Understanding Infertility and the Potential Role of Stem Cells in Infertility Treatment: A Short Communication

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Abstract

Infertility is increasing at a great rate across the globe. Various male as well as female factors are known to contribute to infertility. Although hormonal replacement therapy and assisted reproduction treatments like *in vitro* fertilization and intracytoplasmic sperm injection are well established clinical modalities to treat infertility, stem cells are now being considered as potentially new therapeutic agents for the treatment of infertility due to their high differentiation potential. Several studieshave shown that stem cell transplantation, also known as stem cell based therapy facilitates endometrial regeneration, ovarian regeneration, oocyte production in females; and activates the process of spermatogenesis in males. The present mini review is an attempt to understand the gravity of infertility as a disease, discuss some of the major causes leading to infertility in males and females and to summarize the current knowledge regarding the use of stem cells in reproductive medicine.

Introduction

Infertility or sub fertility is growing at an epic speed in India and in the rest of the world. About one in seven couples trying to conceive face difficulty in conceiving. Infertility is defined as failure to conceive after more than 12 months of unprotected intercourse [1].

For many couples, inability to bear a child is a failure on personal, interpersonal, social and religious levels. Many couples experience feelings akin to depression, guilt, frustration, threat and mourning. The family members usually blame one or both partners for the situation aggravating the feelings of emotional distress and marital disharmony [27]. Such situations further lead to social discordance, with some couples being considered as outcasts, and are completely omitted from attending social and family gatherings. In most of the situations, women alone are blamed for infertility and as a result are even subjected to physical violence [2]. Childlessness also increases the chances of co-morbid psychological and physical conditions such as breast cancer and endometrial cancer etc [3].

Infertility is a heterogeneous condition caused by various underlying pathologies. It is possible that some of the mechanisms leading to infertility also play a role in the aetiology of this outcome. In recent years, several advancements have been made in assisted reproduction treatments and therefore now more than 80% of couples experiencing infertility issues are able to conceive a child [2].

Primary infertility is when the woman having regular, unprotected intercourse cannot conceive even after five years of married life, whereas secondary infertility is when the woman has not conceived in the last five years of married life but has had a child sometime in the past [2].

In a normal course, one egg is released from the ovary around day 14th in a month long menstrual cycle. The egg travels along the fallopian tube into the uterus. On the way if it meets a sperm – that has travelled from the vagina by the virtue of its tail, it leads to the accomplishment of a process known as fertilization, thereby forming a very tiny baby called the embryo. The embryo now attaches itself to the endometrium (lining of the uterus) by a process called implantation. After a week of implantation the woman misses her period and the pregnancy is confirmed by doing a urine test. After that the baby grows within the uterus for a period of nine months till it's delivered [4].

Causes Of Infertility

Fertilization is natural process that is well regulated but it may be hampered if the eggs and/or the sperms are of poor quality and/or number. Though 60% of times the reason for reduced sperm counts is not known; varicocoele, hydrocoele, chronic epididymoorchitis are some conditions that lower the sperm count in males. Additionally infections caused by mumps, chlamydia, tuberculosis and sexually transmitted diseases; hypothyroidism or imbalance of reproductive hormones; excessive stress, life style related factors such as tobacco consumption, alcoholism, unhealthy eating habits, lack of exercise leading to chronic illnesses such as diabetes, cardiovascular diseases etc could affect sperm count in men [5]. Another reason especially common in men is exposure to excessive heat and/or to certain chemicals like benzene, toluene, and pesticides which are spermiotoxic leading to generation of gametes that are of poor quality. Only in 10% of men the cause of poor spermatogenesis is genetic in India [6]. Spermatogenesis is an extremely heat sensitive process, thus constant exposure to increased temperatures leads to azoospermia in males [6]. In females, oogenesis is poor mostly due to hormonal imbalances leading to conditions such as polycystic ovarian disease, endometriosis, and premature ovarian failure [7].

In certain cases the gametes are of good quality, but they fail to meet due to blockages in their course, as is commonly observed in tubercular infections of the genital tract and in endometriosis. 10% of Indian infertile woman are known to be positive for tubercular infections with disease manifestations such as irregular menstrual cycle to tubal blockage(s) of varying degrees [8]. Sometimes everything is right, however the embryo is not able to implant due

to failure of the endometrium that receives it. Other factors especially those related to pschycological barriers also play a very critical role in hindering conception. Lastly, there may be a possibility that the embryo is genetically abnormal and thus not continued, a means by which nature itself selects the fittest embryo [9].

One may be able to treat the poor quality and/or number of gametes with the help of hormonal therapy. Infections too can be treated with medication. Yet if pregnancy does not occur one may have to go through a process known as *in vitro* fertilization (IVF), commonly referred to as test tube baby [10] or take aid of other assisted reproductive technologies that are accepted medical treatments for infertility.

Assisted Reproductive Technology In Infertility Treatment

According to the Centers for Disease Control and Prevention, assisted reproductive technology (ART) includes all fertility treatments in which both eggs and sperms are handled. However, they do not include treatments in which only sperm are handled (i.e., intrauterine—or artificial—insemination) or procedures in which a woman takes medicine only to stimulate egg production without the intention of having eggs retrieved (www.cdc.gov/art/). IVF is the most preferred ART. The process of IVF was originally chalked for women who had blocked fallopian tubes, since it is possible to bypass the fallopian tubes and directly access the eggs from the ovaries. In a typical IVF, the woman's ovaries are stimulated to give more than one egg [11]. When the eggs mature, by a small operative procedure the eggs are retrieved outside the body. They are processed by the embryologist and depending on the sperm count of the partner IVF or intracytoplasmic sperm injection (ICSI) are done. For sperm count above 15-20 million/ ml, the eggs are incubated with the sperm in a petri dish (*in vitro* fertilization), but if the sperm count is less then it is advisable to go for micro manipulation, whereby a single, viable sperm is selected and injected directly into the oocyte (ICSI) [12]. For patients with very low sperm counts testicular aspiration of sperms or TESA is preferred, wherein the sperms are sucked out directly from the testis with the help of a needle and syringe and then incubated with the eggs in a petri dish. Typically anywhere between day 3 and day 5 post IVF or ICSI (around 10-12 celled stage), if the number(s) and quality of embryo(s) are good, the embryo(s) are transferred back into the uterus of the woman. Fourteen days post transfer of the embryo(s) pregnancy is confirmed by performing a pregnancy test [13].

