HHS Public Access

Author manuscript

Trends Mol Med. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:

Trends Mol Med. 2021 August ; 27(8): 753–761. doi:10.1016/j.molmed.2021.01.005.

Prolonging Reproductive Life Span and Delaying Menopause: Prime Time for Elective Cryopreservation and Transplantation?

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Abstract

Ovarian tissue cryopreservation and autotransplantation can restore ovarian endocrine function and fertility and recently were changed from experimental to fertility preservation procedures for medical indications by the American Society of Reproductive Medicine. Such advances have resulted in discussions around the utility of ovarian cryopreservation in healthy women to preserve fertility and delay menopause or as a hormone replacement approach. Such 'elective' use of ovarian tissue cryopreservation requires a risk-benefit assessment. Here, we review evidence for and against the utility of ovarian tissue harvesting in healthy women, scrutinize recent and needed advances to enhance the feasibility of such an approach, and provide practice and future research guidelines as this elective procedure may not be ready for prime time just yet.

Ovarian Cryopreservation and Transplantation: A Success Story for Fertility Preservation for Medical Indications

Building on prior animal studies on cryopreservation and transplantation [1], in 1999, Oktay *et al.* performed the first reported autotransplantation with previously cryopreserved ovarian tissue to restore ovarian function. In that particular case, the purpose of the procedure was to alleviate menopausal symptoms that were not aided by hormone replacement therapy (HRT) [2]. Given that the procedure successfully restored ovarian endocrine function and follicle development, efforts since then have focused on improving ovarian cryopreservation and transplantation techniques to preserve fertility in patients with cancer. As a result of

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Declaration of Interests

The authors have nothing to disclose.

Supplemental Information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.molmed.2021.01.005.

the efforts of an international body of clinicians and scientists, ovarian cryopreservation and transplantation techniques evolved, culminating in worldwide live birth rates of ~40% per woman [3]. The success rate is higher in experienced centers, possibly because of the advent of improved surgical approaches, such as robot-assisted techniques with utility of human extracellular matrix and perioperative pharmacological support [4,5].

The culmination of these advances led the American Society of Reproductive Medicine to recently remove ovarian tissue cryopreservation and transplantation from the experimental category for fertility preservation purposes [6]. This is an excellent development for young survivors of cancer because ovarian tissue harvesting for cryopreservation restores ovarian function with spontaneous conception in most women attempting pregnancy.

The success of ovarian tissue cryopreservation and transplantation has resulted in speculations that it could also be used to postpone childbearing and/or delay menopause in healthy women without any medical indications for this procedure [7]. At least two-thirds of women who receive autologous ovarian tissue cryopreservation have ‘menopause reversal’ [3] and some preliminary experience indicates nearly a 100% success rate [8].

Given this progress, here we review the medical facts as well as unknowns about the efficiency of ovarian tissue cryopreservation and transplantation, especially when there is no imminent danger to a female’s fertility from medical causes. This is by and large a risk-benefit assessment, as is the case for all elective procedures. To be able to render this risk-benefit assessment one needs to carefully analyze the efficiency of ovarian cryopreservation and transplantation in preserving primordial follicle reserves, the impact of ovarian tissue harvesting on a healthy woman’s age at natural menopause, and the current and future prospects of the technology. Herein we discuss these issues.

How Efficiently Does the Primordial Follicle Reserve Survive after Ovarian Tissue Cryopreservation and Transplantation?

Prior human ovarian tissue xenografting studies and those in sheep models showed that primordial follicle reserve loss is <10% following the freezing and thawing process [9–11]. However, the same studies showed that the majority of the losses occur during revascularization after autotransplantation. Thus, as it currently stands, less than a quarter of primordial follicles that were previously cryopreserved become functional once the tissues are returned back to the patient. These losses should factor heavily in decision-making on the use of elective ovarian tissue cryopreservation. With the current technologies available, we are not returning the same number of follicles that were previously removed and cryostored. Hence, if the amount of ovarian tissue removed results in loss of years in reproductive life and, once transplanted, cannot restore the same number of years back, there may be a negative balance that may make elective ovarian tissue freezing less feasible.

