

Cell Based Therapy for Infertility: A Review



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1. Introduction

Cell Based Therapy (CBT) is transfer of cells of human with the aim to restore the damaged tissue or cells. With the augmentation of newer technologies, innovations, ideations, many different types of cells are being used for the treatment of diverse disease conditions and disorders. Cells that may be employed are pancreatic islet cells, skeletal muscle stem cells, dendritic cells, mesenchymal stem cells, blood forming cells/ hematopoietic stem cells (HSC). Bone marrow transplant also called HSC transplantation is the most widely used CBT and is utilized in treatment of hematologic conditions and many types of cancers. Impending applications of CBT are numerous for example cancers, urinary problems, repair of spinal cord injuries, immune system improvement, neurological disorders like Alzheimer, Epilepsy etc (1, 2).

2. Need for CBT for Infertility

Worldwide large numbers of couples have problems conceiving. Because of this there is deprivation in having offspring that are genetically related. The treatments to overcome this issue are many like drugs inducing ovulation, Assisted Reproduction Technology (ART). But these treatments develop the risks of multiple pregnancies. To overcome the drawbacks of the traditional treatment methods the basic ability of stem cells to replenish damaged tissues and their ability to differentiate the multiple lineages, the CBT is considered to be a novel technique to deal with the reasons of infertility (3).

3. Causes of Infertility

The age of the woman is the most common risk factor for infertility. If the female's age is more than 35 years the evaluation for the infertility must be started as early as 6 months from the realisation of unable to conceive, whereas if the females age exceeds 40 years immediate evaluation is recommended. However, there are potential contributing factors that need to be evaluated before narrowing down the diagnosis and a therapeutic approach (4). The causes of infertility are summarised in Fig.1.

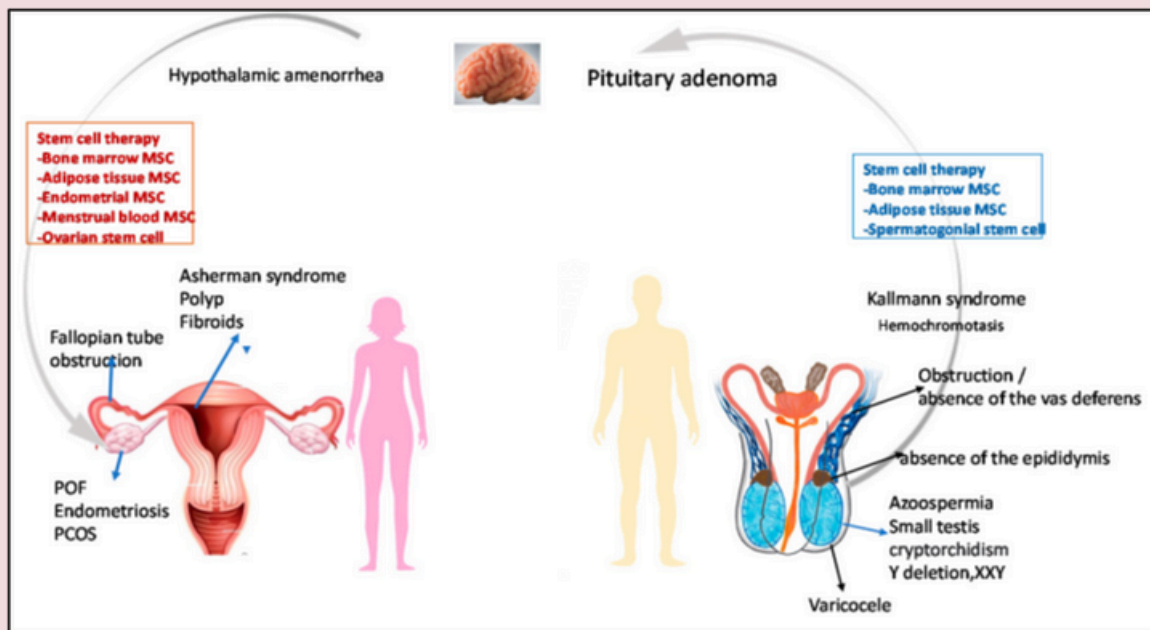


Figure 1: Some causes of infertility

4. Conventional Treatment

To treat male infertility, various measures are incorporated like increase the sperm quality, the causes of endocrinopathy are identified and treated accordingly. In case of Varicocele, surgery interventions are preferred (6).

