and Platelet Plasma Rich Therapy	No results posted
NCT02240823	30	Unknown	Odense University Hospital	Erectile Dysfunction After Prostatectomy	Adipose-Derived Stem Cells (ADMSC)	Intracavernous injection of ADMSC is a safe procedure and resulted in improvement of erectile function ^[115]
NCT02414308	20	Unknown	Man Clinic for Andrology, Male Infertility, and Sexual Dysfunction	Erectile Dysfunction Peyronie' Disease	Adipose Tissue Stem Cell Injection	No results posted
NCT02008799	20	Recruiting	Man Clinic for Andrology, Male Infertility, and Sexual Dysfunction	Azoospermia	Intratesticular Artery Injection of Bone Marrow Stem Cell	No result posted

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