How Does Removal of Ovarian Tissue Affect the Ovarian Reserve and Age at Natural Menopause in Healthy Women?

One of the critical questions in determining the feasibility of elective ovarian tissue freezing to delay and extend reproductive potential is whether tissue harvesting can trigger premature ovarian insufficiency (POI). In a healthy woman, inducing POI by a procedure that is intended to delay menopause is of more significant concern.

There are currently no studies reporting on the impact of ovarian tissue harvesting for fertility preservation in healthy women; however, there have been several studies looking at the impact of ovarian surgery on the age at natural menopause (Table 1). Unfortunately, most of the studies are limited by the fact that the age at unilateral oophorectomy was not specified.

In a cross-sectional study of 24 152 Japanese nurses who underwent unilateral oophorectomy (ULO), the cohort experienced menopause at a mean age of 50.9 versus 52.1 years in the control group with an odds ratio (OR) of POI of 3.32 (1.42–7.77) [12]. Another retrospective study found similar findings, with the mean age at menopause for the study group being 49.59 versus 50.66 years in the controls [OR for POI: 1.27; 95% confidence interval (CI): 1.14–1.41] [13].

A retrospective study considering the beginning of perimenopause as the primary endpoint found that perimenopause began 1 year earlier (age 47 versus 48 years in the controls) in women undergoing ULO, with an OR of 1.93 (95% CI: 1.13–3.31) [14]. In another retrospective study in Black women, the OR of experiencing earlier menopause was 1.17 (95% CI: 0.82–1.66) after ULO [15]. In particular, there was a stronger association between ULO and age at menopause among younger women [hazard ratio (HR): 2.00; 95% CI: 1.09–3.68), who had undergone ovariectomy at an earlier age than the average cohort in that study [15].

None of these studies provided data on the risk of POI based on age at ULO. There have been only two studies that attempted to provide age-specific risk information. A retrospective cohort study found a linear correlation between the age at ULO and age at natural menopause [16]. The age at menopause was 44.7, 46.3, and 48.7 years when ULO was performed at 20, 30, and 45 years of age, respectively [16]. Only one study investigated a young population [17]. In that study, the risk of POI was analyzed after ULO in a cohort of survivors of childhood cancer. The study found that the mean menopause age was 7 years earlier with an OR for POI of 6.3 (95% CI: 3.3–12.2) in those who had ULO versus the controls [17]. Given that the likelihood of success with ovarian autotransplantation (OT) is significantly lower with tissue cryopreserved after the age of 35 [18], studies by Rosendahl *et al.* [16] and Thomas-Teinturier *et al.* [17] may be more applicable to the population of women who may be best suited for elective ovarian tissue freezing. However, these limited data suggest that the younger the age at which the ovarian tissue were harvested, the higher the number of years lost from the reproductive period. This then raises the concern that elective ovarian tissue harvesting may result in earlier menopause in healthy women.

However, the previously described studies were based on ULO. In general, an entire ovary is removed for cryopreservation given the high risk of ovarian insufficiency after cancer treatment and to compensate for the inefficiencies of the cryopreservation and transplantation processes[i]. However, removing an entire ovary may not be justified or medically necessary in the elective setting. Given the data limitations, we do not know the amount of ovarian tissue that can be safely harvested at a specific age without significantly altering the age at natural menopause. Considering that ovarian tissue harvesting procedures are not as common as other reproductive procedures, it may not be feasible to obtain such age-specific information in the near future. Nevertheless, existing data from healthy women suggest that, even though the removal of an entire ovary causes earlier menopause, it does not result in POI (menopause under 40 years of age).

What is the Evidence That Ovarian Autotransplantation with Cryopreserved Tissue Can Restore Ovarian Endocrine Function and Replace Hormone Replacement Therapy?

