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COMMENTARY

Novel use of the ovarian follicular pool to postpone menopause and delay osteoporosis

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Abstract Life expectancy has increased by more than 30 years during the last century and continues to increase. Many women already live decades in menopause deprived of naturally produced oestradiol and progesterone, leading to an increasing incidence of menopause-related disorders such as osteoporosis, cardiovascular diseases and lack of general well-being. Exogenous oestradiol has traditionally been used to alleviate menopause-related effects.

This commentary discusses a radical new method to postpone menopause. Part of the enormous surplus of ovarian follicles can now be cryostored in youth for use after menopause. Excision of ovarian tissue will advance menopause marginally and will not reduce natural fertility. Grafted tissue restores ovarian function with circulating concentrations of sex steroids for years in post-menopausal cancer survivors. Future developments may further utilize the enormous store of ovarian follicles.

Currently, the main goal of ovarian cryopreservation is fertility preservation, but grafting of ovarian tissue may also serve endocrine functions as a physiological solution to prevent the massive medical legacy of osteoporosis and menopause-related conditions in the ageing population. This intriguing solution is now technically available; the question is whether this method qualifies for postponing menopause, perhaps initially for those patients who already have cryostored tissue?

KEYWORDS: Freezing ovarian tissue, HRT, Oestradiol, Ovarian follicles, Postponing menopause

In parallel with increased financial income and better way of life now experienced in many parts of the world, increased life expectancy follows. One century ago the average age corresponding to the natural age of menopause was around 50 years, whereas nowadays the majority of women live beyond 80 years in many countries. In fact, people over the age of 85 years are the fastest growing population group in the USA and people above 65 years will soon constitute more than 20% of the population. Furthermore, a life expectancy of more than 100 years has been estimated for half of all girls born today in many western countries (Christensen et al., 2009). Already now, many women spend around 30–40% of their lives in menopause and face sequelae such as demineralization of bones (i.e. osteoporosis), increased risk of cardiovascular diseases and various cognitive disabilities, well-being and sexuality (Lobo et al., 2014). Society is therefore facing a considerable task in improving the quality of life and longevity for senior women.

Already today menopause-related conditions involve major medical interventions. Approximately one in two women over the age of 50 years will suffer an osteoporosis-related fracture in her remaining lifetime (review: de Vos et al., 2010, www.osteo.org; www.nof.org). The cost of treating osteoporosis is fast increasing: in Canada it is estimated to rise from Can$1.3 billion in 1993 to approximately Can$32.5 billion in 2018 (Goeree et al., 1996). In the USA the medical expense for treating broken bones was estimated to be as high as $18 billion in 2006 (www.osteo.org, Ray et al., 1997).

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Further, many reports have demonstrated a link between cardiovascular disease and women deprived of oestrogens (de Vos et al., 2010). In a cohort of 12,000 post-menopausal women it was shown that those who naturally entered menopause early had a significantly higher risk of cardiovascular mortality than those who naturally entered menopause later (de Vos et al., 2010). Therefore cardiovascular disease in post-menopausal women represents a health hazard, which negatively affects quality of life and well-being.

In parallel with the increased life expectancy the medical and financial burden for treating menopause-related conditions will undoubtedly increase.

The ovary is the key organ in preventing these conditions through its production of sex-steroids, most notably oestradiol and progesterone. The monthly selected follicle constitutes the 'sex-steroid producing factory of the ovary' and produces more than 90% of sex-hormones in each menstrual cycle, exerting a myriad of effects in the body.

Traditionally menopausal effects have been tackled by hormone replacement therapy (HRT), basically mimicking the steroid output from the monthly pre-ovulatory follicle and the accompanying corpus luteum. The HRT approach is well known to have beneficial effects on menopause-related symptoms, but when the Women Health Initiative in California reported an associated increased risk of breast cancer in 2002, utilization of HRT plummeted (Lobo, 2014). Use of HRT is now recovering after several studies have shown that HRT does not increase, or only marginally increases, the risk of breast cancer and cardiovascular disease (Lobo, 2014). Although sooner or later women will become convinced of the new evidence and start to use HRT again, the duration of HRT is often limited only to the menopausal transition for a maximum of 4 to 5 years. The use of HRT for such a short period will only postpone the onset of menopause-related symptoms, but for women spending maybe 30 or more years in menopause there is a considerable risk of experiencing related symptoms anyway. The outlook to an osteoporosis epidemic has prompted a recent paper to call for 'new strategies for long-term osteoporosis prevention' (Karim et al., 2011).

