MedCrave
Step into the World of Research

Journal of Stem Cell Research & Therapeutics

Review article

Open Access

CrossMark

Stem cell based therapy for polycystic ovarian syndrome

Abstract

Polycystic ovarian syndrome is a complex, polyfactorial condition which involves multiple genes and body systems. The development of PCOS may be attributed to several factors such as genetics, epigenetics, hyperandrogenism, insulin resistance, and environmental factors. Current medication used to treat PCOS have been shown to be ineffective and thus the development of novel therapeutics is necessary. Numerous types of stem cells can play a therapeutic role in the treatment of PCOS including mesenchymal stem cells, bone marrow stromal cells, adipose derived stem cells, menstrual blood derived mesenchymal stem cells, umbilical cord mesenchymal stem cells, amniotic fluid stem cells. Potential limitations include transplant rejection, transportation and storage difficulties, commercialization difficulty, and safety issues without monitoring.

Keywords: stem cells, exosomes, PCOS

Volume 9 Issue 1 - 2024

Hetvi Solanki, Vincent S Gallicchio
Department of Biological Sciences, College of Science, Clemson University, USA

Correspondence: Dr. Vincent S. Gallicchio, Department of Biological Sciences, 122 Long Hall College of Science, Clemson University, Clemson, SC 29636, Email vsgal@clemson.edu

Received: April 18, 2024 | **Published:** May 03, 2024

Abbreviations: ADSCs, adipose derived stem cells; AFSCs, amniotic fluid stem cells; AMH, Anti-Mullerian hormone; BMSC, bone marrow stromal cells; CC, cumulus cells; CDC2, cell division control 2; CTGF, connective tissue growth factor; DHEA, dehydroepiandrosterone; E2, estradiol 2; EXO, exosomes; FGF2, fibroblast growth factor 2; FSH, follicular stimulating hormonel; GADD45B, growth arrest and DNA damage inducible beta; IL-1B, interleukin 1 beta; LH, luteinizing hormone; MenSCs, menstrual blood derived mesenchymal stem cells; MSCs, mesenchymal stem cells; MSC-EVs, mesenchymal stem cell-derived extracellular vesicles; OSCs, ovarian stem cells; PCOS, polycystic ovarian syndrome; VEGF, vascular endothelial growth factor; VSELs, very small embryonic-like stem cells; TNFα, tumor necrosis factor alpha; UC-MSCs, umbilical cord mesenchymal stem cells

Introduction

Polycystic ovarian syndrome is one of the leading causes of female infertility in the world.[1] The ovary is multifunctional, possessing secretory and gametogenic functions. Due to this, dysfunction of the ovary can lead to a variety of health issues.[2] PCOS is linked to multiple other conditions such as hyperinsulinemia, insulin resistance, obesity, hyperandrogenism, type 2 diabetes, hypertension, cardiovascular disease, and infertility.[1] Mesenchymal stem cells possess a capacity for self-renewal, potential for differentiation, and immunomodulatory activities especially in diseases associated with inflammation.[1] Studies have shown MSCs may be able to reverse ovarian dysfunction by down-regulating pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1 beta, and interferon-gamma.[1] BMSCs can function as a model system for experiments focused on reproductive dysfunction.[2] ADSCs could successfully regenerate tissue and be easily isolated in a minimally invasive manner.[2] Umbilical cord mesenchymal stem cells display rapid self-renewal, low oncogenicity, noninvasive harvesting, and poor immunogenic characteristics. All these properties contribute to UC-MSCs ability to act as a therapeutic for PCOS.[2] MSC-EVs can function via promoting angiogenesis, regulating immunity, or reducing oxidative stress allowing them to be used as a therapeutic for PCOS.[3]

Epidemiology

Polycystic ovarian syndrome is one of the leading causes of female infertility in the world. It is a complex, polyfactorial condition which involves multiple genes and body systems.[1] Approximately 8-13% of adult women and 6% of adolescent females are afflicted with PCOS.[1] PCOS presents itself as the most common endocrine disorder in women of ages 18-44.[2]

Pathophysiology

Polycystic Ovarian Syndrome is a multisystemic disorder affecting the ovaries as well metabolic and endocrine functions. The ovary is multifunctional, possessing secretory and gametogenic functions. Due to this, dysfunction of the ovary can lead to a variety of health issues. The development of PCOS may be attributed to several factors such as genetics, epigenetics, hyperandrogenism, insulin resistance, and environmental factors. Possessing the Anti-Mullerian hormone coding gene can confer a predisposition for PCOS. Pathologically, a high LH:FSH ratio and an excess of GnRH are widely recognized as features of PCOS. Low-grade chronic inflammation is also commonly present in women with PCOS. Additional symptoms include chronic anovulation, increased ovarian function, excess androgen levels, menstrual abnormalities, and ovarian cysts. PCOS is linked to multiple other conditions such as hyperinsulinemia, insulin resistance, obesity, hyperandrogenism, type 2 diabetes, hypertension, cardiovascular disease, and infertility (Figure 1).[1,2]

