TRANSCELL BIOLOGICS

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INSIDE

CREDITS

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HIGHLIGHTS

Advancements & innovations in Women's reproductive health and Regenerative Medicine, Endometriosis case study

FROM THE EDITOR

It is fundamental that the body and mind are nourished well before they can perform for us like we want them to, and as they should. There has been much speculation in recent years about how Regenerative Medicine, a new branch of Medicine will evolve to address chronic diseases and disease management indirectly affecting the issues of access and cost of Healthcare. Novel regenerative strategies offer great potential to generate advances in clinical practice in the field of women's health, which is not so cared in our society. There are already over 500 regenerative medicine products available in the market.

The hope that many diseases may someday be treated using stem cells is inspired by the historical success using adult stem cells derived from bone marrow to treat patients with leukemia and other cancers, inherited blood disorders. It is to the readers benefit to know that much progress has been made in the fields of stem cell research for the development of therapies and tissue engineering for application in regenerative medicine in women's health, like tissue-engineered vagina, cervix or uterus, medical groups working on clinical translation to reach the suffering patients globally.

S.Dravida

SUMMARY

In this edition, Endometriosis, related adhesion and infertility being treated with autologous bone marrow derived cultured mesenchymal stem cells is discussed, which is path breaking treatment strategy that the gyneco-surgeons can integrate in their regular practice. This novel regenerative medicine treatment strategy to cure Endometriosis is a boon to the practitioners with an opportunity to retrieve the stored stem cells, offering hope to millions of endometriosis patients for who, the existing treatments are inadequate.
Transcell Biologics continues to disseminate the knowledge and information on importance of storing one's healthy stem cells NOW to retrieve for applications in immediate future of the family.

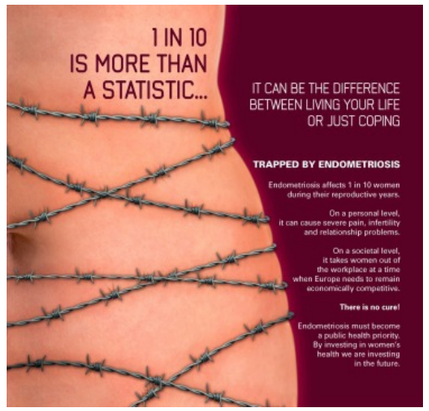
Wishing you all Merry Christmas & Happy New Year 2016!

PREFACE

The incidence of endometriosis is about 5-20 % in India and approximately 30 to 40 % of women with endometriosis are infertile. Since large proportion of patients are asymptomatic, the true incidence of this disorder is not known. The disease is also confined to the reproductive age group of 15-50yrs.The research indicates that the incidence is higher in women belonging to the higher socio economic group due to their inclination to delay child bearing. Presently, there is no known cure for endometriosis globally. Despite the common occurrence of this disease condition, very little research has gone into finding cure to this uncomfortable state of female.

DISEASE-PATHOLOGY

Endometriosis is an unusual condition manifested when the specialized cell layer lining the uterus (endometrium), grows outside of its normal location. This lining is not abnormal in it's growth but the location is the wrong one causing inflammation and discomfort. For women with endometriosis, they may bind an ovary to the side of the pelvic wall, or they may extend between the bladder and the uterus, etc.



Each month, it can cycle just like the normal endometrium in its menstrual cycle. Patients with endometriosis suffer from debilitating pain throughout their child bearing years. Women with endometriosis describe the pain associated with adhesions as “stabbing, sharp, pulling, sickening, intense and nauseating, burning, pinching”. While adhesions are more often looked as a postoperative complication in endometriosis women, who often have had numerous surgeries and thereby, by that factor alone was considered to increase their risk of developing further adhesions.

Endometriosis causes local inflammation, which is a key factor in adhesion formation. Adhesions therefore form as a result of endometrial implants bleeding onto the area around them, causing inflammation, which again leads to the formation of scar tissue as – part of the healing process. Most of the times in endometriotic microenvironment, this injured tissue does not just form a scar it comes into contact with another inflamed area nearby and forms a band of scar tissue – an adhesion – between these two areas.

Though the problem of adhesions in endometriosis is well recognized, there is no known way to prevent them at the moment. Adhesions can lead to adverse outcomes such as infertility, recurrent miscarriage, amenorrhea, pelvic pain, and seriously affect the reproductive health of women of reproductive age.

