Therapeutic endometrial regeneration: clinical application of bone marrow-derived stem cells

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Endometrial dysfunction is a widespread problem that can result in both infertility and pregnancy loss. Perhaps the most extreme variant of endometrial dysfunction is failure to generate sufficient endometrial tissue, resulting in a thin endometrium incapable of supporting embryo implantation. In Asherman syndrome, this is due to destruction of the endometrium, typically after trauma, with subsequent scarring and fibrosis. The aetiology of endometrial atrophy in the absence of Asherman syndrome is generally unknown. The first line of therapy to restore endometrial function in Asherman syndrome is surgical correction of the obliterated or restricted endometrial cavity; when surgery is not successful, medical therapies to restore endometrial function have not been successful. Similarly, there are no treatments for idiopathic endometrial atrophy that have been demonstrated to be effective. Endometrial regeneration using stem cells is the most promising innovation in this field.

The basis of stem cell therapy is derived from the discovery of a normal physiological stem cell flux from bone marrow to endometrium in humans (Taylor JAMA 2004;292:81–5). Mesenchymal stem cells from bone marrow normally travel to and engraft the endometrium. This stem cell trafficking is increased in response to injury and supplies a source of new cells and trophic factors that help to heal the endometrium.

Although these cells help to repair the endometrium, they also have an important physiological role in pregnancy (Tal et al. PLoS Biol 2019;17:e3000421). Large numbers of stem cells engraft the endometrium to support pregnancy. We have recently shown that bone marrow replacement can treat endometrial genetic defects and that transplant of defective bone marrow can lead to pregnancy loss. It is now established that the bone marrow is an essential reproductive tissue! Rather than an artificial regenerative medicine approach, stem cell therapy to the endometrium is probably mimicking a normal physiological process.

The first evidence that supplementation of endometrial stem cells can be used to repair Asherman syndrome or atrophic endometrium came from animal models. (Alawadhi et al. PLoS One 2014;9:e96662; Jing et al. Fertil Steril 2014;101:587–94) Extension to humans followed rapidly in several case reports and clinical case series. The mechanisms responsible for the repair of endometrium by bone-marrow-derived stem cells are still in need of clarification. Although the effects of stem cell therapy are dramatic, the number of engrafted stem cells is quite low; these few engrafted cells are not sufficient to replace the damaged endometrium. It is likely that trophic factors secreted by the stem cells rescue or improve the function of endogenous endometrial progenitor cells, allowing the resident cells to repair and replace the endometrium.

A study by Miguel-Gomez et al. (BJOG 2020; https://doi.org/10.1111/1471-0528.16078) in this issue of BJOG characterises the molecular changes induced by the stem cells. By understanding the molecular mechanisms that drive this regeneration, we hope to replicate the molecular effects of stem cells on endometrium. Stem cell transplantation has achieved pregnancy where it was not previously possible, but a better understanding of how stem cells alter endometrium is the first step towards cell-free therapies to restore endometrium.

Disclosure of interests
Dr Taylor reports grants and personal fees from Abbvie, and personal fees from Bayer, Obseva, Dot Lab and Forendo, outside the submitted work. A completed disclosure of interest form is available to view online as supporting information.