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Author
Assoc. Prof. Dr. Latife Ceyda İRKİN

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Lecturer Dr. Şamil ÖZTÜRK

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[1] Çanakkale Onsekiz Mart University, ORCID ID: 0000-0001-6603-8413

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PREFACE

Intrauterine adhesion (IUA) is a condition that causes multifaceted deficiencies to occur with an increase in the number of diagnosed cases. Although it often occurs after uterine curettage, any uterine surgery can cause IUA. It has been reported that most women diagnosed with this disease have amenorrhea or hypomenorrhea, but in some women menstruation can be normal. Women who can not menstruate, it causes pain due to blood trapped in the endometrium and also causes endometriosis due to retrograde menstruation. Most women with IUA present with menstrual disorders as well as infertility. Over the last fifty years, hysteroscopy became the standard of care for the diagnosis and treatment of IUA. Different techniques have been developed and applied to prevent adhesions and subsequent scar formation.

The development of new forms of treatment that will be more effective and alternative to surgery and hormonal treatment in patients diagnosed with IUA seems indispensable for the future. Because the number of abortions is increasing day by day, both in our country and in the world. At the same time, damage to the uterine tissue may be inevitable during routine gynecological examinations. Today, stem cell studies have developed so rapidly that they have increased the hopes of those looking for cures for everything from cancer, which seems impossible to treat, to metabolic diseases, and even rheumatic and neurodegenerative diseases. Although there have been rapid advances in stem cells and their preclinical applications are still

widespread, new advanced and developing treatment techniques in this field have increased the diversity of therapeutic strategies. We hope that the data in this study will enable the effective and correct use of stem cells in reproductive medicine and pave the way for new applications.

İÇİNDEKİLER

1. INTRODUCTION

1.1. Stem cells

Stem cells are undifferentiated cells that have tremendous self-renewal properties and the ability to transform into many different cell types according to the signals they receive in the living body and in laboratory environments. Stem cell is defined as a "functionally undifferentiated cell with heterogeneous reproductive potential". Stem cells are defined as pioneer cells that renew themselves and keep their numbers constant, can transform into specialized organs such as muscles and nerves, and have the highest level of differentiation ability (Weissman, 2000).

Stem cell studies began with the discovery of hematopoietic stem cells in 1960. After this discovery, developments were advanced with the discovery of stromal (mesenchymal) cells and the detection of neural stem cells discovered in the 1990s. In the following years, the presence of stem cells was detected in many other organs. Three basic stem cells have been defined: embryonic, adult and hematopoietic. By stimulating these cells with various stimuli, they have the potential to transform into specialized cells of the tissues from which they originate or into very different specialized tissue cells (Karaşahin, 2012).

1.2. General Characteristics of Stem Cells

1.2.1. Differentiation

Differentiation is used to define the transformation of cells of multicellular organisms into cells that undertake different functions through a number of changes during the maturation and specialization process (Figure 1). For their differentiation, the necessary cytokines, growth or differentiation factors, extracellular proteins and intercellular communications must interact in a combined manner. The cell that undergoes differentiation stops dividing and prepares to respond to signals from its environment. For this purpose, it generally triggers the initiation of some events in the cell by revealing enzyme-dependent surface receptors, intracellular receptors and activation pathways. Researchers have reported that neuronal stem cells differentiate into glial precursor cells via Notch signaling. Additionally, some oncogenes can reverse differentiation; Thus, an adult cell can gain pluripotent properties and transform cells such as tumor cells. This diseases caused by AIDS (Acquired Immune Deficiency Syndrome), which is infected with human herpesvirus 8 and turns into tumorigenic tissue (Matur and Solmaz, 2011).

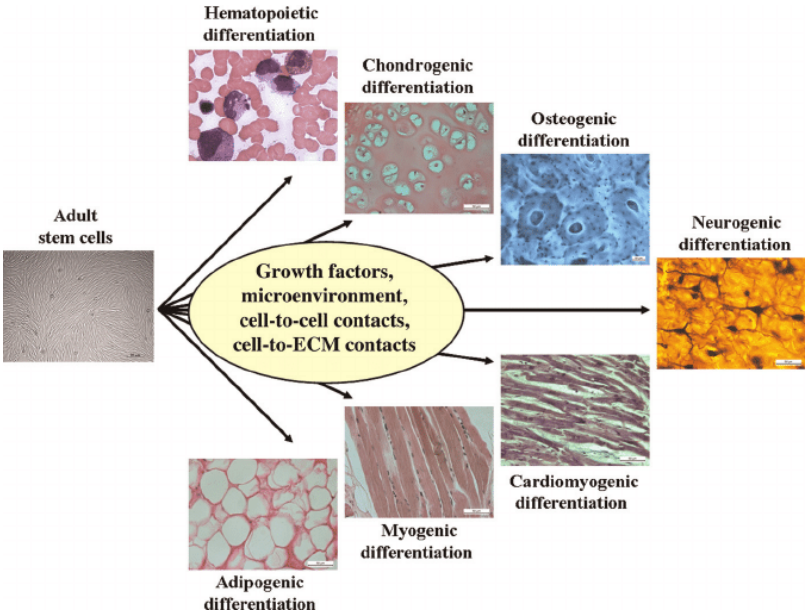

Figure 1. Capacity of adult stem cells to differentiate into different cell types (Danisovic et al., 2011).

1.2.2. Advanced Differentiation

The advanced differentiation process for a cell usually begins at the point where that cell's proliferation process ends. Therefore, the two processes do not occur at the same time. Mechanisms related to differentiation come into play during the proliferation process of the cell in question and involve first reaching a sufficient number and then shutting down the extracellular and intracellular pathways related to proliferation (Figure 2) (Matur and Solmaz, 2011).

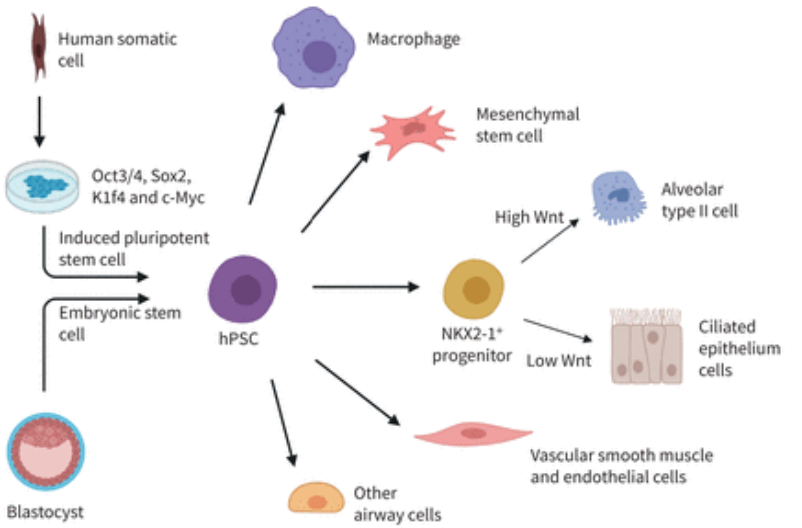

Figure 2. Differentiation abilities of human pluripotent stem cells (Goldsteen et al., 2021).

1.2.3. Directed Differentiation

Differentiation of stem cells in a definite line and differentiation in the laboratory. In order for an adult stem cell to differentiate into a fat cell, certain doses of hormones and chemicals such as insulin, dexamethasone, isobutyl methylxanthine and indomethacin are added to the culture medium (Figure 3). Although the effect of these substances on the transformation of stem cells in vivo is not fully known, it is known that in the in vitro environment, fat cells generally reach cell maturity, which is their in vivo counterpart, within a few weeks. It has been reported that differentiation occurs when dexamethasone, β-glycerophosphate and ascorbic acid added to

the culture medium for osteogenic differentiation (Laperrousaz, 2015).

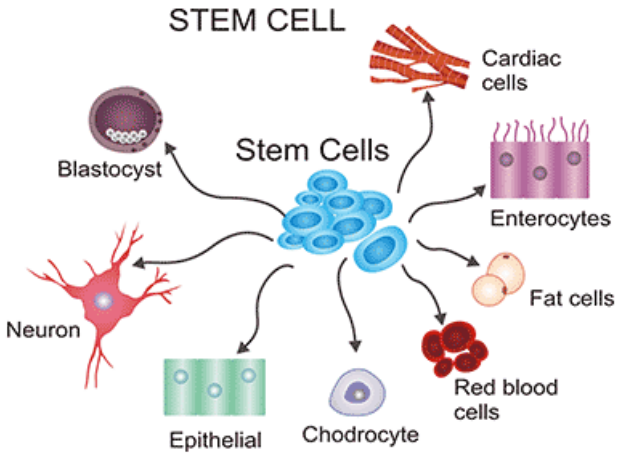

Figure 3. Stem cell differentiation diagram (https://www.cusabio.com/receptor/Stem-Cell-Receptor.html)

1.2.4. Reversing Differentiation

Another means of in vitro differentiation has been discovered using viruses or plasmids. It performs genetic reprogramming using these vectors. Induced pluripotent stem cells are differentiated from adult cells in this way. Somatic cells achieve retrodifferentiation by activating embryonic stem cell-specific genes such as Sox2, Oct3/4, klf4, c-Myc, and so on, using various viral or non-viral vectors (Ullah et al., 2015).

1.2.5. Intermediate Differentiation

Interdifferentiation is the differentiation of a cell differentiated in one direction towards another cell. To occurs in the salamander's eye, the lens in the eye is removed and the iris cells differentiate to form the lens. Since examples similar to this are not often encountered, the concept of intermediate differentiation is still open to debate. However, in pathology, the concept of metaplasia or further differentiation can be considered as an intermediate differentiation model. For example, intestinal epithelial cells are formed as a result of intermediate differentiation (metaplasia) of stomach epithelial cells, and this can be explained as intermediate differentiation (Matur and Solmaz, 2011).

1.2.6. Self Renewal

One of the special feature of stem cells is self-renew. The stem cell proliferates without specialization, making copies of itself throughout its life, and turns into organ and tissue-specific precursor cells when necessary (Figure 4). Cells with this ability differentiate into the precursor cell during division, while at the same time creating their own backup. The basic principle behind the mechanism of this event is asymmetric cell division, thus ensuring that the number of cells in the stem cell pool remains constant throughout life. Asymmetric division is observed in *Drosophila* ovaries (Weissman, 2000).

