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Review

Importance of ovarian tissue cryopreservation in fertility preservation and anti-ageing treatment

Running title: Ovarian tissue cryopreservation in fertility preservation and anti-ageing treatment

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ABSTRACT

The purpose of this review is to analyze the importance of ovarian tissue cryopreservation as a fertility preservation method as well as a hormone replacement treatment in patients with premature ovarian insufficiency occurring following treatment of oncological and non-oncological diseases. Oncological and non-oncological diseases can cause premature ovarian insufficiency and reduce woman`s reproductive potential by the disease itself or required gonadotoxic treatment, and therefore fertility preservation becomes an emerging field of reproductive medicine allowing them to have their own biological children. Although ovarian tissue cryopreservation is currently regarded as an experimental procedure it is a promising, rapidly advancing fertility preservation method which may become established fertility preservation option in the near future. This method does not require ovarian stimulation and a delay in the initiation of cancer treatment, and furthermore orthotopic ovarian tissue transplantation offers the unique opportunity of spontaneous conception. Furthermore, owing to the restoration of endocrine function folllowing the procedure, ovarian tissue cryopreservation may be used as tissue hormone replacement therapy in cases of premature ovarian insufficiency and premature menopause, to postpone menopause and prevent troublesome symptoms and diseases. Although ovarian tissue cryopreservation has the potential to become a new anti-ageing treatment modality, nevertheless its role is still allways very alluring and therefore safety and efficacy of this approach should be further investigated in clinical settings.

KEYWORDS: ovarian tissue cryopreservation, fertility preservation, premature ovarian insufficiency, anti-aging therapy, menopause

Introduction

Reproductive potential in women may be seriously affected by age, autoimmune diseases, genetic syndromes, metabolic diseases, endometriosis, hematopoietic stem cell transplantation, surgical removal or damage to reproductive organs, gonadotoxic treatments (chemotherapy, radiotherapy) and cancer itself. However, all patients at risk of premature ovarian insufficiency (POI) due to oncological or non-oncological diseases should be informed about potential

infertility risk due to disease itself or gonadotoxic treatment and referred to appropriate reproductive specialists to further discuss the risk of infertility and available fertility preservation options [1]. Furthermore, adverse effects of POI may be accompanied with an increased risk for osteoporosis, cardiovascular disease, vulvovaginal atrophy, vasomotor symptoms, dementia, cognitive decline, depression and sleep disorders. Owing to advances in diagnostics and treatment options and postponement of maternity to later in life, an increased number of young women with cancer desiring subsequent pregnancy has been reported and fertility preservation has been most extensively studied in such patients [2-5]. In these women undergoing gonadotoxic cancer treatment the risk of POI and associated symptoms, delay of cancer treatment, available fertility preservation methods, and possibilities of later conception should be discussed as soon as possible in order to increase their chances of successful motherhood [6-8]. During fertility consultation several intrinsic factors including general health status of the patient, psycho-social factors, consent, assessment of ovarian reserve) as well as extrinsic factors like nature of predicted oncologic treatment - high/medium/low/uncertain gonadotoxic risk, available time and expertise in fertility preservation options should be presented [9]. Although embryo and mature oocyte cryopreservation are the only established fertility preservation methods at the moment, but both of them require ovarian stimulation which delays initiation of chemotherapy for at least 2 weeks. Experimental options for fertility preservation include ovarian tissue cryopreservation, cryopreservation of immature oocytes and ovarian suppression with gonadotrophin-releasing hormone (GnRH) analogues. Ovarian tissue cryopreservation is currently considered as one of fertility preservation options which is advancing rapidly and may emerge as a new standard in the future because it can be performed immediately avoiding ovarian stimulation and later restores ovarian function [6].

