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Research Article

Restoration of the Endometrium in Asherman's Syndrome Using Stem Cells

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Abstract
Asherman syndrome (AS) has an adverse effect on reproductive health and fertility by impairing endometrial regeneration. Currently, treatment for Asherman's syndrome is limited and not very effective. Stem cell-based therapy holds promise for future use in activating endometrial receptivity and in vivo remodelling of the endometrium. Stem cells have beneficial effects on tissue regeneration by targeting the damaged site, recruiting other cells through the secretion of chemokines, modulating the immune system, differentiating into other cell types, activating proliferation into daughter cells, and potentially having antimicrobial activity. (1)

Key words: Stem cell transplantation, Asherman's syndrome, Stem cells, Endometrial regeneration.

Introduction

Asherman's syndrome is a gynecological disorder first described by Israeli gynecologist Joseph Asherman in 1948 and characterized by intrauterine adhesions (IUAs, formerly known as gynathresia or synechiae) causing partial or complete obliteration of the cavity accompanied by symptoms. Acquired syndrome results from destruction of the endometrium and often leads to infertility or recurrent pregnancy loss, chronic pelvic pain, menstrual irregularities (hypo- or amenorrhea), or dysmenorrhea. (2) The most common risk factors include postabortion or postpartum curettage, infection, myomectomy and hysteroscopic surgery, i.e., procedures that destroy the basal layer of the endometrium. The syndrome is characterized by damage to the functional layer of the endometrium, obliteration of the uterine cavity by scar tissue, and recurrent pregnancy loss or infertility and may also cause obstetric problems such as abnormal placentation, that is, presentation or accreta. (3) Hysterosalpingography (HSG) and hysterosalpingography/infusion sonography saline solution (SIS) are useful and sensitive diagnostic methods but are not as specific as hysteroscopy (HS); therefore, they should only be used if HSG is not available. MRI is not used for diagnosis.

The incidence of AS among women ranges from 2% to 22%, and its frequency is influenced by the number of abortions performed and the incidence of genital tuberculosis (4-6).

It is believed that the etiology of intrauterine adhesions is associated with fibrosis of the opposite walls of the uterus after destruction of the basal layer of the endometrium. This is a catastrophic process in which uncontrolled deposition of extracellular matrix (ECM) and fibrillar collagens occurs. The stromal part is replaced by fibrous tissue, and the glands are replaced by inactive cubocellular epithelium. Myofibroblasts, which are activated by CTGF (connective tissue growth factor) through TGF-β, have high metabolic activity and express α-smooth muscle actin (SMA), which is involved in the production of ECM, such as fibrillar collagen types I and III. , V and VI [7]. TGF-β is a central mediator of fibrogenesis and is found at significantly higher concentrations in SMA-affected endometrium compared with normal endometrium; it modulates fibroblast phenotype and function, as well as myofibroblast transdifferentiation [7]. Fibrous factors such as TGF-β1, α-SMA, CTGF and collagen I and III are key for the development of IUA, and their increased expression leads to changes in the ecological niche, thereby inhibiting normal regeneration by endometrial mesenchymal stem cells (eMSCs). Subsequent scarring inhibits normal myometrial contractility and reduces steroid perfusion, leading to atrophy [7,8]. In addition, increased expression of disintegrin and metalloproteinase (ADAM) was found in uterine adhesions, which inhibits the activity of ECM degradation enzymes [8]. ADAM-17 activates TNF-α as well as membrane-associated epidermal growth factor receptor (EGFR) ligands, triggering an immune and inflammatory cascade. Similarly, ADAM-15 interacts with beta-integrin-3 and Src protein tyrosine kinases, suggesting its involvement in cell adhesion and signaling [9]. Consequently, a catastrophic pathological cascade follows, disrupting normal endometrial regeneration [7,8].

The greatest challenge in treating Asherman's syndrome is preventing the recurrence of adhesions after initial treatment, which is as high as 66% [11]. Estrogen treatment has historically been used after adhesiolysis to stimulate regeneration and re-epithelialization of the endometrium. The AAGL practice guideline recommends postoperative estrogen hormonal therapy after adhesiolysis; however, there is no standard dosage or schedule [11].