The first OT with cryopreserved tissue was performed to restore ovarian endocrine function and address menopausal symptoms, which could not be alleviated by HRT [2]. The reported patient's first ovary was removed at the age of 17 years, and the remaining ovary was removed and cryopreserved at age 28 ,due to endometriosis, when the patient also demonstrated signs of low ovarian reserve. The patient sought OT a year later because of intractable menopausal symptoms despite HRT. The transplantation subsequently restored ovarian follicle development as well as estrogen and progesterone production. However, ovarian function could only be followed for less than a year since the patient's pretransplantation ovarian follicle density was low, the graft longevity was limited. While that case established the proof of principle that cryopreserved human ovarian tissue can restore ovarian functions after autotransplantation, it did not provide long-term information about the usefulness of the procedure in addressing menopausal symptoms. In a recent meta-analysis [3], data from 309 ovarian cryopreservation and autotransplantation cases were collected. Among those, the intent was to restore fertility in 246 women and in nine, to restore endocrine function only. While the authors found that nearly 40% of women had at least one child after autotransplantation, most had prolonged ovarian endocrine function as defined by cyclical estradiol (E2) production and follicle development [3]. In particular, ovarian endocrine function was restored in 85.2% of all transplanted women [3]. However, when only studies that had defined menopause before OT were considered, the ovarian endocrine function restoration rate was 63.9% [3]. When the ovarian function was not restored, POI was present before cryopreservation, an inadequate quantity of tissue was cryopreserved, or cryopreservation was performed at an advanced age [3]. The same study also showed that, with tissue from about one-third of an ovary cryopreserved at the mean age of 29.3 (9–44) years, the mean longevity of OT was 26.9 (4–144) months [3]. While this longevity is sufficient to establish a reasonable fertility window, because many patients will

[i]Resources
https://youtu.be/CqMl_WXtCmM

cryopreserve surplus embryos for future use before the ovarian graft function ceases, it may not be ideal for hormonal replacement purposes.

There have been reports of prolonged endocrine function with previously cryopreserved tissue, but these generally required multiple transplantation procedures with tissues from 55–100% of an ovary being utilized [19]. Age at the time of cryopreservation has an important role because ovarian reserve decreases with age [20], and the graft faces substantial follicle loss after transplantation due to temporary ischemia [21]. Prior studies in cadavers found <1000 nongrowing follicles remaining in the ovary at the time of menopause [22–24]. Still, a correlation between the number of nongrowing follicles at any age and the age at natural menopause is currently unknown.

In general, there are two main approaches to OT: orthotopic (pelvic) [2] and heterotopic (outside the pelvis) [25,26]. Heterotopic locations may include subcutaneous areas of the abdomen or extremities [25,26] or retroperitoneally in the abdominal wall (instructional video available[i]) [5]. Among these, the subcutaneous heterotopic OT technique may be the most practical site for transplantation when only ovarian endocrine function restoration is desired. The successful restoration of the ovarian follicle and endocrine function by subcutaneous transplantation of ovarian cortical pieces freshly or after cryopreservation in several women has been described [25–27]. Heterotopic subcutaneous transplantation can be performed under local anesthesia. Given their noninvasive nature, repetitive procedures may be more feasible. In theory, a single strip of ovarian tissue is inserted and replaced with a new one when the function of the previous strip begins to wane. This approach would avoid the simultaneous exhaustion of the ovarian reserve in multiple strips; in theory, it may also allow prolonged hormonal function from the cryopreserved tissue. Subcutaneous sites may also offer the advantage of easy monitoring and removal, should there be an abnormal growth in the ovary.

Is There Evidence That OT Can Restore Ovarian Endocrine Function in Healthy Women?