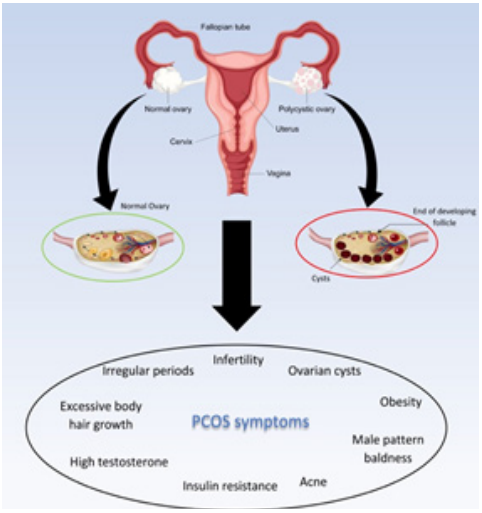

Figure 1 The pathophysiology and symptoms of polycystic ovarian syndrome.[1]

Current standard of care

Current treatments for PCOS are limited. Oftentimes, lifestyle changes including increasing exercise and losing weight are recommended.[4] Oral contraceptives and ovulation stimulating drugs such as letrozole, clomiphene, and metformin are also options.[1] However, current medication used to treat PCOS have been shown to be ineffective and thus the development of novel therapeutics is necessary.

The role of stem cells

Numerous types of stem cells can play a therapeutic role in the treatment of PCOS including mesenchymal stem cells, bone marrow stromal cells, adipose derived stem cells, menstrual blood derived mesenchymal stem cells, umbilical cord mesenchymal stem cells, amniotic fluid stem cells.[2] Mesenchymal stem cells possess a capacity for self-renewal, potential for differentiation, and immunomodulatory activities especially in diseases associated with inflammation. MSCs can also be derived from various sources such as bone marrow, fat tissue, amniotic fluid, umbilical cord tissue, placental tissue, menstrual blood, salivary glands, Wharton jelly, dental pulp and pluripotent stem cells. For this reason, they are promising as therapeutics for PCOS. Studies have shown MSCs may be able to reverse ovarian dysfunction by down-regulating pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1 beta, and interferon-gamma. In addition, connective tissue growth factor and other fibrosis-related genes are also down-regulated. MSCs can modulate PCOS in multiple ways. Ovarian function can be improved potentially via mediation by paracrine signaling pathways. Evidence supporting this is that the RAP1/NFkb pathway regulates MSC paracrine function and NFKb is also involved in inflammatory reproductive system disorders implying a connection between the two. Mitochondrial transfer of MSCs into T cells can potentially control inflammation, however further research is needed. An insufficient number of differentiated MSCs to account for fertility improvement were discovered in a study investigating this topic.[2] MSC-EXOs possess the ability to suppress immune response including inflammation. EXOs derived from adipose MSCs can increase levels of immunomodulatory cytokines, decrease gamma-interferon expression and transcription factors, and limit inflammatory response locally while also promoting tissue regeneration. Furthermore, microRNAs derived from exosomes possess the potential to function as biomarkers to detect and manage PCOS.[1]

Bone marrow stromal cells may also contribute to the treatment of PCOS for several reasons. BMSCs can differentiate into endometrial, endothelial, and granulosa cells. In addition, BMSCs can function as a model system for experiments focused on reproductive dysfunction. A study showed that BMSCs led to an induction of VEGF expression, elevated estradiol levels, downregulated caspase-3 (an apoptotic factor), and restoration of ovarian structure. A limitation of this cell type is its long replication cycle.[2]

Another group of stem cells that may contribute to the treatment of PCOS are adipose derived stem cells. ADSCs can successfully regenerate tissue and be easily isolated in a minimally invasive manner. A broad differentiation capacity and immunosuppressive activity is also exhibited by ADSCs. In rats, ADSC-based therapy upregulated VEGF, stimulated blood vessel growth, and improved ovarian graft quality. An increase in the number of follicles was also observed indicating enhanced ovulation. Further research needed to overcome technical challenges in utilizing this cell type.[2,5]

