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To cite this article: Petra Vuković, Miro Kasum, Darko Orešković, Ermin Čehić, Jelena Raguž, Shkelzen Elezaj & Lidija Beketić-Orešković (2019): Importance of ovarian tissue cryopreservation in fertility preservation and anti-aging treatment, Gynecological Endocrinology, DOI: [10.1080/09513590.2019.1611763](https://doi.org/10.1080/09513590.2019.1611763)

To link to this article: <https://doi.org/10.1080/09513590.2019.1611763>



Published online: 11 Jun 2019.



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REVIEW



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

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### ABSTRACT

Various oncological and non-oncological diseases, as well as their treatments, can cause premature ovarian insufficiency and reduce a woman's reproductive potential. Fertility preservation is, therefore, becoming an emerging field of reproductive medicine allowing these patients to have their own biological children. The aim of this review is to analyze the importance of ovarian tissue cryopreservation as a fertility preservation method as well as its new role as a hormone replacement treatment. Although ovarian tissue cryopreservation is currently regarded as an experimental procedure, it is rapidly advancing and may become an established fertility preservation method in the near future. This method does not require ovarian stimulation or a subsequent delay in the initiation of cancer treatment. Furthermore, orthotopic ovarian tissue transplantation offers the unique opportunity of spontaneous conception. Due to the restoration of endocrine function following the procedure, ovarian tissue cryopreservation may also be used as tissue hormone replacement therapy in cases of premature ovarian insufficiency, to postpone menopause and prevent its troublesome symptoms and diseases. Even though the role of ovarian tissue cryopreservation as a new anti-aging treatment modality is quite promising, the safety and efficacy of this approach should be investigated in clinical settings.

### ARTICLE HISTORY

Received 20 January 2019  
Revised 7 April 2019  
Accepted 23 April 2019  
Published online 10 June 2019

### 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 [1]. 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 the 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 oncological 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, 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) analogs. 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 idiopathic ovarian insufficiency or menopause and in nowadays women live more than a third of their lives following menopause with life expectancy that steadily increased around the world over the past century. In that period of life, women are at increased risk of cardiovascular disease, obesity, metabolic disease, osteoporosis,

dementia, cognitive decline, and cancer. Prevention strategies such as healthy lifestyle, screening for cancer, mental activities, and hormone replacement therapy (HRT) at the onset of menopause help to improve both quality and quantity of a woman's life [10].

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 the addition of progestins 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 the prevention of menopause-related conditions in the aging population due to long-term restoration of endocrine function. Although its main goal is fertility preservation it could be an interesting option to avoid conventional HRT. Nevertheless, despite its technical feasibility, it is questionable whether cryopreservation with reimplantation of frozen-thawed ovarian tissue could be useful for postponing menopause as the anti-aging 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 efficacy of the procedure in women desiring 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. A cortical region of the ovary which contains 90% of a follicular reserve is used for cryopreservation [5]. Four to five pieces of ovarian cortex tissue,  $10 \times 5 \times 1$  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 prepubertal 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 only 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, depending 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 *in vitro* fertilization (IVF) can be avoided because orthotopically transplanted tissue allows spontaneous pregnancies in the presence of functional fallopian tubes. 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, 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 surgery or anesthesia 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. Since ovarian tissue graft is an avascular graft, ischemia is the most prevalent complication and can cause a destruction of a large number of follicles which, alongside with the activation of primordial follicles, can lead to a massive follicle loss resulting in shortened graft longevity [16,24–26].

An alternative to avascular ovarian tissue graft could be transplantation of the whole ovary by vascular anastomosis in order to reduce ischemic injury and achieve longer longevity of graft. Freezing technique for the whole ovary is inadequate because of problematic diffusion of cryoprotectant which can destroy cellular ultrastructures and subsequently ovarian function [27]. Currently, there is no data on successful whole ovarian transplantation after cryopreservation [28].

Several preclinical trials have been conducted 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 [16,29]. It is preferred to retrieve ovarian tissue before chemotherapy exposure, but if the patient is young and have a good ovarian reserve, this method can be performed even in patients who already started chemotherapy [30]. There is a 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 [31]. Ovarian tissue should be adequately examined in centers specialized 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. In addition, 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 [9,32]. Shapira et al. [32] 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 minimizes 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 [9,16,33,34].

### Ovarian tissue cryopreservation as a fertility preservation method for personal reasons

With the current trend of delayed childbirth women now choose to undergo fertility preservation to prevent age-related fertility decline. The standard method for 'AGE banking' is oocyte cryopreservation [35,36].

Ovarian tissue cryopreservation could also offer women reproductive autonomy to store their reproductive potential and have their own biological children. Furthermore, orthotopic ovarian transplantation provides a chance for spontaneous conception [36].

Although the effect of unilateral oophorectomy on the age of onset of menopause seems to be limited, with menopause occurring only 1–2 years earlier compared to women with intact ovaries, the effect is more pronounced with earlier oophorectomy [37–39]. Removal of less than 30% of an ovary is considered to have minimal effect on ovarian reserve and follicular recruitment [15].

### Ovarian tissue cryopreservation as a hormone replacement therapy

Conventional hormone replacement therapy (HRT) is used to reduce adverse effects of menopause such as vasomotor symptoms, dyspareunia, atherosclerosis, osteoporosis and related fractures, although its use associated with certain controversies regarding an increased risk of breast cancer, endometrial cancer, serous and endometrioid ovarian cancer, venous thromboembolism [11,40–45]. An interesting approach could be to use cryopreserved ovarian tissue to postpone menopause, especially if the same benefits could be achieved while potentially avoiding the controversies regarding the use of conventional HRT [13,14].

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 hormones compared to conventional HRT [5]. Reestablishment 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 [46].

Several reports demonstrated reestablishment of ovarian function after ovarian tissue cryopreservation, and rarely cessation of menopausal symptoms [47–53]. Owing to the restoration of ovarian function, ovarian tissue grafting may be advantageous to conventional HRT due to androgen production which could improve woman's sexual function, genitourinary syndrome of menopause and decreased libido [54,55].

The reported duration of the orthotopic graft is ~6–7 years and if repeated activity could be prolonged to more than 11 years [21,56]. 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 could be 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 pregnancies in senior age [13,56]. 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 [56]. 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 [56]. However, heterotopic transplantation site could be a source of cyclic pain, growing lump and discomfort in the heterotopic graft site at the time of follicular enlargement [53].

Although the use of ovarian tissue transplantation for postponement of menopause seems to be very promising, there are several dilemmas regarding this approach as HRT such as potentially increased risk of breast cancer due to longer unphysiological ovarian activity, risk of ovarian cancer arising from ovarian graft, superiority over conventional HRT, especially for those women who underwent hysterectomy who do not need progesterone [13,14,57]. Data suggest that breast cancer risk is dependent on the type of progestin and natural progesterone seems to have a safer risk profile [11,42]. Estrogen alone therapy or suboptimal use of progestin in women with an intact uterus is associated with increased risk of endometrial cancer, while combined estrogen + progestin therapy might even be protective for the risk of endometrial cancer [40,58].

Also, there is possibility of irregular and insufficient hormone production, variable and unpredictable duration of longevity of ovarian graft (especially with heterotopic ovarian transplantation), questions regarding optimal timing of ovarian tissue transplantation and frequency of monitoring of endocrine function [13,14,57,59]. 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 could improve quality of life and lead to significant healthcare savings, preventing osteoporosis and subsequent fractures and cardiovascular risk [57,59].

### Conclusions

Preservation of fertility is one of the most important qualities 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

No potential conflict of interest was reported by the authors.

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