Current therapy strategy for intrauterine adhesions is separation of adhesions, removal of fibrotic tissue using hysteroscopic surgery, adjuvant estrogen or/and progestin therapy after operation. But still a large number of patients fail after repeated surgical treatments, with adhesions reformation in intrauterine cavity. Therefore, most of the patients are advised to undergo surgery to remove all their reproductive organs (hysterectomy and removal of ovaries), causing premature menopause, which is unnatural as a last resort.

ADVANCEMENTS AND INNOVATION

Current research involving stem cells had shed some light on the mysterious mechanisms of this disease while evaluating the role of bone marrow derived and cultured mesenchymal stem cells as therapeutic tools to treat endometriosis related inflammation and injury rejuvenating the health of the lining.
It was found that endometrial repair in the menstrual cycle is essential for fertility, which rely mainly on endometrial stem cells in the basal layer. Recent studies have found that donor bone marrow derived stem cells can be detected in female endometrium after bone marrow transplant, suggesting that non-uterine stem cells contribute to the regeneration of endometrial tissue. Similar phenomenon was observed in animal models: endo- metrium of female mice transplanted with male mice bone marrow derived stem cells were detected as y-chro- mosome positive cells. This finding made it possible to postulate that autologous bone marrow mesenchymal stem cells can be used in treatment of endometrial injury.

The bone marrow is the body's repository of stem cells. Stem cells can be rapidly mobilized and homed to the site of injury to repair tissue. Autologous stem cell therapy by bone marrow aspiration is one of the options with risks and trauma associated. Autologous bone marrow mesenchymal stem cells, isolated, cultured, amplified and then transplanted to patients itself, could be conducive but the aspiration related pain and yield of stem cells are some of the discussion points to evaluate the risk vs benefits matrix in a clinical scenario.

The allogenic cord or tooth pulp or fat tissue derived and cultured mesenchymal stem cells would be ideal therapeutic cellular agents for treating endometriosis related pain, inflammation to restore the vitality of the endometrium while spontaneous pregnancy could be the primary outcome of the treatment.

Case Study

Zhao et al. / Open Journal of Obstetrics and Gynecology 3 (2013) 377-380 378

In March 2011, a 36-year old female patient came to see a doctor in the reproductive medical center of Navy General Hospital, Beijing, China for chief complaint as she didn't get pregnant with oligohypomenorrhea seven months after stopping contraception methods. The patient had been married for ten years and lived with her husband together normally. She had four times medical abortions because of accidental pregnancy. The patient was given uterine curettage because of Early Embryonic Death in May 2009, December 2009 and August 2010 separately. There was progressive oligohypomenorrhea after surgery and the menstrual cycle was completed ahead of time. The menstrual blood loss was about one third of that before last abortion. There was only brown secretion without dysmenorrhea during menstrual period which lasts 5 - 7 days. The hormone level was normal when she came to see a doctor in March 2011. Routine Semen Analysis and sperm DNA integrity test of her husband was normal too. Hormone replacement therapy was given on the second day of menses in May 2011.

The endometrial thickness was 4 millimeters under reexamination of B type ultrasound. Hysteroscopy and adhesion lysis were given to the patients in June 2011 because of the invalid hormone adjustment. The endometrium was thin and large area fibrosis of the uterine cavity was found in the operation (Figure 1). Hormone replacement therapy was given to the patient after surgery but there was no improvement in the endometrium under the B type ultrasound. The endometrial thickness was 4 millimeters at maximum. There was no menses in October 2011 and November 2011 separately. Because of the invalid conventional therapy, after getting the informed consent of the patient, bone marrow puncture was given to the patient and 30 milliliters autologous bone marrow were collected from the patient and was used for abstraction, separation and culture of autologous mesenchymal stem cells. At the second day of the menses, the patient was given hysteroscopy, adhesion lysis and mesenchymal stem cells transplantation under general anesthesia. Adhesive uterine cavity was separated in the operation. After the shape of the uterine cavity was normal, the surgeon underlay the cervix, use the implantation tube to push 1 milliliters (1 × 107) autologous mesenchymal stem cell to the uterine cavity until the mesenchymal stem cells arrived at the cervix under the monitoring of abdominal B ultrasound and withdrew the implantation tube two minutes later. The hormone replacement therapy was given to the patient in artificial cycle for three menstrual cycles after surgery. At the same time 75 milligrams aspirin were given to the patient. At the second day of the first and second menstrual cycle 6 milligrams estradiol valerate (progynova) were given to the patient orally once a day for 25 days.