To treat the infertility in females, ovulation inducing drugs are used based on the diagnosis done. In contrast to conventional treatment, ART improves the rate of fertilization. ART includes several steps in a particular order Ovarian Stimulation, Oocyte retrieval, In vitro fertilization and Embryo culture, Embryo transfer (7,8,9,10,11,12,13,14,15).

Unfortunately, even after the substantial progress of ART, many couples are still unable to be a parent to healthy babies. Moreover the cost involved in ART is high and is an invasive process. CBT presents a new hope to overcome the issues related to above mentioned methods and have success to resolve the infertility of couples.

5. CBT for treating Infertility

A subtype of cells called Stem Cells remain in embryos and human tissues in an undifferentiated form. They can renew on their own and differentiate when needed. In differentiated organs stem cells restores the function of organ damage repair. Based on their origin, these stem cells are of various types. The embryonic stem cells, adult stem cells which are mesenchymal stem cells, induced pluripotent stem cells, spermatogonial stem cells and ovarian stem cells (3).

5.1 Embryonic Stem Cells (ESC)

ESC has an immense capacity of self-renewal, able to differentiate into three segments ectoderm, endoderm and mesoderm, able to maintain the specific karyotype at the time of growth. In humans they are derived from inner blastocysts and transcription factor Oct 4. There is documentary evidence of feasibility of development of functional sperm using gene repaired ESC. Hence we can say ESCs have a promising tool to address the cause of infertility. But due to ethical concerns it is not so commonly used technique (16).

5.2 Induced Pluripotent Stem Cells (iPSC)

The cells derived from skin or blood cells and are reprogrammed back to a pluripotent state is called iPSC. They enable development of boundless source of any type of cell required for therapeutic purpose. For instance, an iPSC can be stimulated to become a beta islet cell to treat diabetes and so on. These iPSCs are considered to be better than ESCs in CBT for the reasons that they originate from adult cells unlike the ESC hence avoids the ethical issue of using embryos and another reason is iPSCs are developed from the patients' somatic cells, therefore comparatively less chance of immune rejections (17, 18). Generation and projected therapeutic suggestions of iPSCs in infertility are presented in Figure 2.

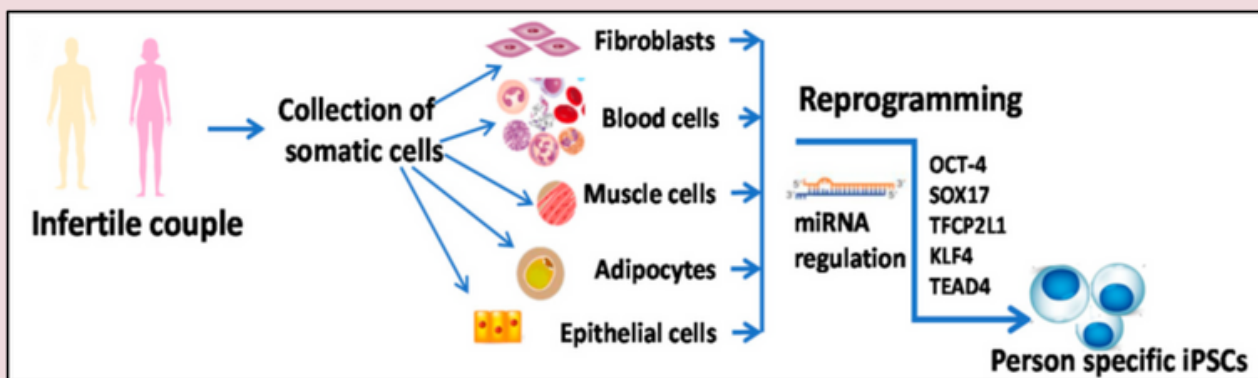


Figure 2: Role of stem cells in generation of patient-specific gamete cells (35).