Reproductive potential is physiologically affected by natural ovarian insuficieny or menopause and in nowadays women live more than a third of their lives following menopause with life expectancy that steadily increases around the world over the past century. Despite increased risk of cardiovascular and metabolic diseases, obesity, osteoporosis, dementia, cognitive decline and cancer in that period of life, life expectancy and quality of life has increased steadily around the world over the past century, owing to the use of hormone replacement therapy (HRT), healthy lifestyle, screening for cancer and mental activities. The use of conventional HRT leads to a reduction of coronary heart disease and mortality when started soon after menopause and decreases the incidence of osteoporotic fractures and various symptoms. Nevertheless,

estrogen-alone therapy has been associated with no or very small risk of breast cancer for both conjugated equine estrogens (CEE) and estradiol, while addition of progesteron contributes some additional risk of breast cancer [10-12]. However, since recently ovarian tissue cryopreservation has been suggested as a novel as a physiological solution in prevention of menopause-related conditions in the ageing population due to long-term restoration of endopcrine function, although its the main goal is fertility preservation and it seems to be an interesting option to avoid conventional HRT. Nevertheless, despite its technical feasability it is questionnable whether cryopreservation with reimplantation of frozen-thawed ovarian tissue could be useful for postponing menopause as the anti-ageing therapy of the future due to insufficient existing evidence so far available [13,14].

Since cryopreserved tissue can be used for generating pregnancies and as a novel method for postponing menopause, the purpose of this review is to analyze the eficacy of the procedure in women desiring fertility fertility preservation and natural HRT. Ovarian tissue cryopreservation as a fertility preservation method. Ovarian tissue cryopreservation is a fertility preservation method in which ovarian tissue is surgically retrieved and cryopreserved afterward. After being thawed, ovarian tissue is grafted back to the patient either on orthotopic site (into the pelvic cavity) or heterotopic sites (subcutaneous regions such as the forearm, abdominal wall) [15]. Therefore this method requires at least two surgical procedures, one to collect and other to graft ovarian tissue. Although the whole ovary can be grafted, usually a cortical region of the ovary which contains 90% of a follicular reserve is taken for cryopreservation [5]. Four to five pieces of ovarian cortex tissue, 10×5×1 mm in size, are taken laparoscopically. The thickness of the ovarian cortex graft is very important because thinner pieces may not contain follicles, as primordial follicles are generally located 0.8 mm from the mesothelium, therefore recommended thickness of ovarian tissue graft is 1–1.5-mm [16]. Currently, a slow-freezing technique is preferred over vitrification because it was more widely used, but the use of vitrification may be the next step further in improving ovarian tissue cryopreservation, as it was the case with oocyte cryopreservation [16-19]. Ovarian tissue cryopreservation is a menstrual cycle independent method, it does not require a male partner or sperm donor and it is the only fertility preservation option for prepuberal cancer patients. A great advantage is that it does not require ovarian stimulation and treatment delay. When patients undergo ovarian stimulation, there is a limited number of oocytes and embryos that can be retrieved from one cycle which is important for cancer patients who usually have time to undergo just one cycle of ovarian stimulation before starting chemotherapy. With the use of ovarian tissue

