

New Hopes for the Treatment of Primary Ovarian Insufficiency/ Premature Ovarian Failure

Primary ovarian insufficiency or premature ovarian failure (POI/POF) is one of the causes of female infertility. POI is defined as cessation of menstrual periods, increased levels of FSH and diminished levels of estrogens before the age of 40. POI occurs in about 1% of women between 30 to 40 years of age, 0.1% of those under 30 and 0.01% of women under the age of 20. Fertility of women with POI is severely diminished, but unlike menopause, POI may be accompanied with spontaneous ovarian activity and natural pregnancies. The major causes of POI include autoimmunity, genetic and environmental factors. At the same time increased prevalence of gynecological and other cancers, improvement in the treatment procedures has led to better survival rates but increased incidence of POI in women during reproductive age during the past few decades (1).

Given the limited treatment options for women with POI, treatment of POI is performed with two purposes: the first being hormone replacement therapy (HRT) to reduce complications due to impaired endocrine function of ovaries, and the second for fertility concerns. Infertility treatments available for POI which may be used before or during ovarian failure, especially in cancer patients, include fertility preservation such as ovarian cortex, oocyte and embryo cryopreservation, oocyte or embryo donation and adoption in women without any ovarian function (1).

In contrast to women, there is no critical age at which fertility or fecundity of men declines. Spermatogenesis continues after forties and even in older age due to the renewing stock of spermatogonial stem cells; therefore, preservation of pre-pubertal or adult spermatogonial stem cells provide an unlimited source of adult stem cells for fertility preservation in men (2).

Until recently, scientific evidence was based on the limited stock of primordial follicles and subsequent limited number of mature oocytes and absence of possible self-renewing stock of stem cells in normal ovaries. But recent findings in animals and humans showed that neonatal and adult ovaries possess rare numbers of oogonial stem cells (OSCs) that can stably proliferate for months and produce mature oocytes *in vitro*, similar to that of the spermatogonial stem cell in adult testis. Injection of labeled OSCs into mouse ovaries lead to differentiation of these cells into mature oocytes that are ovulated, fertilize and generate viable neonates. Studies on the isolation of OSCs from ovaries of aged animals and production of mature normal oocytes in ovaries of young adult animals lead to the recognition of the importance of OSC niche and intraovarian environment on their differentiation to mature, normal oocytes. Therefore, cases of POI that result from defects in ovarian niche and its insufficiency to support differentiation and growth of oocytes and also ovarian aging may be reversible in future (3).

These findings, in addition to large numbers of animal studies, have offered the opportunity for the application of OSCs as a target for POI therapy, restoration of ovarian function and, subsequently, restoration of normal fertility. However, clinical utility of these cells for treatment requires more evidence to confirm their safety, especially the effects from epigenetic changes during *in vitro* culture, and manipulation of produced oocytes and also resultant offspring.

Achieving such success will require allocation of a great deal of time and undertaking huge experimental and clinical studies. Until that time, early diagnosis of POI and offer of cryopreservation may be the only options for fertility preservation in women with POI. Otherwise, they may inevitably embark on donated oocytes and embryos or adopt a child instead but these measures will have psychosocial consequences of their own.

References

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