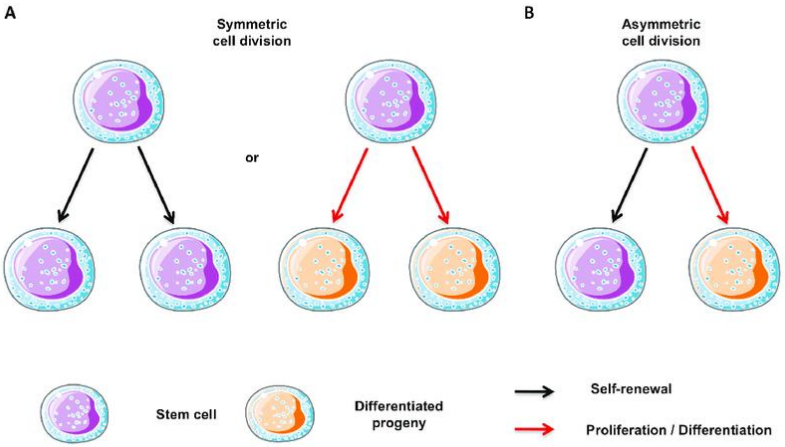

Figure 4. The self-renewal, differentiation and proliferation of stem cells (Laperrousaz, 2015).

Both intracellular and extracellular factors play a role in asymmetric cell division and are controlled together by a very tight control mechanism. Differences in microenvironments also make the fate of cells different. Extracellular matrix components, neighboring cells, and secretory proteins that make up the niche control the number of stem cells. Drosophila ovarian stem cells exemplify this division, and the division axis is determined on the microenviroment side; The mitotic shuttle is setted at right angles to the microenviroment. In this way, while the cells close to the microenviroment maintain their stem cell properties, those far away differentiate and form other cells. Asymmetry is achieved by transferring the RNA (ribonucleic acid), organelles and protein structures within the cell to only one of the daughter cells. DNA

is also transferred to cells with an asymmetric distribution. The end of division, the main DNA arrive to one of the daughter cells and turns into a stable cell, while the one that turns into a pioneer cell synthesizes new DNA from the other cell. This mechanism prevents mutations that may occur in the newly synthesized DNA of cells with stem cell characteristics and ensures that the cells remain the same with the intact genome. The stem cell pool can maintain its current number through asymmetric divisions. However, in terms of the development of the embryo, symmetrical cell division also should also occur to meet the need for new cells required for tissue repair. Especially in cases of damage to tissue functions, this mechanism ensures rapid repair by turning stem cells into precursor cells. However, stem cells also divide symmetrically to form new stem cells (Can, 2014).

The division capacity of cells is determined by the DNA chains called telomeres, located at the ends of the chromosomes. Telomere length determines the division period of cells. What keeps telomeres long is the activity of the telomerase enzyme. Stem cells have a high division capacity (Matur and Solmaz, 2011).

1.2.7. Stemness

Stemness includes the cellular and molecular properties of stem cells that are used to define their characteristics. These features, which can also be called stem cell signatures, are unique genes or post-translational changes, so these cells can maintain

their original structure and functions without being noticed. Stem cell type is determined based on markers that determine signaling pathways or cell-cell adhesion molecules on the surface of the cells. It forms many of these markers as clusters of differentiation (CD, Clusters of differentiation). For hematopoietic stem cell marker, the most common are CD33 and CD45 (Potdar and Jethmalani, 2015; Ullah et al., 2015).

1.3. Classification of Stem Cells

Classification can be defined in two ways, taking into account the source from which they are obtained and their differentiation potential. The highest differentiation of stem cells according to their differentiation ability; totipotent, multiple organ formation awareness; pluripotent, differentiation into different tissue types; differentiation between multipotent and single type of cells; They are called unipotent. In another classification, the source is based and embryonic, cord blood, adult, fetal, placenta and cancer stem cells are defined accordingly (Can, 2014).

1.3.1. Totipotent Stem Cells

Totipotent cells have capacity to form an entire organism. Each blastomere at the morula stage can be considered an example of a totipotent cell (Figure 5), because blastomere cells can develop into separate embryonic and extra-embryonic structures. These cells can form all tissues and organs, including

the embryo, and extra-embryonic membranes and organs. They also can differentiate unlimitedly and go in different directions. In the early embryonal period, all blastomeres up to 8 cells are totipotent (Karaşahin, 2012).

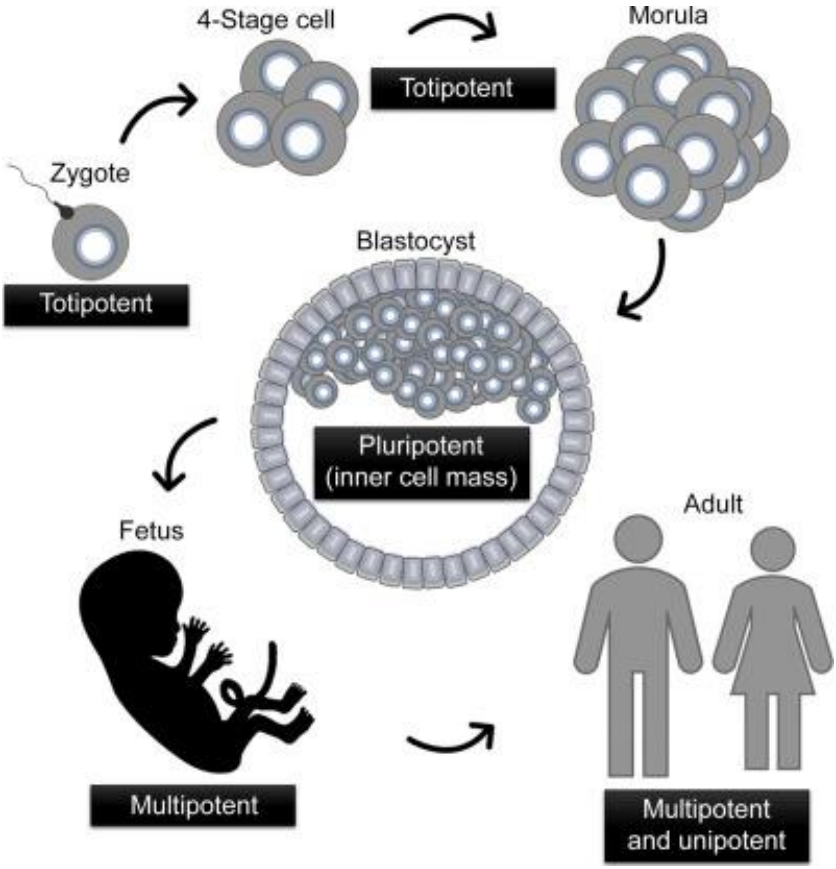

Figure 5. Totipotent, pluripotent and multipotent stem cells according to their differentiation potential (Los et al., 2019)

1.3.2. Pluripotent Stem Cells

Many tissues in the organism are formed by these cells and the source is stem cells. The cells in the inner cell mass that form following compaction and blastocyst formation are these types of cells, and these cells can differentiate into the precursor cells of many cells in the body. (Figure 6). These stem cells have high levels of telomerase activity, and there is no decrease in cell replication and activation. For these reasons, they appear as cells with unlimited proliferation ability (Menon et al., 2016).

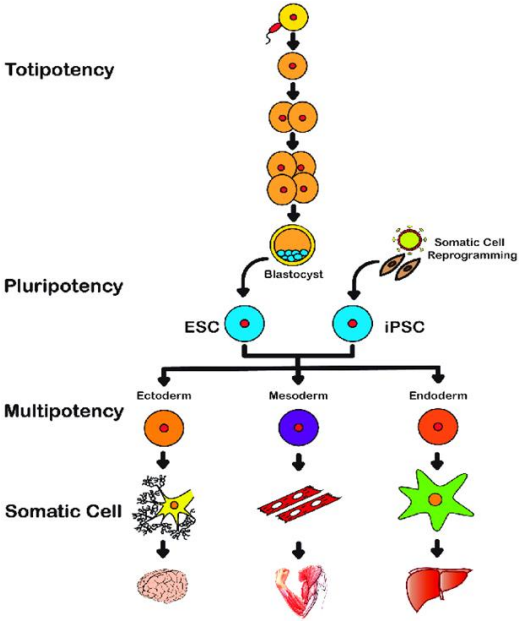

Figure 6. Differentiation aspects of stem cells according to their differentiation potential (Menon et al., 2016).

1.3.3. Multipotent Stem Cells

These cells are stem cells that emerge at a later stage and can differentiate into specialized cells. These are cells that are formed as a result of the division of cells and are programmed to differentiate in a single tissue direction. With development, cells acquire more specialized functions and can develop into adult stem cells (Figure 7). In this way, adult tissue loss transforms these stem cells into the cell types of the tissue in which they play an active role. Cord blood and adult stem cells are multipotent cells (Karaşahin, 2012).

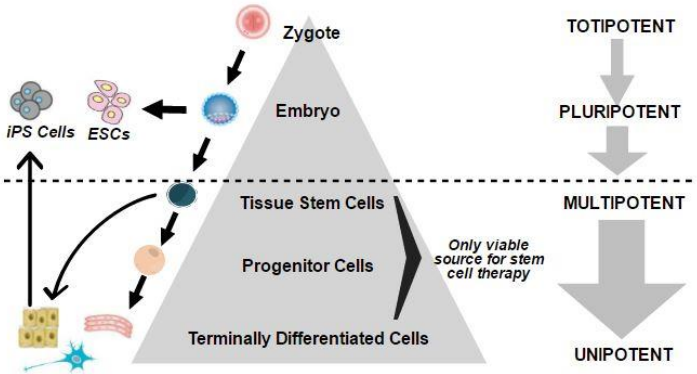

Figure 7. Multipotent stem cell differentiation (https://bioinformant.com/direct-cell-reprogramming).

1.3.4. Unipotent Stem Cells

Unipotent cells, which are stem cells in the final stage of differentiation, can differentiate into a single type of cell;

myosatellite cells in skeletal muscle, endothelial progenitor cells and corneal epithelial cells are unipotent cells (Holterman and Rudnicki, 2005; Takahashi et al., 2007; Yu et al., 2007).

1.5. Stem Cells Source

1.5.1. Embryonic Stem Cells

They are isolated from the inner cell mass at the blastocyst stage in early stages of embryo development. They have the ability to transform into any cells. The cells obtained from ESC are called embryoid body. Apart from the placenta, they can differentiate into any cell type originating from the embryonic germ sheets, ectoderm, mesoderm and endoderm layers (Wobus, 2001). The inner cell mass collected with the help of complement is placed in a culture containing mouse embryonic fibroblasts. This cell layer is called the feeder cell layer, and the cells in the feeder layer are inactive in terms of division and proliferation. They only enable ESCs to proliferate without differentiation. In mice, ESCs can proliferate without differentiation in the presence of leukemia inhibitory factor (LIF) without a nutritional layer. With lower passages, millions of ESC series can be obtained from the inner cell mass after six months. Human ESCs express pluripotent and undifferentiated cell markers CD9, CD24, LIN28 etc., octamer binding protein and alkaline phosphatase (Trounson, 2006). Cells with these expressions show high telomerase activity for a long time in vitro. ESCs have unlimited

self-renewal capacity and can differentiate into all fetal and adult tissues.