cryopreservation we can preserve hundreds of primordial follicles at once which can significantly increase future chances of subsequent pregnancy [15,20]. Furthermore, transplantation of ovarian tissue not only restores fertility but it also restores ovarian endocrine function. After orthotopic reimplantation ovarian endocrine function is restored in more than 95% of patients with a duration of ovarian activity 4-5 years up to 7 years, dependent on the follicular density [15,21]. So far more than 130 babies have been born using this method, with only one reported twin pregnancy after heterotopic ovarian transplantation [15,22]. A recent meta-analysis reported live birth and ongoing pregnancy rate of 37.7% for ovarian tissue cryopreservation [23]. Another advantage of ovarian tissue cryopreservation is that we can avoid in vitro fertilization (IVF) because orthotopically transplanted tissue allows spontaneous pregnancies in the presence of functional fallopian tubes and half of the children born using this method have been conceived by natural conception [5,15]. Suggested criteria for selection of the patients for ovarian tissue cryopreservation are: age younger than 35 years which is dependent on anti-Mullerian hormone (AMH) level and biological age of the patient, a high risk of POI (>50%), a realistic chance of 5-year survival, no previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, no signs of metastatic disease, no contraindications for operation or anaesthesia and informed consent [20]. Age of the patient and the remaining ovarian reserve are the most limiting factors for the success of this method along with revascularization. Ovarian tissue graft is an avascular graft and ischemia can be problematic and cause a death of a large number of follicles along with activation of primordial follicles leading to massive follicle loss resulting in shortened graft longevity [16,24-26]. Several preclinical efforts have been invested to increase vascularization and reduce apoptosis of grafted tissue in order to improve follicle survival and longevity of ovarian tissue graft after transplantation using angiogenic and antiapoptotic factors, antioxidants, adipose tissue-derived stem cells [16,27]. It is preferred to retrieve ovarian tissue before chemotherapy exposure, but if the patient is young and have good ovarian reserve this method can be performed even in patients who already started chemotherapy [28]. There is concern that ovarian tissue could contain malignant cells which can be potentially reintroduced back to the patient, especially for the patients with leukemia, neuroblastoma and Burkitt lymphoma who have the highest risk of ovarian metastasis [29]. Ovarian tissue should be adequately examined in centers specializing in minimal residual disease detection implementing the most recent available technologies before ovarian tissue is reimplanted. A downside is the fact that these tests are destructive and sufficient amount of ovarian tissue needs to be preserved for cancer detection tests and even if the presence of malignant cells is excluded on

tested tissue this does not guarantee the absence of malignant cells in the transplanted ovarian tissue [9, 30]. Shapira et al. [30] published a case report about a successful ovarian tissue re-transplantation in sterile acute myeloid leukemia survivor resulting with a delivery, using light microscopy, cytogenetic analysis, next-generation sequencing and xenotransplantation to severe combined immunodeficiency (SCID) mice for 6 months to confirm the absence of malignant cells. Promising new option which minimalizes the risk of malignant cells transfer is the formation of the artificial ovary in which isolated follicles and ovarian stromal and endothelial cells are encapsulated together inside a matrix. Ovarian stromal cells are needed to control primordial-to-primary follicle transition and to be differentiated into theca cells, while endothelial cells are important for adequate vascularization and functioning of an artificial ovary. This ovarian-like environment allows follicles to grow and develop and to be safely grafted to the patient [9,16,31,32].

Ovarian tissue cryopreservation as a fertility preservation method for non-medical reasons

With the current trend of delayed childbirth for different reasons such as persuit of career, financial issues or lack of male partner who is willing to commit to parenthood, women now choose to undergo fertility preservation for non-medical reasons to prevent age-related fertility decline, mostly using oocyte cryopreservation. Ovarian tissue cryopreservation could also offer these women reproductive autonomy to have their own biological children. Furthermore, it gives women a chance for spontaneous conception. It also provides an opportunity to later use ovarian tissue to postpone menopause [33,34]. As mentioned before [15,16], limiting factor for the success of ovarian tissue cryopreservation is advanced age at the time of ovarian tissue retrieval. Aging contributes to both quantitative and qualitative decline of oocytes with increased aneuploidy rates in older patients. Nevertheless, increased age is associated with increased miscarriage and obstetrical risks (preeclampsia, gestational diabetes, placenta previa, placental abruption, need for cesarean section and maternal deaths) [33].