Petrokovski and Zharov recently reported their experience of five women who underwent heterotopic OT to the armpit for managing symptomatic menopause [28]. Ovarian wedge resections amounting to 20–25% of an ovary were obtained from women at the mean age of 28.2 ± 4.3 years during routine obstetrical or gynecological procedures. These women then underwent autotransplantation of their tissues at the mean age of 47.4 ± 5.1 years, after experiencing natural menopause. Of the five transplants, four functioned, while one had to be removed due to site infection. The time to function for the graft was 9 ± 2.6 weeks. All four women reported acceptable or excellent results within the 6 months of follow-up. At the time of the report, all four grafts had been functioning for at least 6 months [28]. Although encouraging, these data are preliminary, and a larger number of women with longer follow-up will be needed to reach valid conclusions.

Can Advances in Ovarian Cryopreservation, Thawing, and Transplantation Techniques Make Elective Ovarian Cryopreservation More Feasible?

The future success of elective ovarian tissue harvesting depends on advances in cryopreservation, thawing, and transplantation techniques. There has already been significant progress in these areas. As discussed earlier, the freezing and thawing process typically results in the loss of a small percentage of follicles. Nevertheless, the original slow-freezing and rapid-thawing approach has improved over the past two decades. Furthermore, preliminary data have given promising results with an open and closed system specifically designed for ovarian issue vitrification [29].

Another area of progress is with vascularization-enhancing approaches. OT is performed akin to skin grafting, where ovarian cortical strips are attached to vascular pelvic structures with full revascularization spontaneously occurring over 10 days [21]. During this period, ischemia may result in the loss of around two-thirds of the pre-existing primordial follicle reserve. Therefore, the most significant improvement in OT success would likely come from approaches that can enhance this vascularization process.

Sphingosine-1-phosphate (S1P) is a naturally occurring phospholipid messenger previously tested for preserving human ovarian primordial follicle reserve against chemotherapy-induced death [30]. However, it might also have effects on endothelial cell migration. Thus, Oktay and colleagues hypothesized that S1P could improve the revascularization process and primordial follicle survival in OT. They found that S1P significantly accelerated the revascularization of ovarian grafts, allowing full revascularization to occur in 2–3 days instead of 10 days in the controls. It also resulted in the doubling of the microvascular density by the tenth day of administration compared with controls. This resulted in significantly reduced tissue hypoxia, improved stromal cell survival, and reduced primordial follicle apoptosis [21]. While S1P is not approved for clinical use, its synthetic analog FTY-720 has been approved to treat multiple sclerosis [31] [fingolimod (Gilenya™), Novartis]. However, in the aforementioned xenograft study, FTY-720 paradoxically resulted in reduced vascularization, possibly due to the use of high doses that downregulated receptor function. Hence, further dose-finding studies are needed in human ovarian xenograft models before this drug can be tested in clinical trials to improve OT longevity [21].

There have been other attempts at improving ovarian graft longevity with stem cells, growth factors [erythropoietin (EPO), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF)], antioxidants [vitamin E, *N*-acetyl cysteine (NAC), and melatonin], and androgens, among others [32–47]. These are summarized in Table 2. Since these approaches are not at the translational stage, they are not detailed further here.

Another improvement could come from the utility of neovascularizing membranes [48,49]. Alloderm is a decellularized extracellular tissue matrix (ECM) scaffold widely used in clinical practice to repair tissue defects, reconstruction, and bridging neovascularization from adjacent tissue edges, especially in the dental field and to repair skin wounds. Alloderm is immunologically inert and allows cell proliferation and migration from the recipient’s tissues [48]. In previous basic science experiments, it was shown that ECM

is critical in primordial follicle growth and development [49,50]. In subsequent studies, it was surmised that the ECM scaffold may enhance ovarian graft revascularization and function [4]. In initial studies where the utility of the ECM scaffold was combined with the robot-assisted laparoscopic techniques, a larger than expected amount of follicle growth in ovarian grafts upon stimulation was found [4]. The method resulted in multiple live births in women who initially underwent these procedures. While these preliminary developments are promising, work to enhance ovarian cryopreservation and autotransplantation is continuing and further research will be needed to determine the best practices to restore ovarian function by these procedures.