Menstrual blood derived mesenchymal stem cells can restore ovarian function. Benefits of this cell type include that they are plentiful and do not display autoimmune rejection. They have been found to play a protective role against granulosa cell death in ovarian instersitium in an animal model. This observed effect could be due to downregulation of GADD45B and upregulation of CDC2 and cyclin B1. Another study showed that fibroblast growth factor 2 was upregulated via MenSCs which is beneficial in an ovarian structure and function context.[2]

Umbilical cord mesenchymal stem cells display rapid self-renewal, low oncogenicity, noninvasive harvesting, and poor immunogenic characteristics. All these properties contribute to UC-MSCs ability to act as a therapeutic for PCOS. In mice, UC-MSC transplantation led to a restoration of ovarian function in DHEA-induced PCOS. Inflammatory cytokines including IL-1B, TNFA, and interferon gamma were downregulated. In addition, fibroblast related genes including CTGF, were also downregulated. This exhibits the potential of UC-MSCs to be mobilized as a therapeutic for a chronic inflammatory disease such as PCOS.[2]

Amniotic fluid stem cells have also displayed immunomodulatory characteristics in relation to PCOS, however further research is needed.[2]

Extracellular vesicles derived from MSCs display greater biological stability and lower immunogenicity while retaining similar functions as MSCs. MSC-EVs can function via promoting angiogenesis, regulating immunity, or reducing oxidative stress allowing them to be used as a therapeutic for PCOS. Studies have implicated MSC-EVs in the improvement of ovarian health in women with PCOS (Table 1, Figure 2).[3]

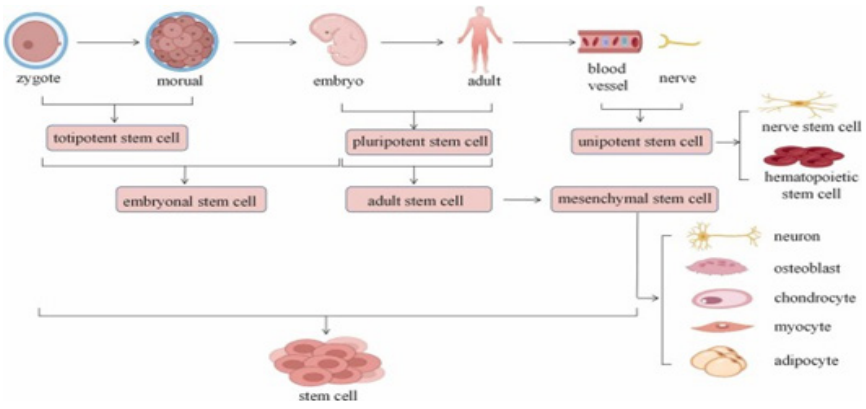

Figure 2 The potency of stem cells throughout development is shown here. In addition, numerous sources of stem cells are shown. The ability of mesenchymal stem cells to differentiate into multiple tissue types is also depicted.[4]

Citation: Solanki H, Gallicchio VS. Stem cell based therapy for polycystic ovarian syndrome. *J Stem Cell Res Ther.* 2024;9(1):4–7.
DOI: 10.15406/jsrt.2024.09.00165

Table 1 Types of stem cells and their advantages and disadvantages as a therapeutic

Type	Advantages	Disadvantages
Mesenchymal	self-renewal	lack standardized methods of:
	potential for differentiation	purification
	immunomodulatory activities	identification
	effective in diseases associated with inflammation	storage
		transportation
		administration
		safety
Bone Marrow	can differentiate into endometrial, endothelial, and granulosa cells	lack standardized methods of:
	function as a model for reproductive dysfunction	purification
		identification
		storage
		transportation
		administration
		safety
Adipose Derived	regenerative	lack standardized methods of:
	easily isolated in minimally invasive manner	purification
		identification
		storage
		transportation
		administration
		safety
Menstrual Blood Derived	restore ovarian function	lack standardized methods of:
	plentiful	purification
	no autoimmune rejection	identification
		storage
		transportation
		administration
		safety
Umbilical Cord	rapid self-renewal	lack standardized methods of:
	low oncogenicity	purification
	noninvasive harvesting	identification
		storage
		transportation
		administration
		safety
Amniotic Fluid	immunomodulatory characteristics	lack standardized methods of:
		purification
		identification
		storage
		transportation
		administration
		safety