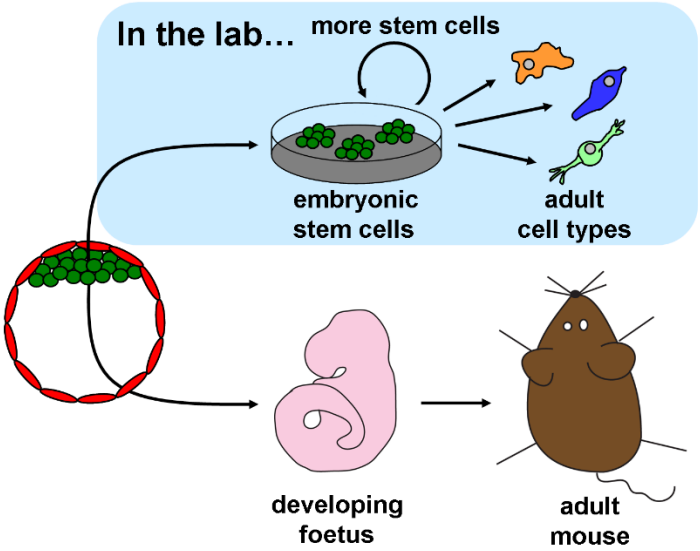

Figure 8. Embryonic stem cells (https://www.eurostemcell.org/embryonic-stem-cells-where-do-they-come-and-what-can-they-do)

 Non-embryonic stem cells; These are undifferentiated cells located among differentiated cells in any tissue or organ. They have typical stem cell properties. They can renew themselves and differentiate into specialized cells of the tissue. The main functions of these cells in the organism are to repair the tissue in which they are located and to maintain the integrity of the tissue. They are examined in three different groups:

1- Hematopoietic stem cells
2- Stromal (mesenchymal) stem cells
3- Other adult stem cells

In basic sciences, the development of human tissues and transplantation medicine are pioneers among the basic research topics using embryonic stem cells. In addition, studies conducted with embryonic stem cells are a ray of hope for diseases that are impossible to treat in the future. In this way, diseases that develop due to cells with limited self-renewal and repair capacity can be treated. These diseases include neuronal diseases such as Parkinson's and Alzheimer's, strokes and other diseases that develop due to neuron loss, heart muscle failure, cancer and immune system diseases and diabetes (Kovach et al., 2015; Schweizer et al., 2015).

There are both ethical and medical issues that limit the use of ESC. The first step of this cells requires culture and feeder layer. Particularly pathogen contaminations are the most important risk factor and precautions need to be taken. In addition, these stem cells can differentiate uncontrollably due to their high genomic instability, and uncontrollability increases in their long-term development. In addition, these uncontrolled differentiated cells trigger immune rejection by expressing molecules that induce the immune system. How to transfer the cells used by differentiating them into a special cell with controlled proliferation to the appropriate area of the patient and

how to obtain them with the function is one of the problems that must be overcome before therapy (Matur and Solmaz, 2011).

1.5.2. Fetal Stem Cells

These are stem cell types obtained from women who have miscarried and can divide indefinitely and have the ability to renew themselves. These cells are pluripotent stem cells, that is, they can transform into various cell types when the necessary conditions are met. The fetal stem cell can differentiate, reduce its chromosome number by half, and turn into an egg or sperm cell. However, it does not have the potential to form an organism on its own. Since stem cells obtained from the fetus are obtained at a later stage of development, their proliferation potential is less than embryonic stem cells (Ishii and Eto, 2014).

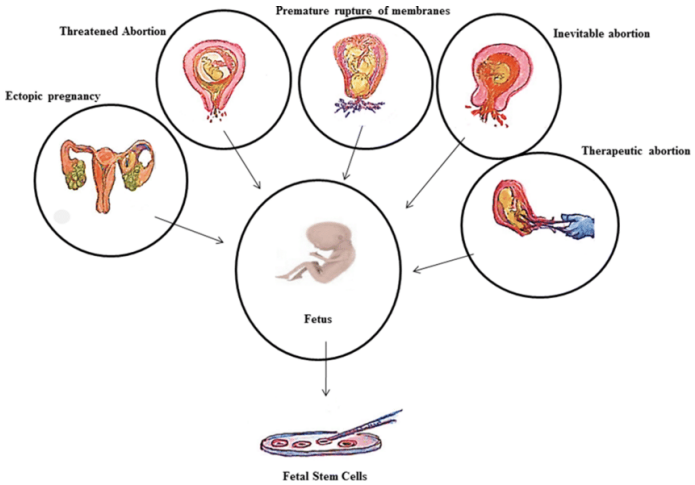

Figure 9. Fetal stem cells (Goodri et al., 2019).

1.5.3. Cord Blood Stem Cells

It was realized that the umbilical cord and placenta are sources of hematopoietic stem cells. The development process of the fetus during pregnancy also supports this issue. The umbilical cord, which provides connection between the mother and the baby throughout pregnancy and provides the baby with nutrients and oxygen, contains blood cells such as erythrocytes, leukocytes and platelets that we see in adult blood, and a higher majority of stem cells. Cord blood, discarded in the past, used for treatment point or can be stored under special conditions. Nowadays, they are widely used in blood and immune system diseases. Since cord blood can be obtained at a volume of 100 ml, the amount of hematopoietic stem cells is correspondingly low. It has been observed that the cells obtained are fewer, especially when compared to other stem cell sources. Therefore, cord blood recipients are mostly children. However, in recent years, it has been reported that blood collected from several cords can also be used in adults when applied to a patient. Currently, it is most commonly used all over the world for the treatment of patients who require stem cell transplantation but cannot find a suitable donor among their family members. However, it is important that the histocompatibility molecules of the cells obtained from the cord bacillus are compatible between the recipient patient and the donor (Liao et al., 2011; Matur and Solmaz, 2011).

Within the family, a donor whose Human Leukocyte Antigens are compatible or one antigen incompatible is the ideal donor for bone marrow blood stem cells. If the donor lacks these characteristics, unrelated donors become important. While we can tolerate an antigen mismatch in inter-relative transplants, in unrelated donor research, allele level compatibility must be ensured in both Class 1, consisting of HLA-A, -B, -C, and high-resolution typing of HLA regions. The graft versus host rise in case of one allele incompatibility, and in case of more than one allele incompatibility, life expectancy is shortened compared to those who are fully compatible (Gluckman, 2011; Liao et al., 2011).

Children with Fanconi anemia, the first successful cord blood transplantation, rapid progress has been made in the collection and therapeutic application of these cells. It is reported that there are approximately 13,000 donors for transplantation purposes for patients in need of hematopoietic stem cells, supported by the placenta blood programme center at the largest cord blood bank in New York. Cord blood has been collected in this center since 1992 and units of blood are stored in this center for thousands of patients (Gluckman, 2011; Liao et al., 2011; Matur and Solmaz, 2011).

1.5.4. Placenta Stem Cells

In 2004, three different groups of researchers found and isolated mesenchymal stem cells in human placenta (Yen et al.,

2008). Huang and colleagues found that multipotent cells obtained from the placenta could differentiate into neuronal and gilial cells along with epatocyte-like cells after in vitro culture under appropriate conditions (Zhang et al., 2004). For these reasons, placenta may be an alternative source for multipotent stem cells.

1.5.6. Amniotic Fluid Stem Cells

Amniocytes, a heterogeneous cell pool, are defined as embryonic or fetal stem cells because they express transcription regulators and cell surface antigens compatible with stem cell characteristics (Roubelakis et al., 2012). Since the amniotic fluid containing amniocytes is a structure rich in stem cells shed from both the fetus and the amniotic membrane of the fetus, it is used in stem cell acquisition and characterization studies. The ease of obtaining amniotic fluid in the first trimester of pregnancy and the ease and cheapness of culture and storage of the obtained amniotic fluid cells (AFC) have led to the use of AFCs in applications such as genetic diseases and drug development studies. In recent years, data have been obtained indicating that AFCs have multipotent epidermal, mesenchymal, hematopoietic and neuronal stem cell characteristics (Gholizadeh-Ghalehaziz et al., 2015). There are ethical concerns regarding the use of ESCs, which have the capacity to differentiate into all cell types, in regenerative medicine, and there are difficulties in the production and proliferation of induced pluripotent cells (iPSCs). Cells in the

amniotic cell pool that have a heterogeneous structure, have not fully completed the differentiation stages, and are in primitive form can be programmed more easily than iPSCs (Galende et al., 2010). Amniocytes are pluripotent; It has been observed that they can be transformed into cells of mesenchymal, endodermal and ectodermal origin, and thus AFCs can differentiate into many different cell types such as cardiomyocytes, hepatocytes, kidney and nerve cells (Roubelakis et al., 2007).

Whether a cell has stem cell characteristics is determined by whether or not it expresses pluripotency markers. The first study on the molecular characterization of human AFCs and their capacity to transform into different cells was conducted by Bossolasco and his colleagues (Bossolasco et al., 2006). In this study, the differentiation potential of AFCs was examined and, using mesenchymal, epithelial and neuroglial markers, it was shown that they are progenitor cells with the capacity to transform into different cell lineages. Kang et al (2015); Some stem cell markers (KLF4, SOX2, MYC, UTF1, GDF3, REX1, SALL4, DAX1, TCL1, NACC1, TERT) were expressed in AFCs, some markers (OCT3/OCT4, NANOG, LIN28B, KIT, DPPA5, FOXD3, FGF4) showed that they were not expressed. However, there are conflicting results due to reasons such as the expression of genes at different rates specific to cell type, AFCs forming a pool of many cell types, the presence of cells at different levels of pluripotency, and the small number of samples used. In this study, OCT3/OCT4, MYC, NANOG, DPPA3, UTF1, KIT, SALL4 and

NACC1 stem cell pluripotency markers were used to investigate their expression in AFCs, considering their intracellular functions and importance in stem cell pluripotency has been selected. OCT3/OCT4, SOX2 and NANOG are transcription factors that play a role in both early embryo development and the maintenance of pluripotency in embryonic stem cells (Chen et al., 2008). OCT3/OCT4, KLF4, SOX2, MYC genes, known as Yamanaka factors, are highly expressed in embryonic stem cells and serve as regulators in the developmental signaling network for embryonic stem cell pluripotency. UTF1 plays a regulatory role by interacting with the OCT3/OCT4 and SOX2 complex. DPPA3 is responsible for transcriptional repression, cell division and cell pluripotency, and DPPA5 is responsible for embryonic germ and embryonic stem cell stability (Zhao et al., 2012).