Several additional treatments after surgery, such as intrauterine devices, adhesion barriers, low-dose aspirin, and intermittent hormone therapy, have also been used to prevent reducing the formation of adhesions and restoring the normal endometrium (6). Additionally, a comprehensive approach combining the various mentioned measures has been proposed to restore the endometrium and achieve better fertility outcomes (12). However, none of these treatments have proven clinical effectiveness and satisfactory pregnancy outcomes (13). To prevent relapse and promote tissue regeneration, it is necessary to uncover the underlying pathology and molecular mechanisms of AS and explore more effective and precise treatments. Studies have shown that severe damage to the basal layer of the endometrium leads to a decrease in the number of resident endometrial stem/progenitor cells (14–16). Therefore, most research has focused on stem cell-based therapies to treat damaged endometrium and restore fertility.

The most promising treatment for Asherman's syndrome is stem cell transplantation. There have been many reports on the therapeutic effects of mesenchymal stem cell (MSC) transplantation for Asherman's syndrome in animals and humans. MSCs isolated from adipose tissue, bone marrow, placenta and umbilical cord are characterized by nonimmunogenic, angiogenic, antifibrotic, antiapoptotic and anti-inflammatory properties. Various paracrine signaling molecules, including cytokines, chemokines, and growth factors secreted by MSCs, are needed for tissue repair (17–18).

Implantation of autologous haematopoietic adult stem cells into the subendometrial zone (the junction between the myometrium and endometrium), with the notion that implanted stem cells can

transdifferentiate into resident endometrial stem cells and lead to endometrial regeneration, is a new but promising approach.

Materials and Methods:

In this case report, we describe a case of treatment of Asherman syndrome with autologous adult stem cells for endometrial regeneration, resulting in conception after in vitro fertilization-embryo transfer (IVF-ET).

Woman born in 1985.

In 2009, there was a history of early pregnancy loss (nondeveloping pregnancy 9 weeks).
In 2010, she had a normal birth at 39 weeks. The weight of the fetus was 3200 gr, and the gender was female. Natural birth was complicated by postpartum hemorrhage. Ultrasound examination revealed intrauterine remnants of placental tissue. Curettage of the uterine cavity was performed on days 7 and 15 after birth. As a result of surgical interventions, the patient developed Asherman's syndrome. The patient complained of amenorrhea; when taking estrogen orally in phase 1 and progesterone in phase 2 of the cycle, scant menstruation-like discharge was observed.

In 2012, the patient underwent hysteroscopy with resection of synechiae. In 2014, as a result of a relapse, a repeat hysteroscopy was performed, adhesions were separated, and an intrauterine device was placed. An IUD-Cu (T-shape) was placed to support the surgically reconstructed uterine cavity. The patient was simultaneously prescribed hormonal therapy. She was treated with cyclic estrogens and progesterones with ethinyl estradiol 0.05 mg from the 5th to 25th day of the cycle and medroxyprogesterone acetate 10 mg from the 20th to 25th day for 6 months to obtain a functional endometrium. During this period, she had scanty bloody discharge. After 6 months, the IUD was removed.

Ultrasound assessment of the endometrium in the next cycle showed a lack of endometrial growth in the preovulatory and secretory phases of the menstrual cycle, despite the normal development of follicles, ovulation and the formation of the corpus luteum. The endometrium was consistently thin, 2-3 mm, with branches of spiral vessels visible only to the junction of the endometrium and myometrium. In 2017, a patient was diagnosed with Asherman Syndrome. Secondary infertility" decided to undergo an IVF course. As a result of controlled ovarian stimulation followed by oocyte collection, 13 oocytes were obtained, from which 9 embryos developed as a result of fertilization (3 categories AA, 4 BB, 2 categories CC). Embryo transfer was not performed due to the thin endometrium not amenable to therapy. All embryos were cryopreserved. All alternative treatments used were unsuccessful.