Animal trials

In a rat model, AMSC-EXOs exhibited the ability to treat PCOS, improve fertility, and shield against metabolic issues. AMSC-EXOs transferred miR-21-5p thus resulting in the activation of the IRS1/AKT pathway and improving hepatic metabolism. PCOS symptoms were reduced via AMSC-EXOs edited with miR-323-3p due to the inhibition of cumulus cell apoptosis and increase of cell proliferation via engagement of programmed cell death protein 4. Further research indicated EXOs derived from hU-MSCs decreased the generation of TNFa and FN-y while increasing IL-10 levels and anti-inflammatory cytokines ultimately reducing ovarian granulosa cell apoptosis and suppressing inflammation.[1] Fertility was restored in a mouse model of PCOS by MSC-derived exosomes. In an *in vitro* model, androgen synthesis was regulated by MSC-EXOs.[1]

Therapeutic potential has been displayed by intravenous and intraovarian injections in a PCOS context. A more favorable outcome in systemic regulation is seen by intravenous administration. Intraovarian injections were more effective in inducing the recovery of ovarian function. PCOS was induced in female rats via letrozole. Treatment with both BM-MSC-EXOs and BM-MSC-conditional media of stem cells and exosome seemed promising.[1]

A study in mice found a relation between VSELs/OSCs and PCOS. Germ cell nest breakdown, meiosis, primordial follicle assembly and

unassembled ooctyes are affected by endocrine disruption in fetal and perinatal mice. These processes are related to very small embryonic-like stem cells (VSELs) and ovarian stem cells (OSCs) expressing Era, ERb, and FSHR undergoing cyclic changes and neo-oogenesis. Exposure to E2 (estradiol E2) an endocrine disruptor led to symptoms of PCOS including hyperandrogenism, infertility, increased stromal compartment, absent corpus lutea, and cystic follicles. Exposure to another endocrine disruptor DES, led to multi-ovular and cystic follicles. The immortal nature and surface expression of Era and ERb by VSELs makes them vulnerable to carry endocrine disruptions that occur during development into adult life. The oocyte defects observed could be due to dysfunction of VSELs/OSCs.[6]

Clinical trials

Numerous pre-clinical and clinical trials have been conducted and have confirmed the efficacy of MSCs in various diseases including female reproductive disorders. Potential limitations include- transplant rejection, transportation and storage difficulties, commercialization difficulty, and safety issues without monitoring.

A study has found that MSC-EVs showed potential to relieve PCOS via insertion of miR-323-3p by inhibiting apoptosis and promoting growth of CCs thus improving their viability. Limitations include lack of standardized methods for purification and identification of MSC-EVs including large-scale generation, storage and transport considerations, mechanism, and safety of MSC-EVs, and limited yield.[5]

Conclusion

Current treatments for polycystic ovarian syndrome include weight loss, oral contraceptives, and ovulation stimulating drugs. Despite the presence of these various treatments, they lack efficacy. For this reason, the development of new therapeutics is needed. Stem cells possess great potential to treat inflammatory diseases such as polycystic ovarian syndrome. Further research is needed to standardize methods of purification and identification, storage and transportation, and administration mechanism and safety.

Acknowledgments

None.

Conflicts of interest

The author declares that there are no conflicts of interests.

References

1. Hadidi M, Karimabadi K, Ghanbari E, et al. Stem cells and exosomes: as biological agents in the diagnosis and treatment of polycystic ovary syndrome (PCOS). *Front Endocrinol*. 2023;14:1269266.
2. Esfandyari S, Chugh RM, Park HS, et al. Mesenchymal stem cells as a bio organ for treatment of female infertility. *Cells*. 2020;9(10):2253.
3. Liao Z, Liu C, Wang L, et al. Therapeutic role of mesenchymal stem cell-derived extracellular vesicles in female reproductive diseases. *Front Endocrinol*. 2021;12:665645.
4. Zheng X, Zhao D, Liu Y, et al. Regeneration and anti-inflammatory effects of stem cells and their extracellular vesicles in gynecological diseases. *Biomed Pharmacother*. 2023;168:115739.
5. Cao M, Zhao Y, Chen T, et al. Adipose mesenchymal stem cell-derived exosomal microRNAs ameliorate polycystic ovary syndrome by protecting against metabolic disturbances. *Biomaterials*. 2022;288:121739.
6. Sharma D, Bhartiya D. Dysfunctional ovarian stem cells due to neonatal endocrine disruption result in PCOS and ovarian insufficiency in adult mice. *Stem Cell Rev Rep*. 2022;18(8):2912–2927.

Citation: Solanki H, Gallicchio VS. Stem cell based therapy for polycystic ovarian syndrome. *J Stem Cell Res Ther.* 2024;9(1):4–7.
DOI: 10.15406/jsrt.2024.09.00165