Role of Autologous Stem Cell Therapy in Asherman’s Syndrome and Thin Endometrium: A Case Series

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Abstract: Stem cells are the cells that perpetually produce another alike cells (self renewal) and have the capacity to differentiate in to diverse cell types if need arise, in all multi-cellular organisms for repair and regeneration of damaged tissue. Lately group of epithelial progenitor cells and mesenchymal stromal cells were found to be responsible for regenerating the functional layer of endometrium after menstruation and parturition. Any injury, surgery, trauma, or infection can damage to the endometrial lining thus causing scarring and fibrosis of endometrium along with thinning of endometrium which is known as Asherman’s syndrome. Thus transplantation of mesenchymal stem cells [MSCs] and hematopoietic stem cell [HSCs] in the uterus along with growth factors will help in regeneration of endometrium with healing of fibrosis. The purpose of this study is to evaluate whether autologous stem cell transplantation in uterus may improve endometrial thickness and reduce scarring in case of Asherman’s syndrome. Five married women with secondary sterility with amenorrhoea in 2 patients and scanty and irregular menses in 3 patients due to endometrial factor were selected on the basis of clinical features and investigations, who have been treated for Asherman’s syndrome by different modalities with no avail and were, advised surrogacy. MSCS & HSCs were implanted at endometrial (basal layer) myometrial junction, at 3-4 sites, Endometrial response was assessed by USG at monthly interval. All 5 patients got relief in term of resumption of menstruation, in 2 amenorrhoeic pt; rest 3 patients have improvement in menstrual flow. Adult Autologous MSCS & HSCs transplantation in uterus helps in reversal of chronic inflammatory changes with regrowth of endometrium, in turn improved symptoms & prospect of fertility.

Keywords: Adult autologous stem cells, MSCs, HSCs, endometrial regeneration, Asherman’s syndrome, growth factors

INTRODUCTION
Asherman’s syndrome or hypo endometrium is a major cause of sterility. It’s a chronic problem with Hypomenorrhoea, irregular or absent menses with increased economic burden and serious long term consequences like PID, infertility, recurrent abortion. Pathophysiology: Severe trauma to the basalis layer of the endometrium with subsequent tissue bridge formation leads to intrauterine synechie; chronic irritation causes injury to endometrial basal layer. Symptoms are amenorhea, spotting in between menses, irregular menses, hypo menorrhea, oligomenorrhea, infertility to recurrent abotions and pregnancy loss. Causes/risk factors are past uterine or cervical surgery, infection related to use of IUCD, severe PID, and infection such as tuberculosis in developing world, very rarely congenially absent endometrium. It is diagnosed by HSG, sono-salpingography, hysteroscopy –multiple filling defects due to synechie, on endometrial biopsy – inflammatory infiltrate or more secretary endometrium. Routinely treated by course of local and systemic antibiotics, cyclical oestrogen and progesterone, IUCD insertion, hysteroscopic resection of synechie.

When this patient did not got satisfactory outcome, we decided to treat these patients with adult autologous mesenchymal Stem cells, haematopoietic stem cells and growth factors. It is an attempt to treat disease by using patients own biological system to regenerate the endometrium.

ICMR guidelines says Autologous stem cells therapy comes under - Permissible area, Umbilical cord stem cells in Restricted area and Embryonic stem cells are Prohibited to use due to Ethical &legal issues.

PROCEDURE - Written & Informed consent taken.
Five married women with secondary sterility due to endometrial factor were selected on the basis of clinical features and investigations, who have been treated for Asherman’s syndrome by different modalities with no avail and were, advised surrogacy. Around 200 ml autologous bone marrow from PSIS...
was harvested and collected in marrow bag, and 100 ml of adipose tissue from anterior abdominal wall was harvested by liposuction using fat aspiration cannula in a sterile jar. Lation & processing of SCs done in the laboratory with maximum quality and safety. Around 10 ml fraction containing (110 Million cells) was prepared for infiltration in to the endometrium. Remaining cells were infused IV, patient was given sedation using midazolam and put in lithotomy position covered TVS probe of USG along with aligner attached to it was introduced in the lateral fornix then a ovum pickup needle was slided into the aligner and its course was negotiated under USG guidance in the myometrium, then each 2ml.concentrate was injected into the sub endometrial location: anteriorly, posteriorly on lateral walls and into the endometrial cavity. It was a day care stitch less scar less procedure. Follow-up at 2month for - clinical benefits & at 6 month for Doppler USG. No adverse events were observed.