Stem Cell Based Therapy: A Novel Approach In Infertility Treatment

In addition to the above established assisted reproductive treatments, scientists are now developing novel cell based approaches for infertility treatment. One approach that is being looked upon with great interest is the use of stem cells or stem cell based therapies[13]. Stem cells are highly unspecialized cells in the body that have the capacity to replenish the other cells in the body. Adult stem cells are known to be present in various body organs like the skin, the bone marrow, the brain, the heart etc. These cells although mostly present in the quiescent stage, get stimulated by secretion of soluble factors for the replenishment of cells. Hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) are well characterized and extensively studied adult stem cells. While HSCs can give rise to all the blood cell lineages; MSCs can differentiate into bone, cartilage, adipocytes and neuronal cells [14]. It is now know that these MSC like cells are also present in the endometrial lining and are known as endometrial stem cells (ESCs) [15]. Research has shown that ESCs play a very important role in the implantation and development of the embryo. People have tried to co-culture embryos with endometrial like cells *in vitro* that mimics the natural environment thereby improving the chances of the embryo to successfully undergo implantation when put into the uterus [16]. Patients in whom the endometrial growth of the cells is poor even in response to the hormonal treatment, scientists are developing ways to generate a healthy endometrium *in vitro* which could then be transplanted into the patient's uterus. Simultaneously, lot of work has been done and is being done to understand the role of the endometrial

microenvironment in contributing towards promoting fertility and pregnancy in women [17].

Asherman's syndrome is a condition where there is adhesion and fibrosis of the endometrium such that there is very little healthy endometrium for implantation. It is known to occur post dilation and curettage and also due to endometrial tuberculosis. The patient may present with reduced or no menstrual bleeding, pain and infertility [18]. In a single case reported from India, bone marrow derived stem cells have been used to treat Asherman's syndrome in an infertile patient. MSCs harvested from the bone marrow of the patient were cultured *in vitro* and then transplanted into the uterine cavity of the same patient (autologous transplantation). With the help of hormones the endometrium was stimulated to grow till the desired thickness was achieved, after which the embryo transfer was done*in utero*. The woman who underwent autologous transplantation using the bone marrow-derived MSCs successfully conceived [19].

Following the success of the above study another study was done in six patients with Asherman's syndrome following gential tuberculosis. Scientists transferred bone marrow derived stem cells into the sub-endometrial region of their uterus. The endometrium did not grow beyond 6.7 mm and pregnancy was not achieved. However all the patients experienced regular menstruation after the stem cell therapy. This experiment showed that initiation of a previously affected natural process like menstruation can certainly be restarted with the help of stem cell based treatments [20].

The exact mode of action of the MSCs is not known. However, studies show that MSCs tend to secrete antifibrotic, angiogenic, antiapoptotic, immune suppressive factors in a paracrine manner which promote the regeneration of the endometrial lining of the uterus [21]. Several signaling pathways such as Wnt, AKT are seen to play a very important role in mediating the regeneration potential of MSCs. AKT is a growth regulating pathway that blocks apoptosis leading to cell survival whereas Wnt/beta-catenin pathway controls cell growth and differentiation of the endometrial stem cells [22]. In another study of a different type, the human embryonic stem cells were differentiated into hormone sensitive endometrial cells that were then xenografted into a mouse uterus. Functional analysis of the endometrium showed that the embryonic stem cells-derived epithelium resembled the adult human endometrium [21].

Human spermatogonial stem cells have also been identified and cultured *in vitro*. They are present in the testes and can be maintained in long term culture. They can undergo self-renewal and can also give rise to all three germ lines when allowed to undergo differentiation [23]. Although germ cell transplantation is not ready for the human infertility clinic, this technique has become an important research tool in rodents, although at an experimental stage [28]. In studies conducted using monkey sperm cells, it has been observed that sperm production is restored after spermatological stem cell transplants [24]; this research offers tremendous scope and potential for conducting advanced research on human azoospermia [25]. Such studies hope to bring a new significance to the preservation of male fertility by providing a better understanding of stem cell regulation in the testes, that eventually will also be a novel target for male infertility and testicular cancers [28, 29]

Similarly scientists are exploring the potential of MSCs in improving the functioning of the ovaries too. In an experiment scientists transplanted the MSCs into the ovaries and found that not only did the transplanted MSCs block the onset of ischemia but they also reduced follicular atresia after frozen tissue transplant [26].

Another application of endometrial derived MSCs is its potential to repair vaginal vault prolapse. Vaginal prolapse is known to occur in patients with injury during vaginal delivery. Scientists are trying to build constructs which can be used to rebuild the fascia and construct the vaginal wall in such patients using endometrial MSCs [21].

Perspective

During past few years considerable progress has been made in the derivation of male and female germ cells. Although much research has been done to improve the reproductive health using stem cell based approaches none have been incorporated as a part of a regular treatment protocol. In the coming years it is predicted that infertility will become an epidemic and it is therefore imperative that stem cell based strategies are explored and proposed as future clinical therapies for treating infertility.

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