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COMMENTARY

Cryopreservation and transplantation of ovarian tissue exclusively to postpone menopause: technically possible but endocrinologically doubtful

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Abstract Transplantation of cryopreserved ovarian tissue has been shown to induce pregnancies and puberty successfully. Therefore, using cryopreserved ovarian tissue to postpone menopause (tissue hormone therapy [THT]) seems to be an interesting option to avoid conventional menopause hormone therapy (MHT). Pregnancy induction and replacing MHT by THT, however, are completely different topics as different requirements need to be met. First, MHT requires long-lasting and continuous hormone production. It still needs to be proven if the transplanted tissue is active for at least 5 years with a continuous follicle growth to avoid phases with low oestrogen production, which would otherwise cause menopausal symptoms and could reduce the postulated benefit for women's health. Second, the advantage of a physiological hormone production over a non-physiological MHT is still hypothetical. Third, women who have undergone hysterectomies who do not need progesterone for endometrial protection would only require oestrogens, imposing more health benefits (cardiovascular system, mammary gland) than oestrogen and progesterone production or replacement. Therefore, transplanting ovarian tissue exclusively to postpone menopause is endocrinologically doubtful and should only be carried out within clinical trials.

KEYWORDS: cryopreservation, menopausal hormone therapy, menopause, ovarian tissue, transplantation

Introduction

The first live birth to take place after ovarian tissue transplantation was in 2004 (Donnez et al., 2004). Since then, cryopreservation of ovarian tissue has become a widely used fertility-preservation technique for women with maligancies about to undergo cytotoxic therapies. Currently, the delivery rate per transplantation is about 24% (Liebenthron et al., 2015). Ovarian tissue activity remains in up to 70% of cases 1 year after transplantation (Liebenthron et al., 2015); however, the delivery rate per transplantation is expected to further increase. Also, as only about one-third to one-half of the cryopreserved tissue is used per transplantation, re-transplantations will be possible in most cases.

Ovarian tissue has also been used to induce puberty in children with ovarian failure owing to previous cytotoxic therapy (Ernst et al., 2013), proving that tissue hormone therapy (THT) may induce a sufficient rise in serum oestrogen levels, and may also replace exogenous hormone replacement therapy in certain cases.

Therefore, a consequential next step would be to use cryopreserved ovarian tissue to postpone menopause instead

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of applying a conventional menopausal hormone therapy (MHT). As this option has already been suggested by reproductive physicians and biologists without adequately addressing the endocrinological aspects (Andersen and Kristensen, 2015), our discussion will focus on the latter. To make a better comparison of both treatment options, we have coined the expression 'tissue hormone therapy' (THT) as a counterpart to the commonly known MHT.

Endocrinological aspects

The Women's Health Initiative is a prospective, randomized, placebo-controlled trial, aimed to assess the risk and preventive factors associated with the most common causes of death, disability and reduced quality of life in postmenopausal women (Manson et al., 2013). Subsequent subanalyses and randomized-controlled trials have provided a better picture of the risk–benefit profile of MHT. In the Women's Health Initiative (Manson et al., 2013), postmenopausal women with an intact uterus were treated with either conjugated equine oestrogens (CEE) (0.625 mg/d) combined with medroxyprogesterone acetate (MPA) (2.5 mg/d) or placebo, whereas women who had undergone hysterectomies received either CEE (0.625 mg/d) or placebo, respectively. During the CEE plus MPA intervention phase, risk of stroke, pulmonary embolism, invasive breast cancer and dementia (in women aged ≥65 years) was increased, whereas benefits included decreased vasomotor symptoms, hip fractures and diabetes, respectively (Manson et al., 2013). For combined MHT, however, breast cancer risk may differ for various progestogens, as the breast profile has been reported to be 'safer' for oestrogens combined with micronized (natural) progesterone. Risks and benefits were more balanced during the CEE alone intervention. Importantly, breast cancer risk was non-significantly reduced during the intervention phase, becoming significant during cumulative follow-up (Manson et al., 2013). Furthermore, for CEE alone, younger women (aged 50–59 years) had more favourable results for myocardial infarction, all-cause mortality and the global index (Manson et al., 2013). All these findings clearly demonstrate that MHT is beneficial for women aged around 50–59 years, and especially for menopausal women who have underone hysterectomies (no need for a progestagen).

Therefore, the key questions arising in the debate about MHT and THT for postponing menopause are as follows: is natural late menopause (>age 55 years), as a model for extended physiological ovarian activity, beneficial for women's health at all? Does THT create a more physiological hormonal profile? And, if yes, is THT, therefore, more beneficial than MHT, assuming long-term tissue activity after transplantation?

Late menopause has been associated with a decreased risk for coronary artery disease (Barrett-Connor, 2013), whereas breast cancer risk was increased (Monninkhof et al., 1999). Accordingly, cardiovascular mortality has been found to be decreased in women with late menopause (Jacobsen et al., 2000). Overall mortality, however, has been reported to be decreased (Jacobsen et al., 2003) or unchanged (Jacobsen et al., 1999). Therefore, cardiovascular health will be the main end-point when considering THT for postponing menopause.

Ovaries produce a broad spectrum of oestrogenic, progestagenic and androgenic hormones that are released in a defined pulsatile rhythm. It is assumed, but not yet proven, that transplanted ovarian tissue produces the same pulsatile spectrum of steroid hormones. We do not know, however, if a more physiological steroid hormone profile is more beneficial than a fixed combination of one or two hormones within an MHT preparation. Furthermore, we do not know when the optimal time point for ovarian tissue transplantation would be, as already slight hormonal changes during the perimenopause may be associated with symptoms such as hot flushes, sleep disorders and abnormal uterine bleeding in need of treatment. It might be that transplanted ovarian tissue with only a small follicle pool will result in a similar but not better hormonal profile compared with the natural menopausal transition warranting additional MHT.

Reproductive aspects

Social freezing to postpone child bearing has also become a topic of interest. So far, it is limited to cryopreservation of oocytes. Although social freezing is already widely offered and carried out, it is still controversial (von Wolff et al., 2015). For example, social freezing may not solve social problems but only postpone them. Pregnant women are potentially becoming older, leading to higher obstetrical risks. Social freezing usually requires IVF. In mice and humans, IVF has been found to increase risk of malformations and functional disorders, such as an increased carotis–intima–media thickness, leading to an increased pulmonary blood pressure (von Wolff et al., 2015). The increased risk of malformation may be attributed to a general predisposition owing to the infertility itself; however, functional disorders, which are probably caused by epigenetic modifications, cannot. Therefore, social freezing using ovarian tissue followed by IVF is possibly associated with an increased health risk for the offspring.

Pregnancies may also be achieved after transplantation of ovarian tissue without IVF. Tissue transplanted into the remaining ovary and even into a peritoneal pocket can lead to spontaneous pregnancies (Liebenthron et al., 2015). Therefore, cryopreservation of ovarian tissue might also be an interesting alternative to social freezing. Data on the technique's efficacy and on children's outcome after having used this technique are still limited; therefore, cryopreservation of ovarian tissue to postpone child bearing cannot yet be generally recommended.

Discussion

As life expectancy increases, women spend about one-third of their lives after menopause; that is, in a state of oestrogen deficiency. Considering the predominantly beneficial effect of late menopause and MHT on women's health, one might hypothesize that postponing menopause by transplanting previously cryopreserved functioning ovarian tissue may have a beneficial effect on the individual. Some objections have been made to this hypothesis. First, restoring one organ's function does not necessarily imply a benefit for the whole