At the sixteenth day of progynova administration 20 milligrams dydrogesterone (duphaston) were given to the patient orally once a day for 10 days. The treatment was stopped for the menses. There was a little bit of improvement in the endometrium under B ultra-sound and at the third day of the third menstrual cycle 6 milligrams estradiol valerate (progynova) were given to the patient orally once a day for 30 days. The endometrial thickness was 2.5 millimeters and partial endometrium was B type at the eighth day of the menses under B type ultrasound. The doctors also found that there small fluid chamber with obscure endometrium profile and the lower segment of the uterine cavity was slightly separated. The white pill of femonston was given to the patient in the vagina for 24 days and the grey pill of femonston was given to the patient in the vagina for 14 days. Hormone intervention was not given in the fourth menstrual cycle. At the ninth day (April 25, 2012) of the menses, the thickness of the uterine fundus was 3.2 millimeters and the endometriums of the lower uterine cavity and the left uterine fundus were thin (**Figure 2**). Patient was instructed to have inter- course based on monitoring ovulation. At the 37th day of the menses, the urine pregnancy test was positive and the concentration of blood HCG was 686 mIU/ml. At the same time the concentration of estradiol was 325 pg/ml and the concentration of progesterone was 15.2 ng/ml. All the three data indicated that the patient was pregnant. At the 52nd day of the menses, there was early pregnancy in the uterine cavity and the size of gestational sac was 1.9 × 3.8 × 1.2 under B type ultrasound. The diameter of the yolk sac was 0.32 centimeters. The length of fetal bud was 0.3 centimeters. Embryonic heartbeats could be seen (**Figure 3**).

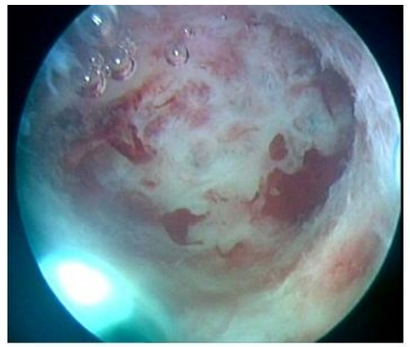


Figure 1. Hysteroscopic picture indicating a large number of fibrotic tissues covering the endometrial surface.

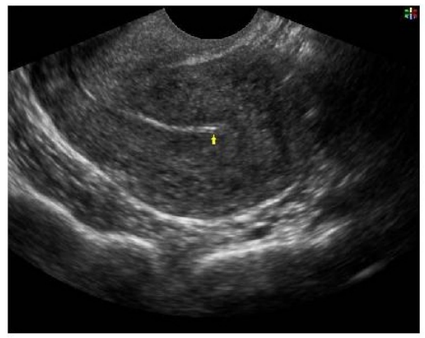


Figure 2. Ultrasound image indicating endometrial recovery (arrow).

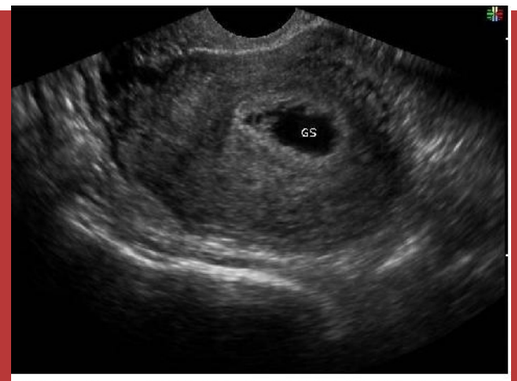


Figure 3. The ultrasound image of intrauterine fetus (8 weeks).

Endometrial Cancer

The abnormal tissue implants that grow as a result of endometriosis aren't tumorigenic. They are benign tissues that grow in areas where they aren't meant to grow. Endometriosis very rarely causes endometrial cancer or uterine cancer, as these cancers are seen in fewer than 1 percent of women with endometriosis. When associated with any type of uterine cancer, endometriosis is found with a type called endometrioid cancer — however, research hasn't shown that endometriosis causes this type of cancer.

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