1.5.7. Adult Stem Cells

Adult stem cells have the capacity to renew themselves for a long time and are cells that have the ability to differentiate into precursor cells in adult tissues. Precursor cells are partially differentiated cells that can differentiate into specific cell lineages. However, these cells do not have the capacity to renew themselves. Adult stem cells can be obtained from many tissues of adults, as well as from the placenta, umbilical cord blood and bone marrow. Some of the tissues from which stem cells are obtained are; Organs such as heart, kidney, brain, skin, eye, gastro-intestinal system, liver, pancreas, lung, breast, ovary,

prostate and testicle have been reported (Shamblott et al., 1998; Pittenger et al., 1999; Fauza, 2004).

1.5.8. Hematopoietic Stem Cells

Hematopoietic stem cells are multipotent stem cells isolated from bone marrow or blood They develop by passing from the bone marrow into the bloodstream. They can also undergo programmed cellular death by apoptosis. The continuity of processes such as these stem cells remaining silent in the G0 phase, adhering to their environment, proliferating, maturing, differentiating and entering the circulation depends on their self-renewal and the special microenvironment in the bone marrow. Stromal cells, osteoblasts and osteoclasts, which are cells specific to the bone marrow, keep up with the microenvironment and ensure the stability of hematopoiesis as a result of their interaction with extracellular matrix components. Surface markers include CD59+, Thy1+, CD34+, CD38±, and c-kit± (Matur and Solmaz, 2011; Mojsilović et al., 2015).

Bone marrow is the classic source of HSC. They have been performing bone marrow transplantation for more than 40 years by extracting cells from the stem cell donor's bone marrow under anesthesia, typically by puncturing the hip bone with a syringe. It is estimated that 1/10,000-100,000 of the cells obtained from bone marrow may be stem cells. Collecting stem cells from peripheral donors for transplantation is used as a new method in the clinic. There are a small number of stem cells and progenitor

cells in the circulating bloodstream. Over the past 10 years, researchers realized that by injecting cytokines such as granulocyte colony-stimulating factor (G-CSF), they can remove cells from the bone marrow into the peripheral circulation. Following the collection of cells, the process begins by injecting G-CSF a few days before. Doctors place a tube into the vein of the donor whose cells will be collected, and thanks to the filter system between it and the blood, leukocytes containing CD34+ cells are collected and the erythrocytes are given back to the donor. About 5-10% of these collected cells are stem cells. Thus, research commonly prefers peripheral blood for stem cell collection. Actually; peripheral CD34+ cells are mixture of leukocytes, stem cells, and progenitor cells to varying degrees of maturity. In the last 3 years, leukocytes taken from the peripheral route rather than the bone marrow have been mostly used for autologous and allogeneic bone marrow transplantation. This cell was used in the treatment of leukemia leaded by the proliferation of leukocytes. Transplantation increases mortality to both infection and graft versus host disease. However, recently it has been reported that the life expectancy of many patients has increased (Bernardo and Fibbe, 2015).

1.5.9. Mesenchymal Stem Cells

They are the most abundant cells in living things and have the most characteristic features of human stem cells. At the same time, mesenchymal stem cells (MSCs) are a type of adult stem

cells. Since they generally have “support cell” properties due to their stromal origin, these cells form the basis for their use in many areas of medicine (Conget et al., 1999). At this point, both technological developments and innovations in medicine enable MSCs, which constitute an important part of regenerative medicine, to be obtained under in vitro conditions and produced in petri dishes. They can be easily isolated from many tissues. They are durable cells that are suitable for reproduction in numbers. The factors they secrete contribute significantly to the functions of special cells of the tissues they are in (Diefenderfer et al., 2003). The microenvironment attracts great attention with its immunomodulatory properties, thanks to its important components (Dominici et al., 2001).

MSCs are the principal cells of connective tissue. They can differentiate into cells such as adipocyte, osteocyte, chondrocyte, and myocyte (Sekiya et al., 2004). They also form the origin of stromal cells in other tissues. Fridenstein mentioned cell colonies with adhesion ability and resembling fibroblast morphology in the bone marrow cultures he made in fetal calf serum, and showed that they were capable of differentiating into bone and fat cells. Over the years, with new studies, it has been revealed that the cells are non-hematopoietic pluripotent stem cells and differentiate into cells originating from the three germ sheets. These cells, which were initially named “Bone marrow stromal fibroblasts” and CFU-F (Colony forming unit fibroblast), are now defined as mesenchymal stem/stromal cells (Gregory et al.,

2005). Stem cells can be autologous or allogeneic and can be applied systemically or locally (Şahin et al., 2005). Researchers are sometimes conflicted in defining the distinctive features of MSCs. Many laboratories use various methods for MSC isolation, propagation and differentiation, using protocols that do not differ much from each other. In addition, in the nomenclature of this association, it has been suggested that they be called "mesenchymal stromal cell" or "multipotent mesenchymal stromal cell" instead of "stem cell". In addition, in many different studies, the ability of cells to transform into endoderm and ectoderm-derived cells as well as connective tissues has been demonstrated, causing these cells to be described as "MSCs" by many researchers. The most commonly used features in defining MSC are; expression of surface antigens with stromal character, adhesion to the plastic surface and multipotent differentiation potential (Silva et al., 2003).

The most important disadvantage of MSCs in basic science research and clinical use is that they must be propagated in vitro because they are obtained in very small numbers. Various stimuli and factors to which they are exposed as a result of passage in the culture environment for their proliferation lead to differences in their immunological, phenotypic and other biological properties (Tuli et al., 2003). Since most of the basic research on MSCs was developed in an in vitro environment, their defined properties are far from reflecting their in vivo properties. Such a situation is a disadvantage, especially in clinical applications. There is a risk of

cell senescence, cytogenetic disorders and a small risk of malignant transformation due to in vitro passaged propagation (Tae et al., 2006).

1.6. Microenvironment (Niche)

Stem cells need a microenvironment that provides them with support and allows regulatory signals to be transmitted to the cells. The microenvironment, called the "niche", consists of cellular and molecular factors that control and regulate the functions of cells (Figure 7). Although the microenvironment varies in different tissues, there are microenvironments that contain regulatory factors for both stem cells and stem cell precursors (Zhang and Li, 2008). Niches not only create a suitable environment for the life of stem cells, but also contain factors that direct their proliferation and differentiation. Many studies have been conducted in this field and these studies contain very important information. Multipotent stem cells can also be found in a niche. Most stem cells turn into a permanent cell that will continue in the niche and a precursor cell that will differentiate with the signals it receives from the niche and differentiate into another cell as a result of asymmetric division. The cell remaining in the niche also proliferates by symmetric division. Niche is very important for stem cells because when the tissue in which they are located is damaged, these cells separate from their microenvironment and migrate to the damaged area. It is very important to balance the number of permanent stem cells in the microenvironment to replace the decreasing number of stem cells

after migration. (Conway and Schaffer, 2012; Krause et al., 2013).

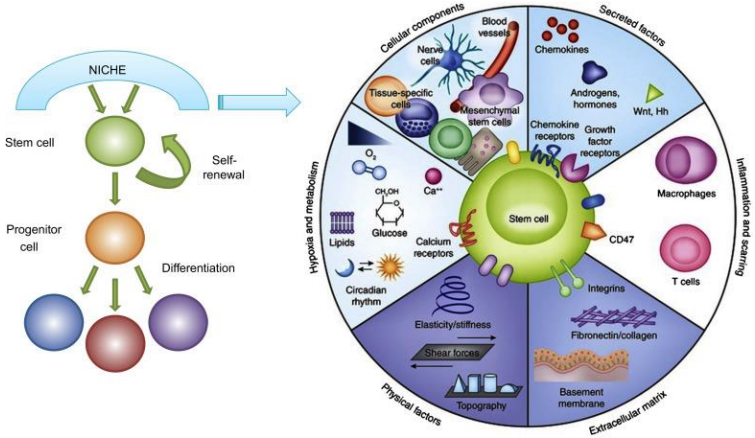

Figure 7. Components of the stem cell microenvironment (Lane et al., 2014).

2. INTRAUTERINE ADHESIONS

Intrauterine adhesion (IUA or Asherman Syndrome) was described by Fritsch in 1894 (March, 1995). Dr. was the first to describe the disease as "traumatic amenorrhea". It is referred to as Asherman Syndrome (AS) because it was caused by Joseph G. Asherman (Asherman, 1948). Some authors have proposed defining the term 'Asherman syndrome' for patients with amenorrhea, those with a completely obstructed uterus, or those who have recently given birth by caesarean section (surgical operation). Others use the term 'intrauterine adhesion (IUA)'; This term is clearer and more descriptive, but patients who have a surface deficiency of the endometrium without fibrous bridges between the uterine walls are exceptional cases. Women with

such a condition similarly experience other pregnancy complications such as menstrual bleeding, infertility, recurrent pregnancy loss, uterine growth restriction, problems with implantation, and adhesions (March, 2010). Uterine adhesion, which can also occur after AS, pregnancy complications or many gynecological surgeries, arises as a question. Due to the increase in its incidence, the search for alternative treatments continues (Yuksel et al., 2014). IUA or AS reveals a picture that causes multifaceted deficiencies to emerge, with the number of diagnosed patients increasing day by day. Although it usually occurs after uterine curettage, any gynecological surgery can cause AS. Women who cannot menstruate, menstrual pelvic pain due to trapped blood flow and accompanying retrograde menstruation may cause endometriosis. In addition to menstrual disorders, most women with AS present with infertility or recurrent spontaneous miscarriage.

Non-obstetric causes of IUAs include curettage (1.6%), uterine septum resection (6.7%), hysteroscopic myomectomy (31-45%), and abdominal myomectomy (1.3%). Apart from these, there are very few reasons; pelvic radiotherapy, uterine artery embolization and pelvic tuberculosis (Deans and Abbott, 2010; Roman et al., 2005).

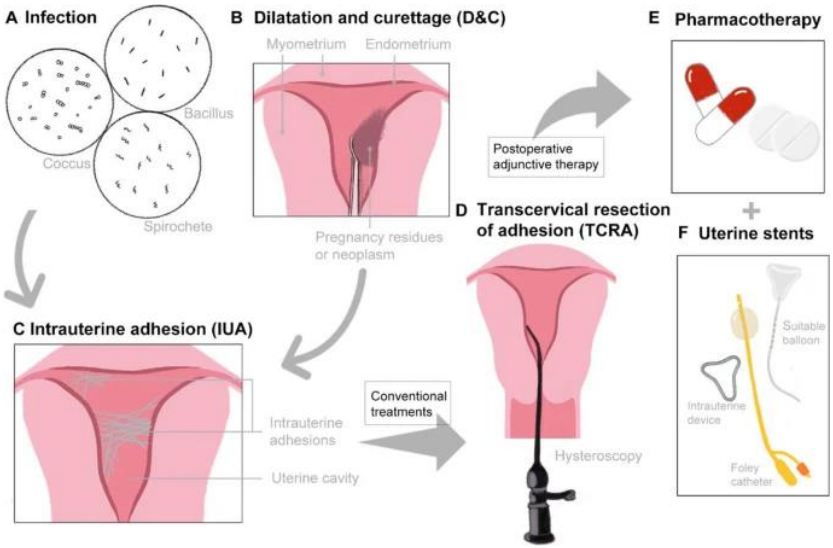

Figure 8. Schematic view of intrauterine adhesion (Ma et al., 2021).