One such new strategy is available. Recent developments in the ability to freeze ovarian tissue now allow menopause to be postponed. Ovarian tissue may be cryopreserved in youth and then transplanted after menopause to provide continued menstrual cycles. The method is used for fertility preservation in women facing a potentially sterilizing gonadotoxic treatment, developed almost two decades ago (Hovatta et al., 1997; Picton and Gosden, 2000), but may also be used for postponing menopause. This radical option makes use of the enormous endogenous store of ovarian follicles that otherwise normally undergo atresia (**Figure 1A**).

The ovaries of a newborn girl contain an average of one million eggs, which are present in resting follicles. This final store is the exclusive source of eggs securing fertility and menstrual cycles after puberty until it become exhausted at menopause. Independent of age, some resting follicles will embark on growth continuously but only one single follicle will be selected each month for ovulation and provide the oocyte with potential for new offspring. A woman will normally ovulate around 450 times from puberty to menopause, whereas all other follicles, representing 99.9%, will undergo degeneration. Many of the follicles constituting this enormous loss possess the ability for growth and development and hence sex-steroid secretion, but may not contain oocytes best suited for reproduction. In connection with assisted reproduction, it is well known that many follicles possess the capacity to escape degeneration and continue to grow and secrete sex hormones.

Further, it is now well established that women with one ovary remain as fertile as women with two ovaries (Lass et al., 1997). A woman with one ovary will produce around 20% fewer mature oocytes compared with a woman with both ovaries following ovarian stimulation, reflecting that follicle atresia in the remaining ovary has become reduced and more follicles will survive to the pre-ovulatory stage (Lass et al., 1997). The age at menopause in normal women is only marginally affected by having one ovary removed (Bjelland et al., 2014; Yasui et al., 2012). Both studies found that women with one ovary enter menopause around one year earlier than women with two ovaries, illustrating the enormous surplus of ovarian follicles. Basically normal women will experience little if any effect on fertility and age of menopause by having ovarian tissue removed when young.

It is now well established that cryopreservation of ovarian tissue maintains viable follicles that support fertility and menstrual cycles upon transplantation (Andersen et al., 2012a). Current experience from our centre shows that tissue remains active for surprisingly long periods. In total, four patients had the first tissue transplanted more than 10 years ago in our centre. All have had a second (or in one case three) transplantation performed since then. The first patient received all the tissue from one ovary through three separate transplantations and maintains ovarian activity almost 11 years after the first transplant. Another woman experienced ovarian activity for almost 7 years after having 55% of one ovary transplanted. She is now in her forties with no permanent partner and is not interested in having the remaining tissue transplanted for fertility purposes. The third woman experienced ovarian activity for almost 6 years by having all tissue transplanted. The tissue has now stopped functioning. The last patient has had regular menstrual cycles for 10.5 years after having 62% of one ovary transplanted. The tissue is still active and the patient has an opportunity to undergo one additional transplantation. Others also report on a prolonged period of function from transplanted ovarian tissue (Silber et al., 2015).

It is noticeable that tissue in these patients has been transplanted with the intention of providing fertility, which requires a larger pool of follicles (i.e. more tissue) to be transplanted than for providing menstrual cycles alone. Therefore the longevity of this tissue if the aim was to postpone menopause would probably be longer.

Follicular recruitment in transplanted tissue appears to occur sequentially, often with regular menstrual cycles as in a normal ovary. In normal women it has been shown that the number of resting follicles recruited per month decreases towards menopause while maintaining capacity to provide one pre-ovulatory follicle per month (Wallace and Kelsey, 2010). Therefore by removing ovarian tissue and cryostoring it, the overall rate of follicular degeneration will be reduced. Furthermore, ovarian cortical tissue from one ovary is usually separated into around 25 pieces frozen in individual ampoules. If the number of resting follicles recruited for growth per month in each of these 25 pieces of ovarian cortex occurs at a reduced rate as in peri-menopausal ovaries of normal women (Wallace and Kelsey, 2010), grafting pieces one-by-one may further expand the period with endogenous

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