A woman came to our clinic in 2020. She was offered an experimental treatment method with mesenchymal stem cells obtained from adipose tissue.

The patient underwent liposuction of abdominal fat tissue under local anaesthesia with strict asepsis. The aspirate was sent to a specialized stem cell laboratory operating according to clinical standards.

On the sixth day of the menstrual cycle, an intrauterine insemination catheter attached to a 1-ml syringe filled with a 1-ml stem cell suspension was advanced through the cervix to the fundic end of

the endometrium under transabdominal ultrasound guidance. When the tip of the catheter was 0.5 cm below the bottom, the plunger was advanced slowly to ensure a slow, steady flow of cell suspension into the uterine cavity. It was then very carefully and slowly pulled out from the inner throat and then from the outer throat, maintaining constant pressure on the piston to prevent backflow. Further treatment: estradiol valerate 6 mg daily and aspirin 100 mg were started on the same day and continued. The patient was prepared for the transfer of cryopreserved embryos according to the appropriate protocol. On the day of transfer, the thickness of the endometrium on ultrasound was 6.2 mm, and vascularization reached the intraendometrial area. Three AA class embryos were transferred. Pregnancy began and lasted until the 15th week. At week 15, all 3 embryos were developmentally delayed. The pregnancy was terminated by abortion.

However, the patient's menstrual function was restored. A year later, in January 2021, the 1st cryopreserved embryo of class BB was retransferred, without regenerative preparation of the endometrium for transfer. The attempt was unsuccessful.

In March, to prepare the endometrium for the retransplantation of a cryopreserved embryo, PRP-endometrial therapy was performed. PRP therapy is an opportunity to restore the endometrium by introducing into the uterus plasma of one's own blood, enriched with platelets and a large number of growth factors that are necessary for tissue regeneration and growth of new cells. Intrauterine administration of platelet-rich plasma was performed on days 6 and 8 of the menstrual cycle. On the day of transfer, the thickness of the endometrium was 5.6 mm. The first cryo-preserved embryo of class BB was retransferred. Clinical pregnancy has occurred. Despite complications during pregnancy, such as:
threat of miscarriage at 20 weeks, cervical incompetence, and installation of a cervical pessary to prevent premature birth.

Had COVID-19 at 32 weeks.

Uteroplacental vascular insufficiency, pregnancy hypertension.

By caesarean section, a healthy baby girl was born prematurely at 35 weeks.

This was a case of secondary infertility with Asherman's syndrome.

Results:

Stem cells are a promising therapeutic method for endometrial regeneration in patients with refractory Asherman's syndrome. Numerous studies have demonstrated their therapeutic potential in both preclinical models and clinical trials. Stem cells participate in the natural regeneration of the endometrium in each menstrual cycle, as well as in the postpartum period, after abortion and after iatrogenic procedures that destroy the basal layer. Stem cells have many important functions in regeneration, including but not limited to clonality, differentiation, paracrine signaling, angiogenesis, immunomodulation, and inhibition of fibrosis. Stem cells involved in tissue repair come not only from damaged tissue but also from other organs. Experiments with stem cell therapy in patients and animals with Asherman's syndrome are still in their infancy but have led to several conclusions: (1) less differentiated stem cells may be more effective than more differentiated stem cells in endometrial regeneration, (2) systemic administration of stem cells may have a greater effect on recruitment to the

damaged site than local administration, (3) stem cells can be isolated from different tissues, with each type having a different ability and effect on endometrial regeneration, and (4) stem cells exert their effects on damaged tissues through multiple systems, each of which promotes physiological regeneration and inhibition of pathological scarring. In conclusion, stem cells may be a reasonable therapy for people with recalcitrant Asherman's syndrome. Obstetric problems such as abnormal placentation, that is, presentation or accreta. (3) Hysterosalpingography (HSG) and hysterosalpingography/infusion sonography saline solution (SIS) are useful and sensitive diagnostic methods but are not as specific as hysteroscopy (HS); therefore, they should only be used if HSG is not available. MRI is not used for diagnosis.

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