2.1. Diagnosis

If the following findings occur in a woman who had no previous complaints after the curettage procedure, AS should be considered first.

- Lack of menstruation (amenorrhea 42%)
- Decrease in the amount of menstrual bleeding
- Infertility (63%)
- Recurrent abortion

In the presence of the above conditions and if previous curettage is detected in the history, AS should be considered. Sometimes, no findings may be found during gynecological

examination. In classical ultrasonography, the endometrium can be observed close to normal. However, adhesions in the uterine cavity can be observed during ultrasonography, which is examined by administering fluid into the uterus. Sonohysterography, ultrasonography, hysterosalpingography (HSG) and hysteroscopy are used to make the diagnosis. Definitive diagnosis can be easily made with uterine HSG (Magos, 2002).

2.2. Etiological factors

The cause of IUA can be any event that will damage the endometrium. In their study of IUA in 1856, it was determined that 67% of the cases developed after curettage related to miscarriage or early pregnancy loss (Schenker and Margalioth, 1982). According to this study, missed abortion cases are the causes of IUA at a rate of 31% and incomplete abortion cases at a rate of 6.4%. In the study in which they randomly divided the treatment of incomplete abortion cases into medical and surgical treatments, no adhesion was detected in the hysteroscopic impressions of the medically treated cases at the end of the 6th month, while an adhesive structure was encountered in the surgically treated cases (7.7%) (Tam et al., 2002). IUA has been detected at a rate of up to 39% in recurrent miscarriages (Ventolini et al., 2004). Friedler et al. reported in their study that the increase in the number of curettages increased the frequency of adhesions and the severity of adhesions (Friedler et al., 1993). Although the effect of the environment created by infections on

adhesion formation is controversial, the opinion that it can increase the adhesion formation process is more dominant (Kodaman and Arıcı, 2007).

It has been determined that cesarean sections cause IUAs at a rate of 2%. Postpartum bleeding can cause IUAs in around 9%. In cases where curettage is applied after birth, this rate increases to 40%. Especially the first four weeks after birth are very important. While curettages performed between these weeks cause more serious and more frequent IUA, curettage cases within the first 48 hours after birth cause less adhesion due to the high estrogen level in this period (Schenker and Margalioth, 1982).

2.3. Pathological findings

In AS pathology, fibrosis predominates in the endometrium. Inactive cubocolumnar epithelium is typically observed in the glands. Stratum functionalis and basalis layers are intertwined. Functional layer; It takes on a layered structure that remains unresponsive to hormonal stimulation. Avascularization increases and due to fibrosis, myometrium contractility decreases and vascularity decreases. Therefore, sex steroids cannot show their effect on endometrial tissue.

2.4. Treatment

Over the last 40 years, hysteroscopy has become the standard method for diagnosing and treating this condition. The most effective in the current circumstances seems to be the use of

miniature scissors for adhesiolysis and the placement of a balloon stent in the uterus immediately after surgery. Additionally, postometric estrogen therapy is given to stimulate endometrial regrowth. Careful monitoring and follow-up studies of patients for cervical insufficiency, placenta accreta, and intrauterine growth restriction are mandatory before trying to become pregnant (March, 2010).

Hysteroscopy is the most important treatment method in the treatment of IUAs. The use of microscissors with the help of an operative hysteroscope reduces damage to the endometrium. In addition, in case of endometrial destruction, it is given priority because the risk of superficial injury is lower compared to other adhesiolysis methods. The adhesion release process starts from the center and bottom, and fine adhesions always have priority. At deeper levels, the uterine cavity is opened thoroughly and finally, lateral adhesions, which have a high rate of perforation, are opened. Thus, the uterine cavity is normalized (Thomson et al., 2007). While perforation is seen in 2-5% and hemorrhage is seen in 6-27% during hysteroscopic adhesion opening, clinical conditions similar to cervical insufficiency have been reported after the operation due to fluid-electrolyte balance disturbance (Friedler et al., 1993).

After the adhesiolysis procedure, early pregnancy losses were found to be 20%, close to normal. In cases with prolonged duration, intrauterine growth retardation, placentation anomalies, premature birth (40-50%) and uterine rupture complications may

occur. Ruptures are more common in cases with perforation during the procedure (Yasmin and Adeghe, 2004; Shiau et al., 2005). Pregnancies with a history of hysteroscopic surgery due to AS should be considered high risk, and the third trimester should be followed closely, especially.

2.5. Supplementary Methods

Recurrence of adhesions in IUA or AS treatment compromises the success of the operation and is directly related to the severity of the lesion. Recurrent adhesions have been reported in 3.1-23.5% for all cases and 20-62.5% for more severe cases. After the hysteroscopic procedure, the intrauterine device (IUD) creates a physical obstruction that prevents the contact of the uterine surfaces. Although there are many articles reporting that IUDs prevent adhesion re-formation after adhesiolysis, there is no first-class study yet. The importance of the type of IUD used has been revealed through research. It has been reported for Copper T models that they can trigger an inflammatory response in the uterus. It has also been suggested that because they are small, they cannot prevent the contact of uterine surfaces (Yu, 2008; Deans and Abbott, 2010). Although the loop is considered the best model among IUDs, it is not used in many countries. Due to its suppressive effects, systems containing Levonorgestrel should not be used in the endometrium.

Some studies have reported that it is effective in preventing the recurrence of IUA when the Foley balloon catheter is inflated

in the uterine cavity and stopped for 3-10 days. When IUD and Foley balloon catheter were compared, Foley balloon was found to be more effective in regulating normal menstruation than IUD application (Orhue et al., 2003). However, it should not be forgotten that the Foley catheter may cause infection in the cervical canal and that the inflated balloon will exert pressure and have a negative effect on endometrium regeneration.

In another study, when the freshly removed amniotic membrane was kept in the uterine cavity wrapped around a Foley catheter balloon for two weeks, mild adhesions were observed in 48% of cases (Amer and Abd-El-Maeboud, 2006). In another study, it was shown that Hyaluronic acid gel could keep endometrial surfaces away from each other in 72 hours. In this study, it was also reported that re-adhesion developed after the operation in the proportion of patients who received gel after the operation (14%) and in the control group (32%) (Tsapanos et al., 2002). Although estrogen treatment after curettage has been shown to have a positive effect on the endometrium, there is no study showing whether these positive effects occur during pregnancy and re-adhesion. The recommended application is to add Estradiol valerate 4 mg/day for four weeks and medroxyprogesterone acetate 10 mg/day for the last 10 days. Results showing restoration of fertility in the early postoperative periods with hysteroscopic adhesiolysis have been reported. Although treatments that can increase uterine perfusion have been tried, their use cannot be recommended today, especially

considering the use of drugs such as aspirin, nitroglycerin, and sildenafil outside their mechanism of action and their adverse effects (Deans and Abbott, 2010).

3. CLINICAL USES OF STEM CELLS

In the early 1900s, researchers realized that all different blood cells originate from a single cell. In 1958, the first in vitro fertilization IVF was performed in rabbits. It was shown in mice in 1960 that teratocarcinomas arise from embryonic germ cells and that embryonal carcinoma cells are a kind of main cell source. Canadian researchers Ernest McCulloch and James Till; They quantitatively described that mouse bone marrow cells can renew themselves after transplantation. In 1968, the first human egg was obtained via IVF.

The first in vitro fertilization baby Louise Brown was born in England. They obtained mouse embryonic stem cells (ESCs) from the inner cell masses of blastocysts. They defined the necessary culture conditions to propagate pluripotent mouse ESCs in vitro (Evans and Kaufman, 1981). Thomson et al. In 1995, primate ESCs were obtained from Rhesus monkeys and marmosets and implanted in vitro (Thomson et al., 1998). Thus, it has been pointed out that it may be possible to propagate human ESCs in vitro. James Thomson and his team from the University of Wisconsin reported that they produced five human ESC series from 36 embryos in the IVF laboratory (Thomson et al., 1998). This was considered a milestone for stem cells because

afterwards, research and discussions spread rapidly. In 2013, Science magazine listed developments related to "Stem Cells" among the 10 most important medical events. So why are stem cells so important, how can diseases be treated with these cells? (Regenerative medicine or Reparative medicine); CHs are the main source of all cells in our body and the main building block of tissues and organs; unlimited divisibility and self-renewal; They are undifferentiated cells that can only originate differentiated cells and, with this feature, have the ability to re-proliferate the damaged tissue and restore its former function. The hope of using stem cells for treatment of diseases, which started with BMSCs in the 1960s.

Today, it is progressing at full speed under scientific, ethical and social debates. The aim of treatment with stem cells or cellular therapy, which has been the most promising treatment option in recent years; It is to repair or renew the function of a cell/tissue or organ that is damaged or has problems in its function, by using STS. In order to achieve this, it is necessary to "transfer isolated and purified cells to the damaged tissue in a number and quality that will allow the damaged tissue to perform its function" (Ates, 2016). For the success of stem cell-centered treatment methods, a multidisciplinary approach is needed, including tissue engineering, molecular biology, genetics, embryology, cell biology and clinical sciences. In case of any tissue or organ damage; Treatment can be provided with cells of sufficient number and quality to restore the functions of that

organ. Cell-based or cell-based therapies; It has emerged as such a treatment strategy for many diseases in humans. Stem cells are indispensable for cell-based therapies. We predicted stem cells for the treatment of AS due to all this historical development and promising developments for the future. Success in cellular therapy cannot be seen without trying the experimental phase, and the clinic always remains the next step. For this reason, we tried to determine an alternative to surgical procedures and a non-recurring treatment element to eliminate uterine adhesions, which is an important infertility problem. Our findings strongly support our hypothesis. Because in real terms, both morphological and statistical data between groups. It has shed light on the fact that good treatment success can be achieved when BMSC is applied in sufficient numbers in endometrial damage. In similar studies, the results were also positive. Therefore, an effort was made to contribute to the scientific world in terms of stem cell research (Kollar et al., 2009; Hu et al., 2010).