KLF4: Kruppel-like factor 4; miRNA:Micro RNA; OCT-4: octamer-binding transcription; SOX17: endoderm regulator SRY-box 17;TEAD4: trophoctoderm regulator TEA domain transcription factor 4; TFCP2L1: TFCP2L1: pluripotency factors transcription factor CP2-like 1. Reprinted with permission (43)

Though the iPSC technology does not abolish the embryos, the chances to exploit embryos generated from gametes established after iPSCs reprogramming mandate ethical consent from the institutional review board and the assembly of informed consent from the cells or tissue donor previous to obtaining sample for development of iPSC for research purpose. For their solicitation in animal models, consent is essential from IACUC.

5.3 Mesenchymal Stem Cells (MSCs)

They are also known as mesenchymal stromal cells or medicinal signalling cells are multipotent stromal cells. They have plastic-adhesion properties; can segregate into various types of cells, involving osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and adipocytes (fat cells which give rise to marrow adipose tissue). Based on their origin they are of many types like

1. bone marrow stromal cells
2. adipose-derived stem cells
3. menstrual-blood-derived MSCs
4. umbilical-cord-derived MSCs
5. amniotic-fluid-derived MSCs
6. placental-tissue-derived MSCs
7. salivary-gland-derived MSCs, and
8. dental-pulp-derived MSCs

The MSCs work by travelling to the damaged ovary and there they help in restoring the ovarian function by the release of various cytokines by paracrine mechanism. The cytokines induces the formation of newer vessels, prevents apoptosis, fibrosis and therefore ameliorate ovarian dysfunction. The MSCs also helps in endometrial regeneration through release of many bioactive molecules which modulate inflammation and other immunological reactions. They also help in activating tissue-specific progenitor cells. The potential therapeutic use of MSCs for the treatment of infertility caused by ovarian and endometrial abnormalities has been reported in a number of preclinical and clinical trials. According to reports, as people become older, MSCs become less potent and abundant as well as less able to divide and differentiate into distinct lineages (19, 20, 21).

5.3.1 Bone Marrow Mesenchymal Stem Cells (BMSC)

They are separated from one another using a density gradient centrifuge, and after that, the incubation for growth and expansion procedure is performed. In rat models, the BMSC were proven to be effective in endometrial and follicular cell growth, endometrial mending, hormonal resuscitation, and conception. Infertile patients' endometrial thickness, the quantity of developed blood vessels, and the kind of menstruation they had all showed improvement. There is proof that BMSCs may offer renewed hope for individuals suffering from ovarian or uterine disorders(22).

5.3.2 Menstrual Blood Mesenchymal Stem Cell (MB-MSc)

These cells may be obtained by non-invasive methods that are simple, secure, and free from moral dilemmas and minor immunological responses, allowing for therapeutic use. According to study, angiogenesis and the production of anti-inflammatory factors by MB-MSc can restore fertility in animals with damaged uterine walls (23, 24).

5.3.3 Endometrial Stem Cells (EndSCs)

Stromal cells, epithelial progenitor cells, and endothelial cells constitute the EndSC microenvironment. The distinct stem cells are present in the endometrium in a resting, undifferentiated state when there is no lesion. Mesenchymal stem cells (MSCs), epithelial stem cells (ESCs), endometrial side population cells (ESPs), and endometrial regenerative cells are all descended from endometrial stem cells (ERC). ERCs, like MSCs, may differentiate into diverse tissues, including adipose tissue, neural tissue, bones, and cartilage. In an animal transplantation model, it was shown that insufficient neovascularization led to the endometrium's thinning, probably as a result of the vascular endothelial growth factor's defective discharge. Therefore, the therapeutic use of endometrial stem cells for endometrial regeneration may involve their angiogenic potential (25). The Figure 3 encapsulates the various mechanisms for restoring the endometrium.

5.3.4 Umbilical Cord Mesenchymal Stem Cells (UC-MSCs)

UC-MSCs have emerged as a common cell-based therapy technology for the restoration of fertility due to their low tumorigenicity, quick capacity for self-renewal, ease of resource availability, lowest ethical issues, and low immunogenicity. Due to their antiapoptotic action over granulosa cells and manipulation of hormone levels, UC-MSCs restored ovarian function in multiple experimental animals who had early ovarian impairment (26, 27).