RESULTS
These women at 2nd month of follow showed clinical improvement of symptoms with restoration of the menstruation and improved flow suggested endometrial regeneration. Doppler USG done at 6 month confirmed increased thickness, vascularity and uniformity of the endometrium due to healing of the focal defects. Improved general well being was the effect of intravenous infusion of remaining cells and growth factor which helps in physiological anti aging. Two patients who were amenorrhic started having menstruation, rest three responded with increased menstrual blood flow.

DISSSCUTION
It is proved that multipotent pool of stem cells that capable of producing progenitor cells and further differentiate into epithelial, stromal and endothelial cells are found within the deeper basalis layer in the human endometrium [1, 2] so It is clear that repair of endometrium is very fast and that too without scarring [3].

In our study we have transplanted cells in sub endometrial zone as well as in the endometrial cavity (4) we transplanted both adipose and bone marrow derived stem cells (HSCs from bone marrow: cluster differentiation CD 34 + & CD 45 + marker, MSCs from adipose tissue: cluster differentiation CD 73 +, CD 90 + and CD 105 + marker) [14 has they secrete as well as induce certain bioactive molecules that promote regeneration, repair angiogenesis , act as
immunomodulator and inhibit inflammation and activate specific progenitor cells [29, 30], all the MNCs were transplanted thus which cell type got differentiated cannot be specified. We did not do curettage prior to transplantation as studies say it stimulates regeneration. Limited study group was the only downside of this study but as it is a ongoing work more number of patients will be included and specific marker positive stem cells will be transplanted for specification of cell type and better outcome [5]. Mechanism of repair and remodelling is [1-3 ] Most wounds heal with scarring and this is not generally seen in endometrial repair in women, it has been proposed that stem cell reservoirs will be present only in adult tissues that are capable of constant mature cell production or post injury regeneration (Lemischka, 2001). Identification of the microenvironments within the niches in a tissue where different types of precursor or stem cells reside is a major challenge and endometrium certainly fulfils these requirements. (Padykula (1991) subsequently postulated that there is a multipotent pool of stem cells within the deeper basalis layer in the human endometrium, capable of producing progenitor cells that further differentiate into epithelial, stromal and endothelial cells. These growth factors can be derived from both stromal and epithelial cells or from leucocytes. It is clear that repair is very rapid and occurs without scarring, and that the endometrium can be regenerated even after its almost complete removal. Regeneration the endometrium certainly fulfils these requirements. Identification of the microenvironments within the niches in a tissue where different types of precursor or stem cells reside is a major challenge and it leads to epigenetic manipulation of cells [15]. The growth factors can be derived from both stromal and epithelial cells or from leucocytes. So it is clear that repair is very rapid and occurs without scarring. The fact is that even after its almost complete removal the endometrium can be regenerated this potential of endometrium we have encouraged by transplanting stem cells in damaged endometrial surface.

CONCLUSION

AASCs is a promising treatment for scarred and damaged endometrial tissue, we have shown that AASCs and growth factors as a natural biological reagents are safe, effective, ethical and viable option not only in curing the disease but also in improving the quality of endometrium of a woman and protecting her from its significant consequences with improved chances of conception [11, 16, 17].

Future Indications –

Infertility, premature ovarian failure, cancer cure, hypoplastic uterus, in utero transfer of cells to manage congenital disorders. Cosmetic gynecology in rejuvenation of perineum and management of menopausal symptoms.

Ethical clearance

The study was done with permission by the Institutional Committee for Stem Cell Research and Therapy and Human Ethics Committee of the institute. The study procedure was in accordance with guidelines of the Helsinki Declaration of 2000

Source of Support: patient and self

Conflict of Interest: None declared.

REFERRENCES

2. Berek & Novak’s Book of Gynecology, Mentioned existence of endometrial stem cells & its role in treatment of Asherman’s syndrome.174-175.
3. Panayotidis C, Weyers S, Bosteels J, van Herendael B. Intrauterine adhesions (IUA): has there been progress in understanding and treatment over the last 20 years?. Gynecological surgery. 2009 Sep 1; 6(3):197-211.

Available Online: http://saspjournals.com/sjmcr

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14. Xavier Santamaria, MD, PhD Carlos Simon, MD, PhD. Bone Marrow Stem Cell Treatment for Asherman's Syndrome and Endometrial Atrophy (BMSCT) Clinical Trials.Gov. NCt02144987.