In stem cell studies on cardiovascular diseases, autologous bone marrow MSCs were given via coronary artery to 69 patients with acute myocardial infarction and showed that it increased ventricular functions (Chen et al., 2004). In 2011, autologous BMSC was administered to eight patients with chronic ischemic heart disease into the myocardium, and they observed that regional contractility increased and end-diastolic/end-systolic volumes decreased (Williams et al., 2011). In a randomized double-blind and placebo-controlled study conducted in 2015, 37

patients with ischemic heart failure between the ages of 30 and 80 were given intramyocardial autologous BMSC, and 18 patients were given placebo. The primary end point was determined by measuring left ventricular end-systolic volume change with MRI and computed tomography at six-month follow-up. In the sixth month, while its value decreased in the MSC group, it increased in the placebo group (Mathiasen et al., 2015). In a study they conducted in 2015 on chronic total occlusion; They randomly transplanted MSCs obtained from the umbilical cord to 15 patients and observed a significant decrease in the infarct areas of the patients, while the ejection fraction in the left ventricle increased significantly (Li et al., 2015).

Damage to the heart muscle resulting from myocardial infarction due to occlusion of the coronary arteries causes significant losses in regional heart functions. Cellular treatments aim to eliminate this damage. For this purpose, bypass surgery and reperfusion therapy are limited treatment options for these diseases, they also increase the risk of death. It has been shown that recovery may be possible due to tissue regeneration with these cells, which will be enabled to migrate to damaged heart tissue with MSC treatment. The biggest benefit of stem cell therapy and the reason why it is frequently preferred is that it does not require a surgical procedure (Ke et al., 2011; Lai et al., 2011). After intravenous administration of stem cells in the acute phase, there is no guarantee that these cells will go to the damaged area. It has been reported that the majority of stem cells administered

ex vivo in the myocardial infarction model are trapped in the lung. The same authors showed that stem cell infusion into the left ventricle with ischemic myocardium improved the infusion cavity (Barbash et al., 2003). In the chronic phase due to the reduction in neutrophil activation and improved chemotaxis of stem cells, intrauterine administration is not necessary. Based on these data, we can say that it is more practical and less costly to apply stem cells intraperitoneally from the area close to the damaged area, instead of intravenously.

In neurological diseases, MSCs have been of particular interest in the treatment of diseases such as spinal cord injuries, MS, Parkinson's and amyotrophic lateral sclerosis (Ucelli et al., 2011). Mesenchymal stem cells are used in the treatment of these diseases, and long-term results are expected. In a randomized, placebo-controlled phase II study conducted in 2014, MSCs were administered intravenously at 1-2x106 per kilogram to nine MS patients. Consistent immunological changes such as a lower pro-inflammatory T cell profile and a decrease in the IFN-c ratio were observed in patients. As a result, MSCs administered to patients reduced inflammatory parameters with their immunomodulatory properties (Llufriu et al., 2014).

In a study on spinal cord injury, they evaluated the long-term results of intramedullary MSC administration to 10 patients. MSCs from the patients were isolated from the bone marrow and cultured for four weeks. 8x106 MSCs were injected directly into

the spinal cord and 4x107 MSCs were injected into the intradural space, and an additional 5x107 cells were injected into each patient after four and eight weeks. MRI and electrophysiological recordings were taken to evaluate the results. At the six-month follow-up, the motor power of the upper extremity improved in six out of 10 patients, the daily living activities of three patients increased and improved, and changes such as a decrease in the cavity size were observed in MRIs (Park et al. 2012). Studies have shown that effective regenerative treatments for spinal cord injuries may be possible in the near future (Assunção-Silva et al., 2015).

In a study conducted on amyotrophic lateral sclerosis (ALS) patients, they transplanted neurotrophic factor (NTF)-secreting MSCs as a single dose to 26 patients with ALS. This study, which observed a decrease in the ALS functional rating score in 87% of the patients and an improvement of at least 25% in the patients six months after the treatment, concluded that clinical benefit could be achieved with NTF-secreting MSC treatment in ALS patients (Petrou et al., 2016).

Studies are planned to use MSCs in developmental anomalies related to the skeletal system, bone infections, trauma, degenerative diseases and tumors such as osteoarthritis and osteoporosis. It seems more appropriate to use mesenchymal stem cells in injuries that require cartilage and bone repair, and in osteoarthritis that occurs as a result of trauma and old age. The most successful results were obtained in patients with

osteogenesis imperfecta; Increased height, decrease in fractures and improvements in motor functions have been reported in patients. However, the number of patients treated for this purpose is very low (Chanda, 2010).

The first cellular therapy used in the treatment of type 1 diabetes, known as the "Edmonton method", was applied in 1999 by transplanting cells obtained from the donor's pancreatic tissue after various enzymatic processes to the recipient whose immune system was suppressed with various chemotherapeutics (Scully, 2012). Today, MSC transplantation studies for the treatment of diabetes are still at the experimental stage, and according to studies conducted on various stem cell types, CD34+ bone marrow and cord blood stem cells have yielded better results than mesenchymal cells obtained from other sources (El-Badri and Ghoneim, 2012). The first applications did not show very efficient results. Although the method has been developed, the small number of donors, the insufficient number of cells obtained, and the suppression of the recipient's immune system for a long time reduce the usefulness of the method in question.

MSCs have recently be used as an alternative treatment of graft versus host disease due to their immunomodulatory effects and immune response regulation (Vianello, 2008). MSCs have been a source of hope for liver cirrhosis and hepatitis disease. In the phase I study conducted in this field, they administered autologous MSC (31.73x106) via peripheral vein to four patients

with decompensated liver cirrhosis. During the evaluation, primarily the safety and feasibility of the procedure, and secondarily, the end-stage liver disease score and the patients' quality of life were taken into consideration, and no side effects were observed in the patients during the follow-up period. The end-stage liver disease score has improved by increasing 3-4 points from 1 (Mohamadnejad et al., 2007). Phase I and phase II clinical studies are being conducted on the application of MSC in fistula repair in Crohn's disease, which is a chronic inflammatory gastrointestinal system disease with a progressive and destructive course. In Phase I studies, MSC-specific expressions were demonstrated and growth rates were studied, and the reliability and feasibility of applying autologous adipose tissue-derived MSCs were studied. The effect of MSCs given in the third passage of cultured cells was checked weekly for eight weeks in eight fistulas of four patients, and it was observed that six of the fistulas closed by epithelialization of the outward-facing parts towards the end of the eighth week, and the other two fistulas partially recovered (Garcia-Olmo et al., 2009).

Damage to the heart muscle as a result of occlusion of the coronary arteries causes significant losses in regional heart functions. Mesenchymal stem cell (MSC) transfer, which will provide cardiomyocytes to the damaged myocardium, seems promising for patients who currently have no treatment options other than heart transplantation. Although bypass surgery and reperfusion therapy are limited treatment options known for a

long time for these diseases, they also increase the risk of death. It has been shown that with mesenchymal stem cell therapy, healing may be possible due to tissue regeneration as a result of the migration of these cells to the damaged heart tissue (Ke et al., 2011; Lai et al., 2011).

Studies are planned to use MSCs in developmental anomalies related to the skeletal system, bone infections, trauma, degenerative diseases such as osteoarthritis and osteoporosis, and tumors. It seems more appropriate to use mesenchymal stem cells in injuries that require cartilage and bone repair, and in osteoarthritis that occurs as a result of trauma and old age (Chanda, 2010).

MSCs are an alternative in meniscus treatment. While treatment applications focus on cartilage tissue cells, many experimental studies are being conducted on MSC applications for bone and muscle tissue (Kömürcü and Özkan, 2006). Studies have shown that effective regenerative treatments for spinal cord injuries may be possible in the near future (Assunção-Silva et al., 2015). The most successful results were obtained in patients with osteogenesis imperfecta; Increased height, decrease in fractures and improvements in motor functions have been reported in patients. However, the number of patients treated for this purpose is very low (Chanda, 2010).

In Asherman syndrome, which is a clinical condition, it is not possible to correct the thinned endometrium with classical

treatments and it is thought that success will be achieved with MSC application. In a study conducted for this purpose, female rats were given an intravenous infusion of bone marrow stromal stem cells at a rate of 50,000 cells/microliter, and their uteruses were removed in their third estrus and examined histologically. After stem cell application, it was observed that endometrial thickness increased and glands and capillaries proliferated. It was observed that cytokeratin, integrin beta-3 and leukemia inhibition factor (LIF) expressions were positive, especially in the cytoplasm of endometrial epithelium, and vimentin was positive in the cytoplasm of endometrial stromal cells. It has been determined that there is a stronger staining with stem cell application. It was possible to demonstrate the Y chromosome in the recipient uterus by obtaining 107 stem cells administered intravenously from male donors. Additionally, Bromodeoxyuridine (BrdU) staining revealed that the cells were present in the third cycle, especially around the vessels. It has been reported that after stem cell application, a significant decrease was found in TNF-alpha, IL-1 and IL-6 mRNAs, and that the stem cell exerts its effect on inflammatory cytokines (Jing et al., 2014).

The endometrium, which cycles approximately 400 times in a human, is a highly regenerative tissue and thickens by approximately 4-10 mm in each cycle. Normally, stem cells in the functional layer of the endometrium enable this regeneration to occur. The deficiency or disorder of the stem cells here cannot

provide adequate endometrial thickening, preventing the baby from attaching and progressing. The first evidence of the presence of adult stem cells in the human endometrium was the cloning of less than 1% as EpCAM+ in cells isolated from epithelium and EpCAM- in stromal cells. While these showed nearly thirty divisions, they formed large gland-like structures within the matrigel and differentiated into many different cells. Especially stromal ones were thought to be MSC-like cells. A group of cells called the edge population was also differentiated by staining with the vital DNA binding dye Hoechst 33342 and they were found to be most abundant in the menstrual and proliferative phase. These cells proliferate much faster than normal stromal stem cells and are seen in the basal layer, especially around blood vessels. It has been shown that these cells form endometrial tissues in culture and increase implantation success by providing regeneration in in vivo conditions. MSCs have also been detected in menstrual blood and are very similar to endometrial ones, and since they do not contain MHC-II molecules, they are less immunogenic. Bone marrow-derived stem cells are found in very small amounts in the endometrium, but they can transform into all cells there. It has been shown that these cells turn into decidualized endometrial fibroblasts much more successfully when transplanted. Circulating endothelial progenitor cells are also thought to be present in the uterus and contribute to endometrial vascularization by around 10%. The endometrium's own stem cells or precursors are the cells with the most capacity for regeneration in the endometrium. These cells, differentiated

by CD146 and PDGF receptor beta, have been shown to behave like MSCs. It was thought that these cells, which proliferate very efficiently, could be used for cellular therapies. It has been shown that human embryonic stem cells can also participate in endometrial regeneration, and human studies on this subject have also been permitted in the United States. In fact, their use in the clinic is being considered by using patient-specific induced pluripotent stem cells with these cells. Apart from these, providing endometrial regeneration through transdifferentiation from other cells in the uterine environment is also an experimental possibility. In particular, directing myoblasts to differentiate into the endometrial epithelium will be an important alternative for the future. In many studies, bone marrow-derived mesenchymal stem cell administration has been observed as GFP+ cells in the stromal and epithelial sections of the damaged mouse uterus. It has been shown that these cells are effective by preventing inflammation and increasing vascularity. It has also been shown in human endometrium that stem cells differentiate into epithelial, stromal and endothelial cells after transplantation (Gil-Sanchis et al., 2015). In summary, as predicted, stem cell applications will be used increasingly for implantation success, and understanding cell behavior will be the most important factor for their clinical impact (Gargett and Ye, 2012).

