Akkoc T, et al., J Reprod Med Gynecol Obstet 2024, 9: 162
DOI: 10.24966/RMGO-2574/100162

HSOA Journal of
Reproductive Medicine, Gynecology & Obstetrics

Review Article

Advancements in Infertility Treatment: The Convergence of Stem Cell and Exosomal Therapeutics

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Abstract

Infertility, a common condition characterized by a couple's inability to conceive after one year of unprotected intercourse. It explores the various factors contributing to infertility, such as genetic variations, lifestyle choices, and environmental factors, and their substantial influence on reproductive health. The text analyzes the constraints of traditional infertility treatments like hormonal therapies and Assisted Reproductive Technologies (ART), emphasizing the need for new therapeutic methods. The paper emphasizes the potential of regenerative medicine, specifically stem cell and exosome therapies, as promising alternatives that can target the fundamental cellular and molecular dysfunctions in infertility. The text delves into the regenerative potential of stem cell therapy for repairing damaged reproductive tissues and the function of exosome therapy in facilitating cellular communication and tissue repair. It highlights their capacity to provide individualized and minimally invasive treatment alternatives. The review also discusses the therapeutic possibilities of Mesenchymal Stem Cell-Derived Extracellular Vesicles (MSC-EVs) for treating female reproductive disorders like Polycystic Ovary Syndrome (PCOS), Premature Ovarian Insufficiency (POI), and Intrauterine Adhesion (IUA). It highlights their inherent therapeutic characteristics, decreased likelihood of causing immune responses, and improved biological durability. The text explores how MSC-EVs aid in functional interactions such as endometrium repair, fibrosis suppression, immunomodulation, and apoptosis inhibition in ovarian granulosa cells. The review supports incorporating regenerative therapies into clinical practice to enhance reproductive outcomes. It presents a fresh viewpoint on the changing field of infertility treatments and their ability to surpass the constraints of conventional methods, giving new hope to individuals and couples dealing with infertility issues.

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Citation: Akkoc T, Kılıç SS (2024) Advancements in Infertility Treatment: The Convergence of Stem Cell and Exosomal Therapeutics. J Reprod Med Gynecol Obstet 9: 162.

Received: February 28, 2024; **Accepted:** March 08, 2024; **Published:** March 15, 2024

Definition and Overview of Infertility

Fertility is the ability of an individual to reproduce, while a woman's reproductive capacity is her biological capability to conceive based on the monthly likelihood of conception [1]. Infertility is the inability of a couple to achieve conception after one year of unprotected sexual intercourse. Several conditions such as ovulation abnormalities, tubal infertility caused by fallopian tube damage, cervical issues like benign growths or stenosis, and hormonal imbalances can lead to female infertility [2,3]. Predominant risk determinants for infertility encompass nicotine dependence, excessive ethanol ingestion, exposure to chemotherapeutic agents or ionizing radiation, protracted administration of high-dosage Nonsteroidal Anti-Inflammatory Agents (NSAIDs), utilization of antipsychotic pharmacotherapies, consumption of psychoactive substances such as cannabis and cocaine, adiposity, senescence, and Sexually Transmitted Infections (STIs). The ascending prevalence of infertility has necessitated a paradigm shift towards environmental etiologies, as genetic attributions prove to be non-exhaustive. The pathogenesis of female infertility is multifactorial, entailing genetic polymorphisms, chromosomal aberrations, lifestyle determinants, ovulatory insufficiencies, tubal pathologies, endometriosis, and cryptogenic infertility. In contemporary research, considerable emphasis has been placed on lifestyle determinants, with a plethora of studies elucidating the negative ramifications of suboptimal lifestyle practices, including dietary patterns, psychological stress, ethanol consumption, tobacco exposure, and adiposity, on female physiological processes in a longitudinal context. These lifestyle modalities exert a profound impact on both somatic health and reproductive efficacy, with a copious body of evidence underscoring a pronounced decrement in fecundability among females [4,5]. Exclusive contributors to female infertility entail dysregulated menstrual patterns, historical instances of tubal gestation, disorders of ovulation, and uterine deviations, including endometriosis, uterine leiomyomas, endometrial polyps, and intrauterine adhesions, the latter of which is frequently designated as Asherman's syndrome [6].

Conventional Therapies

Conventional approaches to infertility management feature hormonal interventions, including follicle-stimulating hormone and human chorionic gonadotropin, tubal repair procedures, and assisted reproductive techniques. Yet, these strategies may precipitate undesirable side effects or adverse outcomes. Specifically, hormonal therapies bear the risk of inducing severe conditions like Ovarian Hyperstimulation Syndrome (OHHS) or contributing to mental health issues [7,8]. Current infertility treatments, which include hormonal

therapies, surgical interventions, and Assisted Reproductive Technologies (ART), provide beneficial solutions but come with potential side effects and differing success rates. The limitations highlight the pressing necessity for innovative approaches that can offer more efficient and less intrusive alternatives for patients [8].

