STEM CELLS IN REFRACTORY ASHERMAN SYNDROME

ABSTRACT

Introduction – Asherman syndrome (AS) is an infrequent and complex gynecological abnormality due to damage to endometrium causing partial or complete obliteration of uterine cavity and/or cervical canal with a prevalence of 2% to 22% in infertile women. Various therapeutic modalities (extended estrogen therapy, low dose aspirin, vitamin E, sildenafil citrate, Pentoxiphylline, Arginine, G-CSF intrauterine infusion, etc.) have been tried to improve thin endometrium. Several Hysteroscopic techniques have been proposed to treat AS but none has helped in reducing its progression to recurrent adhesive disease.Thin endometrium despite treatment in AS leads to lower implantation and pregnancy rates. Stem cell based therapies have shown promising results in thin endometrium

Stem cells –Stem cells have an emerging role in regenerative medicine in treatment of tissue injury and fibrosis.These are undifferentiated cells with the potential to multiply in undifferentiated form (self renewal) as well as to mature and differentiated cells. Two types have been recognized: Embryonic Stem Cells (ESCs) which originate from blastocyst and Adult Stem Cells (ASCs).Bone marrow-derived stem cells (BMDSCs) have been shown to contribute to the repair and regeneration of tissues and organs, including humanandmurine endometrium, primarily by forming endometrial stromal cells. They express biomarkers CD133/VEGFR2,a subpopulation of cells with endothelial progenitor capacity (EPCs).

A recent publication by Carlos Simon et al in Human Reproduction, 2016 have shown very promising results by using stem cells in patients of Asherman's syndrome. In this study after the initial Hysteroscopic diagnosis, BMD SC mobilization was performed by Granulocyte-CSF injection, then CD133+ cells were isolated through peripheral blood aphaeresis to obtain a mean

of 124.39 million cells (range 42–236), which were immediately delivered into the spiral arterioles by catheterization. Subsequently, endometrial treatment after stem cell therapy was assessed in terms of restoration of menses, endometrial thickness (by vaginal ultrasound), and adhesion score (by hysteroscopy), neoangiogenesis and ongoing pregnancy rate. All 11 AS patients exhibited an improved uterine cavity 2months after stem cell therapy.

Endometrial thickness increased from an average of 4.3 mm (range 2.7–5) to 6.7 mm (range 3.1–12) (P ¼ 0.004). Similarly, four of the five EA patients experienced an improved endometrial cavity, and endometrial thickness increased from 4.2 mm (range 2.7–5) to 5.7 mm (range 5–12)(P ¼ 0.03). The beneficial effects of the cell therapy increased the mature vessel density and the duration and intensity of menses in the first 3months, with a return to the initial levels 6 months after the treatment. Three patients became pregnant spontaneously, resulting in one baby boy born, one ongoing pregnancy and a miscarriage. Furthermore, seven pregnancies were obtained after fourteen embryo transfers, resulting in three biochemical pregnancies, one miscarriage, one ectopic pregnancy, one baby born and one ongoing pregnancy.

Our experience–In a prospective case series, 6 cases of refractory AS with failed standard treatment of Hysteroscopic adhesiolysis were enrolled. Bone marrow was aspirated from iliac crest and mononuclear cells (MNCs) isolation done by Ficoll density separation method. MNCs were evaluated for viability, morphology and CD 34+ status and injected in sub-endometrial zone under transvaginal ultrasound guidance. The procedure was followed by oral oestrogen therapy for 12 weeks. Endometrial thickness (ET) was assessed at 3, 6, and 9 months. The maximum Endometrial Thickness achieved by any patient in this series was 6.7 mm. This was the first study where adult stem cell transplantation was tried in patients of AS. In another 5 year follow up study (unpublished data), 25 patients with AS or endometrial atrophy underwent stem

cell implantation. Subjects were followed up at 3, 6, 9 months and 5 years. Majority of patients with amenorrhea resumed menses (6 out of 7). Duration and flow of menses progressively increased in 20 patients at 3 and 6 months post therapy but declined at 9 months. Four pregnancies were achieved in 5 year follow up period. Two patients conceived spontaneously and two were through Assisted Reproductive Technologies (IVF). Three pregnancies resulted in the live births thus had a successful reproductive outcome and one resulted in an ectopic pregnancy.

CONCLUSION - Regenerative medicine may play an important future role in the treatment of incurable infertility in AS.Further studies are mandatory to address other important issues such as dosage, mechanism of action and refining the protocol.CD133+ cells have emerged as the first orphan drug designed for the treatment of AS.