Although the development of amenorrhea due to IUA was first described at the beginning of the 20th century, it was later defined as a disease by Asherman in 1948 and therefore it is also

called Asherman Syndrome. In the examinations carried out to reveal the pathology of this syndrome, it has been reported that avascular fibrous connective tissue bands, which may also be accompanied by glandular tissue, are densely observed, and the risk of intrauterine adhesion in elective pregnancy termination is generally low. In the first four weeks after birth or miscarriage, the basalis layer of the endometrium is very susceptible to damage, so curettage should not be performed during this period unless necessary. While the incidence of AS has increased in recent years due to increased caesarean sections and uterine surgeries, it has also been observed that awareness has increased to determine detailed diagnostic approaches regarding this issue (March, 2010). Thus, it has become very important to collect the developments in the treatment of this syndrome and determine a more effective method. By introducing experimental models to the literature that can carry stem cells, which have increased in popularity in recent years, to the clinic, it will make it easier for mesenchymal stem cells to take their place among alternative treatment options in clinical situations where treatment is not possible or positive response is delayed.

There are no randomized controlled studies on the treatment of IUAs. Standard treatment is to remove adhesions with surgery and direct observation. By removing adhesions, it is aimed to create a cavity with normal anatomy and to provide a functional endometrium. Hysteroscopy is often preferred in current treatment methods. Adhesions can be removed under direct

observation by applying pressure with continuous fluid infusion and adding mechanical sharp scissors, electrosurgery and laser when necessary. In more serious adhesions, care should be taken during dilatation of the cervical canal. Due to the wrong paths created in the cervical canal, passage into the cavity may be quite difficult and may cause uterine perforation. If the disease is severe and the anatomy cannot be clearly defined, the procedure should be performed under the guidance of transabdominal ultrasonography or laparoscopy. Complications are rarely observed during hysteroscopic adhesiolysis. Acutely, uterine perforation, fluid overload, imbalanced electrolyte levels, hemorrhage and infection may occur. As a late-term complication, it manifests itself with recurrent adhesions and uterine rupture in the next pregnancy. Uterine adhesions are frequently observed after incomplete abortion (50%), postpartum bleeding (24%) and elective pregnancy termination (17%) (Salzani et al., 2007). In etiology, adhesions have been reported less frequently with myomectomy, hysterectomy, diagnostic curettage, cesarean section, tuberculosis and uterine compression sutures (Luk et al., 2007). Although hysteroscopy is considered the gold standard in AS, unfortunately, re-adhesion formation after the operation cannot be prevented in many patients. For this reason, hormonal supplements, intrauterine devices or balloon catheters can be used to prevent new adhesion formation after the operation. There are no studies comparing the effectiveness of these methods with untreated patients. Although it has been said that estrogen and progestin supplements used after the procedure

prevent adhesions, their effectiveness has not been proven (Goldenberg et al., 1995).

Although uterine tissue is restored by surgery, the re-formation of adhesions and the risk of complications of uterine surgeries. For the treatment of intrauterine formations such as synechiae; serial flexible hysteroscopies (Robinson et al., 2008), intrauterine adhesion barrier systems (Abbott et al., 2004), fresh amnion graft (Amer et al., 2006), intrauterine insertion of seprafilm, (Tsapanos et al., 2002), hysteroscopic surgery. Clinical or subclinical pelvic infections in contact with the vagina may increase secondary infertility. The point reached recently is Estrogen and progesterone supplementation. The effects of this recommendation do not have the same effect on every patient (Tourgeman et al., 1999). Such problems cause researchers to work harder for new treatment approaches. Artificial hormone therapy with eutrogen is frequently used to support endometrial proliferation and angiogenesis (Chen et al., 2013). Low estrogen may be a risk factor for endometrial fibrosis by increasing the proliferation of fibroblasts. The use of stem cells that induce endometrial growth under hormone stimulation increases its effectiveness. Because stem/progenitor cell loss is the main cause of adhesions in AS. Therefore, hormone therapy alone is inadequate for severe AS as an adult.

In our study, studies on stem cells, which will contribute to alternative methods and will be perhaps the most important

treatment tool of the next century, to eliminate intrauterine adhesions and eliminate synechiae, one of the important infertility problems, have been compiled. As a matter of fact, both macroscopic findings analyzed from the studies; The number of embryos, the number of newborns, the anatomical structure of the endometrium after sacrification, and the histopathological findings obtained as a result of microscopic tissue monitoring have proven this. It was observed that immunohistochemical findings (PCNA and VEGF immunoreactivity) also showed significant increases. It has also been reported that proliferation is triggered and vascularity increases. When compared to the findings in the study evaluating PCNA, Ki-67 and VEGF positivity, the level of significance was similar. Again, the effectiveness of anti-stro-1, anti-c-kit, CD(90+), CD(45+) and CD(49+) markers, which are stem cell markers, in mesenchymal stem cell characterization has been reported (Kılıç et al., 2014).

Stem cell therapy for endometrial restoration has recently moved away from being a peripheral treatment and started to become a central treatment option. In particular, stem cells obtained from bone marrow have become the most frequently used stem cell source. BMSCs can be easily obtained from both humans and rodents due to their extensive migration and pluripotent potential. (Nagori et al., 2014). Ultimately, they make the endometrium ready for implantation. After intrauterine administration of BMSCs in IUA model mice, it was observed that the cells migrated to the endometrium and the number of cells

containing CD45 on the Y chromosome was one thousandth of the cells in the endometrium. In damaged uteruses, the number of these cells doubles. There was no significant difference between the damaged horn and the non-damaged horn. The rate, which was 3/10 in terms of fertility, increased to 9/10 with BMSC. However, there was no difference in terms of the birth process and the size of the babies. This study indicates that implantation success is definitely improved by increasing endometrial receptivity with BMSC. Especially since the endometrium's own stem cells cannot provide endometrial regeneration due to damage, it has been observed that externally applied transplantation stem cells are permanent and functional, increasing the success of implantation. In this study, where Y-positive cells were easily detected due to the use of male BMSC, it was proven that transplanted cells could remain in the uterus even after three months (Alawadhi et al., 2014). Human endometrial tissue is one of the tissues with the strongest dynamism in completing its regeneration perfectly in each menstrual cycle. Although the general belief is that the precursor cells in the functional and basalis layers of the endometrium play a role in this dynamism, there is literature information that BMSCs are also involved in the regenerative ability of the endometrium (Gargett and Mesuda, 2010).

The movement of stem cells to the uterus may be a reparative mechanism against injury or pregnancy. Studies suggest that male bone marrow-derived stem cells may not

contribute at all (Cervello et al., 2012). The number of uterine-adherent BMSCs is low and these cells do not undergo clonal expansion to replace the entire endometrium (Curley et al., 2012; Wang et al., 2012). In cases of severe damage, as seen in severe Asherman syndrome, the limited supply of stem cells may be the limiting factor in the repair process. A reduced pool of stem cells or the ability to recruit them to the uterus likely contributes to IUA. In localized uterine horn damage, BMSCs are inserted into the endometrial stroma of both uterine horns. Inflammation and injury may play an important role in the recruitment of these cells to the endometrium. It is thought that instead of the signal that attracts stem cells locally, signals are released that cause these cells to enter the entire uterine stroma. Even a small damage may be sufficient to collect stem cells, and this may be a move to increase the rate of IVF due to the biological structure of the endometrium. We examined treatment possibilities by intraperitoneally transferring the BMSCs obtained from the tibia and femur bones of male rats to female rats in which we created AS. As a result, contrary to what was mentioned, it was observed that BMSCs obtained from male rats showed a very high level of effect in the Asherman model, allowing embryo implantation in closed uterine horns. In one of the recent studies; In the experimental model in which adhesion was created with phenol mucilage, the level of NF-kB expression was examined and its statistical evaluation was made on the basis of H-score. In the findings, it was reported that the NF-kB level increased. Additionally, by looking at the implantation rate, it was shown

that an average of 5.9 embryos were implanted in AS groups (Wang et al., 2018).

Recently, populations of endometrial epithelial and stromal MSCs that resemble adult MSCs have been very rarely identified in the basal layer of the human endometrium (Gargett et al., 2016). The source of endometrial stem cells remains unclear. However, BMSCs have been recognized to contain many sources, including menstrual blood-derived mesenchymal stem cells and adipose stem cells (Tan et al., 2016). All of these show a strong tendency to heal tissue damage that occurs after endometrial injuries. Among these three types of stem cells, BMSCs are the most commonly used stem cell source in human studies. However, the exact mechanism by which BMSC transplantation enhances endometrial regeneration is unknown. Similarly, menstrual blood-derived stem cells were reported to improve endometrial thickness (5 of 7 subjects) and pregnancy rate (2 of 7 subjects) in an experimental, uncontrolled, prospective 3-year clinical study of 7 cases (Tan et al., 2016). Concerns about these cells are; uncertainties in the sterilization and purification methods of the menstrual cell product. On the other hand, adipose stem cell (ASCs) have not yet been used in human studies, probably due to the need for an invasive procedure for liposuction to obtain fat tissue, the differentiation potential that decreases with age, and the low yield of pure cells (Gargett et al., 2016). ASCs were first administered intrauterinely and were administered intra-peritoneally, imitating other applications such

as intravenous application. The reason for the first route of administration is due to the increase in the harmful effects associated with neutrophil activation and c-reactive protein on the rate of migration, differentiation and survival of stem cells in the acute phase of injuries (Gargett et al., 2016). Experimental models have been tried to be designed using many animals, especially rabbits and rodents, on the IUA model, and alternative treatment methods for uterine adhesions have been tried. Especially in rabbits and rodents, mechanical damage, physical damage, laser damage creation model, curettage model, model in which adhesion is developed by creating infection with lipopolysaccharide curettage suture, and experimental models created using chemicals such as 10% formalin, trichloroacetic acid, polyethylene sponge, phenyl mucilage have been designed and fibrotic tissue. attempts were made to reduce it and increase vascularization (Birkenfeld et al., 1991; Chen et al., 2010; Liu et al., 2013). According to the data analyzed in our study, we reported that BMSCs play a role in endometrium regeneration in an experimental model and that it is very important to transplant the cells, especially with their niche.