Ovarian tissue cryopreservation as a hormone replacement therapy

An interesting approach is to use cryopreserved ovarian tissue to postpone menopause. This approach could lead to a reduction of adverse effects associated with menopause such as hot flushes, night sweats, vaginal dryness, dyspareunia, decreased libido, sleep disorders, mood changes, concentration problems, osteoporosis, atherosclerosis. Also, this tissue hormone therapy is an attractive approach to avoid conventional HRT and controversies regarding its use. It is suggested that ovarian tissue grafts would produce hormones in physiological concentration and under hypothalamus-pituitary-ovary (HPO) feedback leading to lower and safer plasma levels of estrogen compared to conventional HRT to achieve a beneficial effect on bone health [5]. Re-establishment of the HPO axis was confirmed on an animal model using cell HRT on rats, although with lower plasma levels of estradiol and progesterone than in those rats with intact ovaries. In order to achieve a beneficial effect on bone health supra-physiological plasma levels of estrogen were needed with pharmacologic HRT to achieve the same benefit as with cell HRT which was achieved with much lower plasma hormone concentrations [35]. The reported duration of the orthotopic graft is approximately 6-7 years and with repeating the procedure activity can be prolonged to more than 11 years [21,36]. Ovarian function longer than 7 years was reported with heterotopic ovarian transplantation as well. It is important to highlight that duration of endocrine function of ovarian grafts varies significantly among the patients and currently it is not possible to predict a long-term duration of the endocrine function [37]. The factors that affects the longevity of ovarian graft are age of the patient and baseline ovarian reserve at the time of cryopreservation of ovarian tissue, history of gonadotoxic treatment, techniques of ovarian tissue preparation, freezing-thawing protocols, number of cortical section grafted, transplantation techniques and graft sites, degree of post-

transplantation ischemia and number of survived follicles in ovarian graft [20]. If the goal of ovarian tissue cryopreservation is HRT only, than heterotopic graft site is preferable for several reasons: it requires less invasive surgery, allows repetition of procedure, it is feasible even in cases of severe pelvic adhesions, allows easier and closer monitoring in case of malignancy recurrence and prevents chances of late pregnancies/ pregnancies in senior age [13,36,38]. A disadvantage of a heterotopic site is that environmental factors such as vasculature, temperature, local pressure, space for follicular growth and paracrine factors may not be optimal and could influence the efficacy of the graft and oocyte quality [38]. Also, the optimal heterotopic site remains unknown. Sites where ovarian tissue was transplanted heterotopically include subcutaneous tissue of the abdomen, forearm, breast tissue, rectus muscle and subperitoneal tissue. The optimal site should be similar to the physiological environment, greatly vascularized, easily accessible, allow space for follicular development and have a good esthetic effect [38]. There are several open questions regarding this approach as HRT such as potentially increased risk of breast cancer due to longer unphysiological ovarian activity, a possibility of irregular and insufficient hormone production, variable and unpredictable duration of longevity of ovarian graft (especially with heterotopic ovarian transplantation), optimal timing of ovarian tissue transplantation, frequency of monitoring of endocrine function and questions regarding superiority over conventional HRT, especially for those women who underwent hysterectomy [13,14,39,40]. Cost and invasivity of ovarian tissue cryopreservation in this purpose need to be taken into account as well. Ovarian tissue transplantation requires at least two surgical procedures and longer storage of ovarian tissue than for fertility preservation, while conventional HRT is relatively cheap. But on the other hand, when the impact on prevention of menopause-related symptoms and diseases is taken into account it would improve quality of life and could lead to significant healthcare savings, preventing osteoporosis and subsequent fractures and cardiovascular risk [39,40].

Conclusions

Preservation of fertility is one of the most important quality of life issues for young women with threatening POI, especially for young cancer survivors who have not completed their family upon a cancer diagnosis. Although ovarian tissue cryopreservation currently represents an experimental approach it offers not only fertility preservation but a restoration of endocrine function as well. Consequently, orthotopic transplantation of ovarian tissue can restore natural fertility and IVF procedure may not be required. In addition, ovarian tissue cryopreservation could also be a new anti-aging treatment of the future where women`s own ovarian tissue is taken at a young age and later used to postpone menopause and prevent troublesome symptoms and diseases that come with menopause. As a role of ovarian tissue cryopreservation as a fertility preservation method is rapidly advancing and heading to become established fertility preservation method, its role of anti-aging treatment as a tissue hormone replacement therapy is very alluring, but safety and efficacy of this approach need to be investigated in a clinical setting.

Disclosure statement:

The authors report no conflict of interest.

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