What Are the Ethical Concerns Regarding the Autotransplantation of Cryopreserved Tissue to Restore Ovarian Endocrine Function?

Cryopreserved ovarian tissue transplantation can restore ovarian function and fertility in postmenopausal women [6]. This has been widely demonstrated in postmenopausal women after gonadotoxic treatments. However, postponing menopause with ovarian tissue transplantation could mean extending the fertility period to extreme ages, and this has a tremendous ethical impact. Some authors have already highlighted a possible solution to this ethical problem by proposing subcutaneous ovarian tissue transplantation [7]. In addition to preventing the possibility of spontaneous pregnancies, this type of transplant is less invasive than the orthotopic transplant procedure and could also respond to another ethical issue, that of surgical risk, if indeed the advantages brought by the transplantation of ovarian tissue outweigh such risks. However, to obtain ovarian tissue for cryopreservation, abdominal surgery for an ovarian biopsy is required. Women who could achieve a favorable benefit-risk profile are those who must undergo abdominal surgery for other reasons [7]. Many of the effects of menopause can be counteracted with less invasive methods, such as HRT [51]. However, this type of treatment was stopped by many women after the Women’s Health Initiative study reported an increased risk of breast cancer [52]. It was then shown that those data were inappropriately extrapolated from women in the advanced postmenopausal phase (age >60 years) and that there were instead benefits in terms of the prevention of coronary heart disease and mortality when HRT was initiated near the onset of menopause [53,54]. Although the advantage of ovarian tissue transplantation is the production of endogenous hormones rather than the intake of pharmaceutical hormones, the impact of endogenous hormones after ovarian tissue transplantation on women’s health has not yet been studied. Additionally, no studies have been performed to compare the health of postmenopausal women after ovarian tissue transplantation and women taking HRT therapy. Estrogen-only therapy reduces cardiovascular risks more when initiated during early postmenopause compared with combination therapy [55]. Since women who have undergone a hysterectomy can receive estrogen-only treatment, such patients are likely not to benefit from ovarian tissue transplant. Moreover, if delaying menopause can lead to alleviation of climacteric symptoms and a decrease in cardiovascular and osteoporosis risks [56], it can also lead to an increased risk of breast cancer. In fact, late menopause (>55 years) has been associated with an increased risk of breast cancer [57].

Concluding Remarks

Clinical ovarian tissue cryopreservation and transplantation, beginning with the first successful procedure in 1999, opened a new era in fertility preservation and are no longer considered experimental [6]. The procedures provide high live birth rates when utilized for women under the age of 35 years and also restore ovarian endocrine function in most women of the same age. However, less certain is the longevity of endocrine function and whether the estrogen production from these autotransplants provides a steady and reliable source of hormone replacement without the need for supplementation with progesterone.

A key question remains whether the reduction of the length of reproductive life by the partial or total removal of an ovary is matched by the length of endocrine function gained after autotransplantation. Unless there is a ‘zero’ or positive balance, ovarian cryopreservation for future HRT purposes may not be feasible. Moreover, to prevent menopause-related diseases, the ovarian transplant should provide a prompt endocrine restoration with a steady hormonal release over time [56]. It takes 3–6 months from the autotransplantation to endocrine function and, thus, if a woman is already experiencing menopausal symptoms, she will not receive an immediate benefit. However, continual advances in ovarian cryopreservation, thawing, and transplantation techniques may enable women to achieve more extended ovarian function with less tissue.