In another study, after bone marrow transplantation, male donor-derived bone marrow cells were found in the uterine endometrium of female mice, and some of these cells were observed to differentiate into epithelial cells (Du and Taylor, 2007). Another group demonstrated that circulating CD45+ bone marrow cells contribute to more than 80% of the mouse uterine

epithelium during pregnancy (Bratincsák et al., 2007). Moreover, according to a very recent study, it was reported that intrauterine application of autologous stem cells isolated from the patient's bone marrow revitalized the endometrium and subsequently pregnancy occurred (Nagori et al., 2011). When these reports are evaluated, the experimental intrauterine synechiae model Kılıç et al. After being tested by researchers, it was reported with the first experimental rat model that the use of stem cells for the regeneration of the endometrium was beneficial (Kılıç et al., 2014). In this study, adipose stem cells were preferred and treatment was attempted in subjects with chronic synechiae. Adipose stem cells and bone marrow-derived stem cells are very similar stem cells in terms of morphology and markers. Their preparations vary. Because adipose stem cells can be obtained from fat tissue with a simple liposuction. BMSCs, on the other hand, are cell groups that require slightly more invasive procedures but are more effective than the literature. In studies where transpalntasone was performed, it was also reported that the percentages were higher in the endometrial tissue (Taylor, 2004).

The progenitor/stem cells can be located in the uterine endometrium, injured or undamaged, and can differentiate to uterine endometrial stroma and epithelial cells (Taylor, 2004). Adipose-derived stem cells were first administered intrauterinely, and other applications were intra-peritoneal, mimicking intravenous application. The reason for the first route of

administration is due to the increase in the harmful effects associated with neutrophil activation and c-reactive protein (Wu et al., 2011).

IUA is a disease characterized by intrauterine adhesions and fibrosis that occur as a result of loss of endometrium or damage to the basal layer associated with infertility. BMSCs migrate to the endometrium when damage occurs, but they are not cells characterized by endometrial regeneration. Healing and pregnancy rates were evaluated by transplanting BMSCs in a mouse adhesion model created by trauma. In the group in which a single horn was damaged, no significant difference was detected between the damaged and undamaged horns, and a significant difference was detected in the pregnancy rate between the group in which cells were given and the group in which cells were not given. BMSCs are an important treatment option for pregnancy in patients with AS (Alawadhi et al., 2014). Murine endometrium consists of a single layer containing epithelium and stroma. Therefore, murine endometrium is considered to be a suitable uterine endometrial research model.

There is significant evidence that an adult stem cell population exists in endometrium. The endogenous endometrial stem/progenitor cells may be activated or bone marrow-derived stem cells may be transplanted into the uterine cavity for endometrial regeneration in IUA. Six women with refractory IUA cases who had not been successful with hysteroscopic adhesiolysis, which was the standard treatment option in the past,

were included in the study and endometrial thickness was evaluated by implanting mononuclear stem cells into the subendothelial region. It has also been reported that the thickness of the endometrium of women who also received estrogen therapy increased statistically significantly (Singh et al., 2014). In this study, which included transplantation before curettage, there was no ideal endometrium for implantation of the embryo (Endometrial thickness<7 mm). Because the actual stem cell rate in the bone marrow was relatively low. Moreover, it is quite difficult to immobilize the transplanted cells on the endometrial surface. For this reason, cultured mesenchymal stem cells, not mononuclear stem cell sources, should be implanted and repeated application should be made to increase their number.

It has been reported that in the acute inflammatory uterine injury model using lipopolysaccharide in mice, the expression of transcriptional factors SOX2, NANOG and OCT4 peaks and these factors decrease to their lower levels as inflammation decreases. This may be a vital response to repair and regeneration in acute injury. However, in women of reproductive age with IUA, only NANOG is overexpressed in the endometrium. This may mean incompatibility between NANOG (Nanog homebox) and SOX2 (Sex-determining Y-box2) and OCT4 (Octamer-binding protein), which may lead to failure or defect in endometrial repair and replacement with fibrotic tissue in IUA. Further studies should be conducted to define the role of specific transcriptional factors in the pathogenesis of IUA. However, it is

very important to raise interest in these transcription factors to determine whether they may be involved in the formation or restoration of IUA as well as acute uterine injury (Xiao et al., 2017). In one of the studies in which uterine damage was created, a rat adhesion model was created to investigate the potential beneficial effect of insulin-like growth factor-1 (IGF-1) and the levels of IGF-1 and IL-10 secreted by CISCs were determined by RT-PCR and immunoblotting. In addition, a-SMA (alpha smooth muscle actin) associated with these molecules was detected immunohistochemically, and their roles in the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway and the molecular pathways that play a role in endometrial regeneration began to be investigated. Transplantation of IGF-1-overexpressing BMSCs into the injured uterus has been shown to improve the functional regeneration of the injured uterus by inducing IL-10 expression and secretion by increasing the activation of the NF-κB signaling pathway (Wang et al., 2018).

It has been shown that BMSCs injected directly into the uterine cavities of rats whose uterus was damaged by incision as a treatment had a thicker endometrium and a higher expression of endometrial cell protein markers, cytokeratin and vimentin, compared to rats in which cells were not injected. This has been shown that direct infusion of BMSCs into the uterine cavities of rats has properties that protect against cell damage and promote the regeneration of endometrial cells (Zhao et al., 2015). In current studies, on the one hand, attempts are made to eliminate

experimentally caused damage, on the other hand, application options such as intra-cavity, intra-vascular or intra-peritoneal are tried and the most effective stem cell transfer method is tried to be determined. All these developments suggest that AS, an important infertility problem, will be overcome with stem cell therapies in the near future.

Hu et al. They presented the first report describing the role of endometrial stem cells and fibrosis markers in IUAs in 2015. Endometrial stem cells and the microenvironment (niche) are responsible for the renewal of the endometrium. Fibrosis markers were performed by creating a mouse adhesion model. According to the findings obtained, it has been reported that α-SMA, TGF-β, Collagen III and Collagen I, whose expressions increase in fibrosis, prevent regeneration because they change the endometrial stem cell differentiation niche. Endometrial stem cells are misdirected by fibroblasts in IUAs. However, the specific mechanism and pathway of fibrosis in IUAs need to be further investigated (Hu et al., 2015). TGF-β is an important cytokine that regulates homestasis in damaged tissue. In studies conducted for c-Kit, it was observed that in the chronic endometrial ischemia model in rats, endometrial cells underwent apoptosis after ischemia, and endometrial thickness, luminal and glandular epithelial thickness and number of glands decreased. Parallel to this decrease, it was determined that the cells synthesizing c-kit also decreased. This protein, as c-kit, is a

marker related to the differentiation and proliferation potential of endometrial stem cells (Hu and Yuan, 2011).

In studies examining selectin staining, selectins, one of the most important adhesion molecules, play an important role in the formation of the implantation window and the passage of blastocysts through it. Before implantation, this region of the endometrium emerges as pinopods to which blastocysts will adhere, with chemokines, growth factors, and adhesion molecules such as MUC-1. These pinopods, which mature in a short time, such as a day or two, appear at the ends of the microvilli and establish the relationship between the embryo and the endometrium (Sharma and Kumar, 2012). In studies conducted for fibronectin, it is known that it directs adhesion and migration through these extracellular matrix protein receptors that bind to other molecules such as collagen and fibrin. Fibronectin, which plays an important role in cell migration especially during gastrulation, is also an important regulator of trophoblastic invasion. It is reported in the literature that fibronectin, whose staining amount decreases as decidual maturation progresses, decreases significantly on the seventh day. Restructuring of extracellular matrix proteins during maturation of decidual tissue is one of the important keys to implantation success (Kayışlı et al., 2000).

In studies on laminin, extracellular matrix protein laminin and similar proteins appear in different compositions in the endometrial stroma during decidual formation. It is thought to be

important in the implantation window because it is present in all membranes on the blastocyst during the implantation period (Kayışlı et al., 2000).

Intrauterine adhesion is a common disease of the uterine cavity characterized by inadequate regeneration of damaged endometrium. Recently, stem cell transplantation has been suggested to promote the healing process. In a study conducted with human amniotic mesenchymal stem cells; It was investigated whether human amniotic mesenchymal stromal cells (hAMSC), a valuable resource for transplantation therapy, could improve endometrial regeneration in rodent IUA models. In the study carried out by creating mechanical damage in one of the uterine horns, statistically significant differences were detected in the decrease in fibrous areas and increase in the number of glands in the human amniotic stromal stem cells transplanted group compared to the damaged groups. An increase in the mRNA levels of anti-inflammatory cytokines was also determined in the stem cell group. As a result, it has been reported that human amniotic stromal stem cells accelerate regeneration in damaged tissue with their immunomodulatory properties (Gan et al., 2017). In Asherman experimental models, it is reported that fibroblasts in the lamina propria turn into a fibrous structure as a result of excessive collagen synthesis as a result of adhesions in the epithelial tissue (Gan et al., 2017).

Regeneration is very important in endometrial repair. For this reason, stem cell therapies have begun to be considered as a very remarkable treatment option, especially in the last decade. Many diseases are being tried to be overcome by isolating stem cells from different sources. Stem cells show very promising results in this regard. Systemic or local application options are tried to determine the most effective method. Although stem cell treatment studies on AS are very limited, their use in intrauterine adhesions in terms of creating an experimental model and completing the preclinical phase is almost non-existent. New treatment methods are being focused on to eliminate synechiae, which causes significant infertility and problems that negatively affect general life activity. Three methods were initially proposed to regenerate the endometrium. The first is that tissue engineering has provided an alternative option for endometrial repair. Due to the unique physical properties of the uterus and its complicated hormonal environment, reports of uterine reconstruction have been rare (Lin et al., 2013; Kuramoto et al., 2015). The second is the use of endometrial epithelial cell infusions for epithelial repair techniques to prevent scarring. However, harvesting endometrial epithelial cells is not a simple process due to the extremely limited in vitro proliferation capacity of these cells and the highly invasive collection procedures (Song et al., 2015). Third, stem cell therapy has shown great promise for the repair and/or regeneration of damaged tissue (Cervello et al., 2015).

These data suggest that cell therapy is a promising tool for patients with severe IUA. However, there are also disadvantages. Depending on how it is obtained from bone marrow or fat tissue, infection may develop and it may also aggravate pain. Therefore, the method of obtaining cells is also important. When choosing a method, the patient's condition must be taken into consideration and conditions that may cause infection must be eliminated. It was found that bone marrow-derived stem cells are as effective as estrogen in promoting endometrial proliferation. They are particularly effective in eliminating fibrosis and increasing proliferation. The originality of the study is it creates new models for intrauterine synechiae and reveals new findings that will have restorative effects of bone marrow-derived stem cells on the regeneration of endometrial tissue without causing any surgical adhesions. The surgical operations only serve to divide adhesions within the cavity, but can do little about endometrial regeneration and adhesion recurrence. This means that lines with IUA require more than one approach to provide optimal clinical results.

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Author
Assoc. Prof. Dr. Latife Ceyda İRKİN

Editor
Lecturer Dr. Şamil Öztürk

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