Regenerative therapies, such as stem cell and exosome-based treatments, are promising alternatives in this context. Stem cells have the potential to repair damaged reproductive tissues by differentiating into various cell types, addressing infertility at a cellular level. Mesenchymal Stem Cells (MSCs) have demonstrated potential in rejuvenating ovarian function and enhancing uterine receptivity, both crucial aspects of fertility [9,10]. Exosomes have been firmly established as crucial in the field of reproductive biology through scientific investigation. Improved understanding of exosomes' roles in reproductive processes is expected to accelerate the development of new therapeutic approaches to treat infertility and reduce pregnancy-related issues. Anatomical components of the male and female reproductive systems, such as the prostate, epididymis, ovaries, endometrium, oviducts, placenta, and embryos, have been found to be able to produce and release exosomes. Exosomal entities play a crucial role in various important reproductive processes including gametogenesis, fertilization, embryonic development, and implantation. Exosomes play a crucial role in human reproductive processes and have the potential to be used in reproductive medicine and infertility treatment [11,12].

Mesenchymal Stem Cells (Msc) and Exosome Therapies in Regenerative Medicine

MSC and Infertility

Mesenchymal Stem Cells (MSCs) and their exosomes are leading the way in advanced cell-based therapies due to their easy accessibility and fewer moral concerns when compared to embryonic stem cells. MSCs are diverse stromal cells capable of differentiating into various cell types such as osteoblasts, chondrocytes, myocytes, and adipocytes. This highlights their significant potential in regenerative medicine for repairing and regenerating injured tissues [13]. Mesenchymal Stem Cells (MSCs) are multifunctional cells capable of self-renewal and differentiation into different cell types such as adipocytes, chondrocytes and osteocytes [14]. As per the International Society for Cellular Therapy (ISCT) guidelines, Mesenchymal Stem Cells (MSCs) need to stick to plastic in regular culture conditions, show certain cell surface markers like CD73, CD90, and CD105, not have markers like CD14, CD34, CD45, CD19, CD11b, CD79a, and HLA-DR, and demonstrate the capacity to transform into adipocytes, osteocytes, or chondrocytes in a lab setting [15]. MSCs can be obtained from different tissues such as adipose tissue, umbilical cord blood, Wharton's jelly, the placenta, bone marrow, and dental pulp [16,17]. Due to their minimal ethical concerns, ease of acquisition, isolation from tissues, anti-inflammatory properties, and immunomodulatory capabilities, they are considered a very promising treatment for various autoimmune diseases [18].

Stem cells have been used in research on male infertility conditions such as azoospermia, aspermia, oligospermia, and varicocele. Adipose tissue-Derived Mesenchymal Stem Cells (ADSCs) have been used in rat experiments, resulting in improved sperm production and changes in the physical structure of testes. Some studies have reported successful births following this treatment. UCSCs and iPSCs have been utilized in mouse and human models, leading to an augmentation in germ cell quantities and improved testicular tissue organization. Spermatogonial Stem Cells (SSCs) have been used in macaque models to induce spermatogenesis [19-21].

Female reproductive health focuses on conditions like Asherman's syndrome, intrauterine adhesions, and thin endometrium that are linked to infertility and recurrent pregnancy loss. Menstrual Blood-Derived Stromal Cells (MenSCs) and UCSCs have been used in humans to improve the condition of the endometrium. Some studies have reported successful pregnancies and births after this treatment. Endometrial Progenitor Cells (EPCs) have been utilized in mouse models to investigate and resolve endometrial thickness concerns [22]. Various stem cell sources have been studied for ovarian dysfunctions like Polycystic Ovarian Syndrome (PCOS) and premature ovarian failure. Adipose-Derived Stem Cells (ADSCs) have been researched in mouse and rat models, specifically examining follicle development and estradiol hormone production, which are crucial aspects of ovarian health and fertility [23]. Amniotic Fluid Stem Cells (AFSCs) and Bone Marrow Stem Cells (BMSCs) have been studied in mouse models to assess their effects on follicle numbers and hormone levels. The research observed a decrease in follicular stimulating hormone (indicating enhanced ovarian function) and a rise in estradiol levels. Oogonial Stem Cells (OSCs) and Embryonic Stem Cells (ESCs) are being studied for their ability to enhance the production of healthy eggs, potentially resulting in successful pregnancies [24].

The studies cited in that, stem cell therapies offer empirical evidence and in-depth understanding of the effectiveness of these stem cell treatments. The variety of stem cell origins, ranging from adipose tissue to embryonic cells, demonstrates the wide range of potential regenerative treatments for reproductive health problems. This thorough collection highlights the progress in stem cell research focused on reproductive medicine and its potential to address infertility.

