Is hope on the horizon for premature ovarian insufficiency?

Few conditions in reproductive medicine have greater potential to destroy the hope and dreams of parenthood than premature ovarian failure or insufficiency. Patients often view this diagnosis as an insurmountable obstacle on their path to achieving pregnancy. Even when they are counseled regarding the potential for pregnancy, they report a hopeless loss of control. Previous authors have stressed the inaccuracy of the term ovarian "failure" describing it as medically misleading and even offensive and psychologically hurtful, with patients experiencing feelings akin to learning about the death of a family member when given this diagnosis. The term premature ovarian insufficiency (POI) is now preferred and reflects the possibility of future ovarian function (1). In many cases of POI, the etiology is unknown or may represent an autoimmune process. Conversely, genetic abnormalities or exposure to gonadotoxic therapies including chemotherapy and radiation clearly result in ovarian dysfunction. Regardless of the terminology or cause, clinicians often struggle with the lack of proven options to permanently restore ovarian function and truly offer the promise of a successful birth of a genetically related offspring. The article by Herraiz and colleagues (2) raises the possibility that hope is on the horizon for ovarian rejuvenation with mesenchymal stem cell (MSC) technology.

The murine model has been especially productive in preliminary work on the ability of MSCs to contribute to differentiation into functional gametes or contribute to gonadal rejuvenation. Likewise, bone marrow derived stem cells (BMDSCs) have shown early promise utilized immunodeficient female mice with chemotherapy-induced ovarian damage to investigate the possibility that human BMDSC infusion could promote ovarian angiogenesis and improve follicular development (2). Infusion of standard peripheral blood mononuclear cells were used as controls to determine if in fact the regenerative properties were due to the bone marrow derived cells and not circulating blood cells. A second phase of their experiment involved ovariectomized animals who were xenografted with human ovarian cortex from patients with POI and treated with infusion of BMDSCs.

As one would expect, the investigators demonstrated that animals administered a reduced dose of chemotherapy were more likely to retain ovarian function, highlighting the fact that spontaneous return of fertility is not uncommon. In animals with ovarian failure, BMDSC infusion resulted in an increase in ovarian vascularization and weight, reduction in apoptosis and increase in cell proliferation with greater primordial, antral and pre-ovulatory follicle number compared to controls. Likewise, the animals receiving BMDSC infusion had a return of both proestruse and estrus phases, an increase in metaphase II oocytes and increase in fertilization rate. Ultimately, BMDSC treated animals achieved up to three consecutive pregnancies. None of the animals in the control group who received the standard chemotherapy dose demonstrated ovarian rejuvenation or function and none achieved a pregnancy. A crucial element of their experiments was the clear demonstration that the labeled BMDSC infused through the tail clearly tracked or homed to the damaged ovaries as well as the human xenografts. The authors also demonstrated that BMDSC infusion had a regenerative effect on the human ovarian cortex xenografts. BMDSCs resulted in increased cellular proliferation, increased follicular density, improved vascularization and an increase in estradiol secretion. The authors concluded that human BMDSCs infusion promoted ovarian function and resulted in the birth of healthy pups from mice with chemotherapy induced infertility. Although somewhat beyond the scope of their investigation, they also speculated that autologous BMDSC therapies could be an alternative to improve follicular development in aging women and patients with POI not associated with chemotherapy or radiation.

Almost two decades have elapsed since the concept that pluripotent stem cells could differentiate into functional gametes was introduced. In the intervening years, primordial germ cells, very small embryonic-like stem cells (VSELs), multilineage differentiating stress enduring cells and ovarian stem cells (OSCs), to name a few, have been associated with the recruitment and stimulation or conversion into functional gametes. Two recent systematic reviews by Fazeli et al. (3) and Bhartiya et al. (4) have highlighted the tremendous advances in our understanding of the pleuripotency of MSCs relative to germ cells. In addition, it is clear that both paracrine and autocrine signals in the ovarian microenvironment or niche are required for normal function. Both gonadotoxic therapies and aging appear to compromise the ovarian niche. Although it is very unlikely that the ovarian senescence seen with aging mirrors ovarian damage from gonadotoxins, chemotherapy-induced ovarian damage provides an excellent animal model for investigation. The ability of MSCs to migrate or "home" to damaged gonads is a crucial tenet of this theory and is well supported by the current literature. However, the questions remain whether the stem cells differentiate into gametes upon arrival, induce regeneration of nonfunctioning ovaries through paracrine signaling, or do both mechanisms play a role.

Numerous potential extragonadal sources of gametes including bone marrow and somatic organs have been reported. It is not surprising that bone marrow may contain primordial germ cells or other pluripotent stem cells that are capable of conversion to gametes since there is a strong developmental link between the hematopoietic system and reproductive system. Bone marrow expresses numerous germ cell markers and BMDSCs contain both pituitary and sex hormone receptors. Multi-lineage differentiating stress enduring cells are also of particular interest as they migrate into damaged tissue via the bloodstream and differentiate into gamete-like cells. Despite the clear suggestion that extragonadal stem cells possess the ability to differentiate, one can make a strong argument that MSCs have a greater impact on ovarian function through residual stem cells in the ovary (VSELs and OSCs) via paracrine communication. Numerous combinations of growth factors and signaling molecules

produced by MCSs are involved in this process. This concept is supported by several in vitro studies and the fact that MSC's microvesicles and the signaling molecules they contain have a beneficial effect on ovarian function via VSELs. VSELs have been described as a back-up population of ovarian stem cells with the potential to undergo conversion to functional gametes. Transplanting autologous MSCs into nonfunctioning ovaries results in new follicular development from endogenous VSELs. Both VSELs and OSCs also appear to undergo neo-oogenesis and follicular assembly as a result of extragonadal stem cell arrival in the ovary. VSELs are a particularly compelling mechanism for ovarian rejuvenation because they are present in the adult ovary, express receptors for follicle-stimulating hormone and appear to be more resistant to gonadotoxic therapy because of their low metabolic rate. VSELs have been shown to survive chemotherapy in mouse ovaries and rebound with follicle-stimulating hormone stimulation. It is interesting to note that these pluripotent cells have also been observed in ovaries from postmenopausal women as well as those with POI. However, there are conflicting results on the ability of stem cells to differentiate into gamete-like cells, further supporting the notion that paracrine signaling is of paramount importance. Potential problems have also been reported with epigenetic changes and abnormal meiosis in the resulting cells. Previous experience has also warned us of the potential for tumor formation when utilizing stem cell technology. There are also ethical concerns with the use of pleuripotent cells to create gametes and offspring.

Although the exact mechanism is a matter of debate, the biologic plausibility that stem cells can restore ovarian function and fertility potential is without question. Numerous publications have demonstrated successful differentiation of stem cells to gamete-like cells in vitro. In addition, in vivo murine, rat and rabbit models have expanded these findings with the production of competent oocytes and viable offspring following MSC therapy. Investigation of this technology's ability to restore ovarian function in humans clearly holds promise. If proven to rejuvenate ovaries following chemotherapy and radiation, these therapies may be expanded to all cases of POI. Eventually, one cannot help but wonder if cases of diminished ovarian reserve (low egg number or quality) or unexplained infertility may be treated with mesenchymal stem cell technology. The penultimate application of these techniques may be in fighting the ovarian senescence seen with aging. The science of ovarian rejuvenation with stem cell technology is rapidly expanding. Dr. Herraiz and colleagues (2) have contributed greatly to the growing body of literature in this arena. Their well-executed proof of concept offers those who suffer from POI a glimmer of hope, but the routine clinical application of these techniques remains on the horizon, albeit a not too distant one.

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