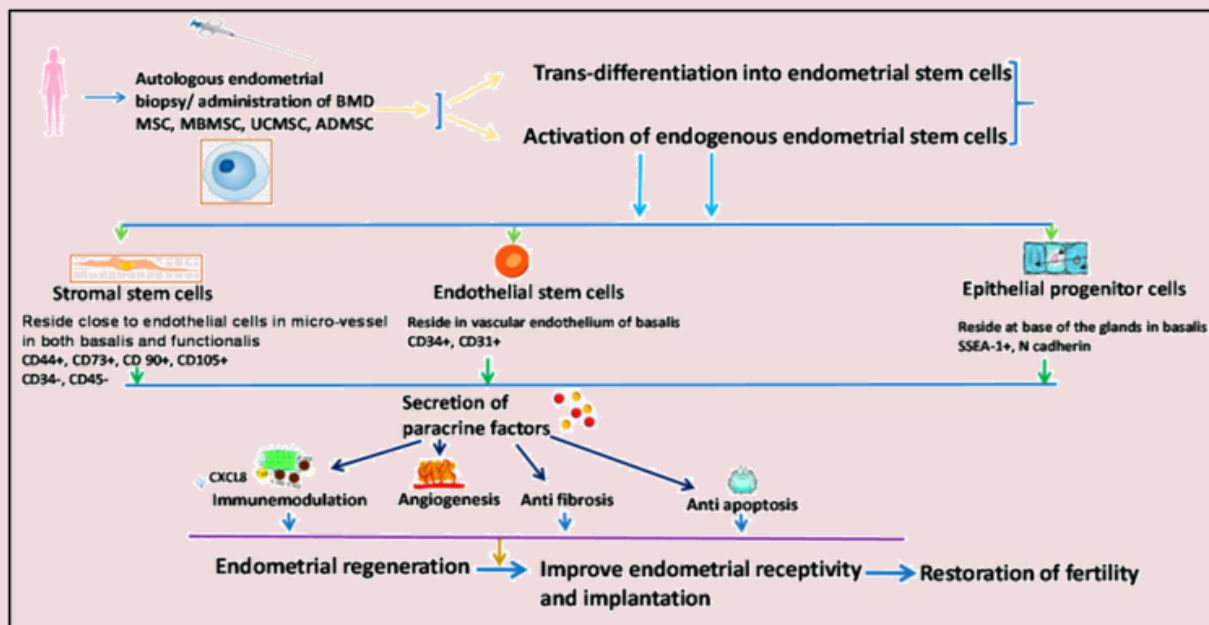


Figure 3: The explanation for restoration of fertility via endometrial regeneration;

ADMSC: adipose-tissue-derived mesenchymal stem cell; BMDMSC: Bone-marrow-derived mesenchymal stem cell; CD: Cluster of differentiation; CXCL: C-X-C motif chemokine ligand; MBMSC: menstrual blood mesenchymal stem cell; SSEA-1: Stage-specific embryonic antigen-1; UCMSC: umbilical cord mesenchymal stem cell. Reprinted with permission (43)

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5.3.5 Amniotic Fluid Stem Cells (AFSCs)

The amniotic fluid, which serves the foetus's nutritional needs, is a significant source of MSCs. There are no strict regulatory requirements or ethical considerations in the AFSCs purchase. Additionally, it has the innate capacity to develop into a variety of cells, including osteocytes, muscles, and adipocytes, making it a very valuable source for regenerative medicine. Studies have demonstrated that AFSCs may aid in the treatment of infertility problems by restoring the activities of the ovaries through the activation of several signalling molecules, including bone morphogenic protein (BMP), epidermal growth factor (EGF), and many more (28, 29, 30).