Exosomes and Infertility

Exosomes released by MSCs, small extracellular vesicles, are crucial for cell-to-cell communication. They transport various bioactive compounds like proteins, lipids, mRNA, and microRNA to recipient cells, affecting different physiological and pathological processes. This interaction is essential for regulating the cellular environment, aiding in tissue repair, immune modulation, and angiogenesis, as well as other regenerative processes. Exosomes, a type of Extracellular Vesicles (EVs) that are 30 to 120 nm in size and originate from endosomes, have garnered growing interest in scientific research. Once considered cellular waste, exosomes are now acknowledged for their function in cellular communication [25]. They are found in various bodily fluids such as blood, urine, saliva, and amniotic fluid. Exosomes contain a wide range of molecules including lipids, proteins, nucleic acids such as miRNA, mRNA, genomic DNA, and mitochondrial DNA [26]. Exosomes have a varied biochemical profile that makes them promising for identifying biomarkers crucial for diagnosing and tracking different diseases [27].

Extracellular Vesicles (EVs) are lipid-encapsulated structures released by all types of cells that play a crucial role in communication between cells. Vesicles play a crucial role in transporting various biological signals and molecular cargo, including proteins, nucleic acids, and other bioactive molecules, between cells to support numerous cellular processes [28] . Extracellular vesicles can trigger specific cellular responses by interacting with membrane proteins of recipient cells via their own surface proteins, going beyond simple molecular

transport [29]. One notable characteristic of these vesicles is their capacity to transfer membrane proteins to another cell by merging with the recipient cell's membrane, incorporating the vesicle membrane into the target cell's membrane.

The durability and reliability of exosomes make them even more attractive as possible methods for delivering genes and pharmaceuticals. New findings have highlighted their involvement in almost all cellular activities, impacting biological processes like differentiation, immune regulation, and angiogenesis. They are also linked to disease-causing processes such as tumor formation and immune system avoidance. Exosomes are being extensively studied for their therapeutic potential, especially in the fields of immunomodulation and tissue regeneration, signaling a new phase in molecular medicine [30].

MSC-derived exosomes are attractive in scientific research because they can mimic the regenerative abilities of their parent cells without the drawbacks of direct cell transplantation, like the potential for immune rejection or cancerous changes. Additionally, using exosomes avoids the ethical and logistical challenges of stem cell therapy, providing a cell-free option that is easier to standardize, preserve and administer. The diverse differentiation abilities of MSCs, along with the distinctive characteristics of their exosomes, particularly their role in facilitating cellular interactions and delivering therapeutic substances, make them crucial assets in the growing field of regenerative medicine and cell-based treatments [27].

In the context of reproductive pathologies, exosomes derived from various biological sources possess distinct molecular profiles that can serve as non-invasive biomarkers and therapeutic agents. The table delineates these exosomal sources and their associated biomolecules for a range of conditions. For Polycystic Ovary Syndrome (PCOS), exosomes obtained from serum plasma, follicular fluid, and adipose tissue exhibit miRNAs like miR-373 and miR-29, which could facilitate early detection and potentially mitigate the disorder by modulating protein expression linked to PCOS pathogenesis [28,31,32]. In cases of reproductive inflammation, exosomes from serum plasma, placental fluid, and amniotic fluid are rich in miRNAs such as miR-126-3p. These biomarkers may assist in the early identification of inflammation and provide insights into inflammatory pathways, paving the way for targeted therapeutic approaches [33,34].

Endometriosis-associated exosomes from serum plasma, follicular fluid, and endometrial stromal cells, containing miRNAs like miR-134-5p, could expedite the diagnosis and enhance treatment strategies for this condition [35-37]. For Gestational Diabetes Mellitus (GDM), exosomal miRNAs isolated from serum plasma, urine, and blood from the umbilical vein, such as miR-16-5p, may offer swift therapeutic options to avert long-term maternal and fetal complications [38-40]. Finally, in Pre-eclampsia, exosomal miRNAs from maternal circulation and cell lines, notably miR-210, may offer prognostic benefits, enabling interventions to forestall the severe consequences of this pregnancy complication [33]. Collectively, these exosomal biomarkers present a promising frontier in the non-invasive monitoring and treatment of reproductive disorders, as evidenced by the referenced literature. The studies provide a foundation for the utility of exosomal content in advancing the diagnosis, understanding, and treatment of reproductive health challenges.

Infertility is discussed in detail, with an emphasis placed on the complex factors that contribute to it. These factors include genetic and lifestyle influences, both of which have the potential to impact reproductive health. Traditional treatments, such as hormonal therapies and assisted reproductive technologies, are effective; however, they also have drawbacks, which is why it is necessary to investigate regenerative methods, such as stem cell and exosome therapies. It has been demonstrated that the novel treatments have the potential to treat infertility by targeting cellular mechanisms. This could result in tissue regeneration and enhanced reproductive capabilities. The research sheds light on the multifaceted nature of infertility as well as the evolving treatment approaches, which are moving toward more individualized and minimally invasive approaches to assist individuals and couples who are struggling with reproductive issues.

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