It is also uncertain whether a clinically useful amount of ovarian tissue can be harvested from healthy women to prolong reproductive life span and delay menopause. At the heart of this issue is the insufficiency of data in determining the minimum amount of ovarian tissue that can be safely removed at a given age without inducing earlier menopause. While studies with patients with cancer, who are typically aged <25 years, suggest that years of ovarian function can be obtained with ovarian cortex from approximately one-third of an ovary, data for women between the ages of 25 and 40 years are scarce. Based on data accumulated from patients with cancer over a decade of experience, we surmise that cortex from one-third of the ovarian surface may provide sufficient primordial follicles to ensure adequate time for spontaneous pregnancy research or *in vitro* fertilization treatments. However, this recommendation should be individualized based on ovarian reserve assessments and age. In fact, when the ovarian cortex is removed in old age, the number of primordial follicles available after transplantation is lower and this may not guarantee adequate hormone production to overcome menopausal disorders. There is a significant and accelerated decline in oocyte quality after the age of 37 [58] and the ovarian reserve is significantly diminished after the age of 40 [58]. Pregnancy outcome data from patients with cancer thus far showed that the oldest age at which the ovarian tissue can be cryopreserved and successfully result in a live birth after transplantation was 39 years [3]. Thus, the current technology may not be clinically useful to cryopreserve ovarian tissue in women older than 40 years of age to preserve fertility and extend ovarian endocrine function [59,60] (see Outstanding Questions). Therefore, we propose guidelines for selecting patients who are most likely to benefit from elective ovarian tissue cryopreservation (see Clinician’s Corner).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Some of the work discussed in this article was funded by research grants from the National Institutes of Health to K.H.O.

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Highlights

The successful use of ovarian tissue cryopreservation and autotransplantation in patients with cancer resulted in their recent change from experimental to fertility preservation procedures, prompting calls for their use to postpone childbearing and/or delay menopause in healthy women.

Current experience with elective ovarian tissue freezing is limited and no direct risk-benefit analyses are available.

Evaluation of the impact of ovarian tissue harvesting on age at natural menopause is necessary for a risk-benefit assessment for this procedure in healthy women.

The large primordial follicle reserve losses during revascularization shortens the longevity of ovarian transplants, a limitation for its use for postponing age-induced infertility or menopause.

Advances in ovarian freezing, thawing, transplantation techniques, and neovascularizing agents may render elective ovarian tissue freezing more feasible in the future.

Clinician's Corner

Proposed Guidelines for Cryopreserving and Transplanting Ovarian Tissue in Healthy Women

- Assess ovarian reserve assessment before harvesting; avoid the procedure if the reserve is already diminished.
- Limit the procedure to women <40 years of age.
- Inform candidates about the uncertainty of benefits, risks, and alternatives, and perform the procedure, preferably under an Institutional Review Board (IRB)-approved protocol.
- When possible, bundle the tissue-harvesting procedure with a medically indicated pelvic surgery (e.g., cesarean section, tubal ligation, or laparoscopy for benign gynecological conditions).
- Limit tissue harvesting to ≤ one-third of the cortex of one ovary to minimize risk of inducing early menopause.
- Avoid wedge resection and perform a superficial cortical biopsy to minimize adhesion risks (see video[i]).
- Consider subcutaneous heterotopic transplantation techniques when the only desire is to restore ovarian endocrine function.

We believe that these guidelines should be followed in order to ethically gather meaningful data and reliably assess the clinical feasibility of ovarian tissue cryopreservation for non-medical indications. Moreover, the data accumulating from patients with cancer should be periodically scanned for information that can contribute to the feasibility assessment of elective ovarian tissue harvesting. Future studies and data analysis will reveal the feasibility of ovarian tissue cryopreservation and transplantation to preserve and restore ovarian functions in healthy women.

Outstanding Questions

What is the mean longevity of the endocrine function of a graft after ovarian tissue transplantation?

Does estrogen production from transplanted ovarian tissue provide a steady and reliable source of hormone replacement?

Is the length of reproductive life reduced by the partial or total removal of an ovary and is this reduction matched or exceeded by the duration of endocrine function gained after autotransplantation?