5.3.6 Amnion-Derived Mesenchymal Stem Cells (AmDMSCs)

The thin membrane forming a closed sac about the embryos is called amnion. The amnion serves as a hopeful source of CBT. The studies are performed for treating the ovarian dysfunction in chemotherapy based animal models. AmDMSCs work through paracrine strategies to enhance the granulosa cells in the physical vicinity while also minimising apoptosis. (31, 32).

5.3.7 Placenta-Derived Mesenchymal Stem Cells (PDMSCs)

The studies conducted on animal models have revealed that PSMSCs act by improving folliculogenesis through cytokine modulation and elevation of hormone levels such as estradiol, LH, FSH and their receptor expressions (33, 34).

5.3.8 Adipose-Tissue-Derived Stem Cells (AD MSC)

ADMSC is a unique form of MSC; while coming from distinct origins, they share comparable biologic characteristics. Because ADMSC may be produced using less traumatic methods and in greater amounts than BMSC, they offer comparative benefits over the latter. These characteristics increase the acceptability of ADMSC for a variety of clinical diseases in regenerative medicine. In an animal model of Asherman syndrome, ADMSCs with hormone treatment might successfully reduce fibrosis and trigger endometrial rejuvenation by angiogenesis (35, 36, 37).

5.4 Ovarian Stem Cells (OSC)

The idea of the existence of OSCs was first suggested by observations of the pace of follicular atresia, associated with the mortality of oocytes and loss of ovarian reserve in mice. It has been proven that these cells were capable of initiating follicle production. However, these cells were hidden for a very long period, most likely as a result of their extremely small number, which made up just 0.0145% of the entire cell population in the ageing mouse ovary. Additionally, similar to their male counterparts, these cells require a longer extent for differentiating in in vitro culture. For people suffering from idiopathic premature ovarian failure, OSCs may provide new hope. Revival of fertility and live births are two examples of OSCs' proven therapeutic uses in age-associated infertility (38, 39).

5.5 Spermatogonial Stem Cell (SSC)

Through self-rejuvenation and limitless segmentation into spermatogonia and haploid spermatozoa, SSCs play a crucial part in maintaining the highly efficient complicated procedure known as spermatogenesis in the seminiferous tubule. Figure 2 depicts the creation of them. These differentiating spermatozoa fertilise the oocytes. Infertility may result from any deviation in these carefully timed stages of spermatogenesis. SSCs are a highly effective method for treating infertility, but due to the small amount of them in testes and the difficulty in recognizing them to gradually separate and grow them, they are not employed as regularly in regenerative medicine. Technology advancements have made it possible to extract and describe SSCs using their distinct, species-specific identifying markers. Rather than sending SSC to testicles, they can be cultivated. SSC may be employed in unique situations such male infertility brought on by chemotherapy since it has been shown to induce spermatogenesis and produce functional sperm. The biggest drawback of this CBT in reproductive medicine is that it may disrupt the testis' natural environment, making SSC transplantation unacceptably risky and ultimately leading to therapeutic failure (40, 41).

6. Conclusions

Across the board, 15% of couples struggle to become pregnant. Infertility cases are on the rise as people are waiting longer to start a family. Infertility can be caused by a variety of reasons, which can affect either the female or the male, or a combination of the two. A thorough investigation of infertility, including measurements of blood hormone levels and semen, may help in identifying the main factors at fault. A significant proportion of couples reportedly experience infertility even after ART. CBT may offer relief in these situations for couples hoping to conceive genetically related children. ESC transplantation has fallen out of favour due to ethical concerns and immunologic interference, leading experts to learn about other stem cell

possibilities. iPSCs are the subject of extensive study since they have little to no ethical concerns and can produce findings that are satisfactory. The use of MSCs is also growing due to their low ethical issues and ease of access to a variety of readily available sources, including bone marrow, adipose tissue, menstrual blood, amnion, amniotic fluid, and placenta. Numerous animal and human research have examined the effect of MB-MSCs in endometrial regeneration and the recovery of ovarian function. Understanding of the role of microRNAs in stem cell differentiation is essential for gaining a thorough grasp of the methods by which stem cells function to restore fertility. Large-scale clinical trials are still necessary to validate the security and effectiveness of stem cell-based treatment in the area of human reproduction, nevertheless.

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