What is the minimum amount of ovarian tissue that can be safely harvested and cryopreserved at a given age to meaningfully prolong the reproductive life span and delay menopause, without inducing earlier menopause?

What is the optimal age range for cryopreserving ovarian tissue to extend ovarian endocrine function?

What are the best practices to cryopreserve, thaw, and transplant ovarian tissues autologously to achieve maximum longevity and success?

Can ovarian transplant longevity be extended with neovascularization-enhancing treatments and can that make elective ovarian tissue freezing more feasible?

What is the cost of elective ovarian tissue freezing to society; is it cost-effective?

What are the ethical issues that need to be addressed with utilizing ovarian tissue harvesting for extending reproductive lifespan?

Should the procedure be limited to medical indications only?

We have now accepted elected egg freezing; why should we not also offer ovarian tissue cryopreservation for elective purposes?

Is elective ovarian tissue freezing superior to elective oocyte freezing?

Table 1.

Impact of ULO on the Risk of Early Perimenopause or Menopause[a]

ULO risk (95% CI) versus control	Median age at ULO	Comments	Refs
1.93 (1.13–3.31)[b]	N/A	- Retrospective study - 2548 women - Median age at inception of perimenopause: 47 years versus 48 years (controls) - Inception of perimenopause considered	[14]
3.32 (1.42–7.77)[c]	N/A	- Cross-sectional study - 24 152 Japanese nurses - Median age at menopause: 50.9 years versus 52.1 years (controls)	[12]
1.23 (1.08–1.34)[c]	See main text	- Retrospective cohort study - 28 731 women - Median age at menopause: 49.5 years versus 51.3 years	[16]
1.27 (1.14–1.41)[c]	N/A	- Retrospective cohort study - 23 580 Norwegian women - Median age at menopause: 49.59 years versus 50.66 years	[13]
6.3 (3.3–12.2)[c]	4 (0–17)	- Retrospective cohort study - 1109 survivors of childhood cancer - Median age at menopause: 42 years versus 49 years	[17]
1.17 (0.82, 1.66)[c]	N/A	- Retrospective study - 17 070 African American women	[15]

[a]Abbreviation: N/A, not available.

[b]Risk of earlier onset of perimenopause.

[c]Risk of earlier onset of menopause.

Table 2.

Other Proposed Interventions to Improve Ovarian Graft Longevity[a]

Treatment	Ovarian tissue donor/recipient	Effect	Refs
bFGF or bFGF+VEGF	Human/SCID mice	bFGF increased vascular density and follicle survival VEGF cotreatment: no additional benefit	[33]
bFGF, VEGF or bFGF+VEGF	Mice/mice	bFGF+VEGF combination improved follicle survival and vascular density	[32]
VEGF	Cynomolgus monkeys/cynomolgus monkeys	Reduced graft survival	[40]
Fibrin with HBP, heparin, and VEGF	Mice/mice	Increased follicle survival	[41]
Ang2	Mice/mice	Increased follicle survival	[45]
ASCs	Human/SCID mice	Improved revascularization and follicular survival	[37]
Gonadotropins	Mice/mice Human/mice	Increased follicle survival Promoted growth of early secondary follicles	[38,43]
Androgens	Human/SCID mice	More developing follicles in male versus female mice	[44]
EPO	Mice/mice Dog/SCID mice Rat/Rat	Increased follicle survival Increased survival of primary and transitional follicles Improved follicular survival	[34,35,42]
NAC	Mice/mice	Improved follicular survival	[36]
Vitamin E	Human/SCID mice	Not beneficial	[44]
Melatonin	Rat/rat	Reduce ovarian tissue necrosis	[39]

[a]Abbreviations: Ang2, angiopoietin-2; ASCs, adipose tissue-derived stem cells; bFGF, basic fibroblast growth factor; EPO, erythropoietin; HBP, heparin-binding peptide; NAC, *N*-acetylcysteine; SCID, severe combined immunodeficiency; VEGF, vascular endothelial growth factor.