Anthem

Clinical UM Guideline

Subject: Cryopreservation of Oocytes or Ovarian Tissue
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Description

This document addresses oocyte and ovarian tissue cryopreservation which are alternative techniques to embryocryopreservation for individuals who are at risk of infertility due to non-elective medical or surgical treatment, including bilateral oophorectomy or gonadotoxic therapies such as chemotherapy or radiation therapy.

Note: Some plans may exclude or limit coverage of oocyte collection, storage, and other associated services. Please check benefit plan descriptions for details.

Clinical Indications

Medically Necessary:

I. Cryopreservation of mature oocytes is considered **medically necessary** when the following criteria are met:
   A. Individual is a candidate based on ovarian reserve and likelihood for successful oocyte cryopreservation (for example, age 45 years or less); **and**
   B. Post-pubertal; **and**
   C. Facing anticipated infertility resulting from medical or surgical treatment, including chemotherapy, radiation therapy, other gonadotoxic therapies, or bilateral oophorectomy; **and**
   D. Anticipated infertility is NOT the result of the following:
      1. Sterilization services, when not for treatment of an illness, injury or disease or its symptoms;**or**
      2. Normal reproductive aging.

II. Cryopreservation of ovarian tissue is considered **medically necessary** when the following criteria are met:
   A. Individual is a candidate based on ovarian reserve and likelihood for successful ovarian cryopreservation (for example, age 45 years or less); **and**
   B. Unable to undergo oocyte cryopreservation that is: individuals who require immediate gonadotoxic treatment or prepubertal; **and**
   C. Facing anticipated infertility resulting from medical or surgical treatment, including chemotherapy, radiation therapy, other gonadotoxic therapies, or bilateral oophorectomy; **and**
   D. Anticipated infertility is NOT the result of the following:
      1. Sterilization services, when not for treatment of an illness, injury or disease or its symptoms'**or**
      2. Normal reproductive aging.

Not Medically Necessary:

I. Cryopreservation of oocytes is considered **not medically necessary** when the criteria above are not met.
II. Cryopreservation of ovarian tissue is considered **not medically necessary** when the criteria above are not met.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
89337	Cryopreservation, mature oocyte(s)
89344	Storage, (per year); reproductive tissue, testicular/ovarian [when specified as ovarian tissue]
89346	Storage (per year); oocyte(s)
89354	Thawing of cryopreserved; reproductive tissue, testicular/ovarian [when specified as ovarian tissue]
89356	Thawing of cryopreserved; oocytes, each aliquot
89398	Unlisted reproductive medicine laboratory procedure [when specified as cryopreservation of ovarian tissue]

ICD-10 Diagnosis	
	All diagnoses

When services are Not Medically Necessary:
For the procedure codes listed above when criteria are not met.

Discussion/General Information

Note: The use of the terms "female/women" and "male/men" refer to sex assignment at birth.

Anticipated Infertility

Women are born with a limited number of oocytes, also known as ovarian reserve. This pool of oocytes decreases over time until menopause or ovarian failure. As ovarian reserve diminishes, so does fertility. Similarly, therapies to treat medical conditions, such as

cancer, may compromise fertility. The American Society of Clinical Oncologists (ASCO®) article *Fertility and Cancer Treatment* (2013) lists chemotherapy agents that are linked to fertility issues, including: cisplatin, alkylators, such as cyclophosphamide, chlorambucil, busulfan, procarbazine, carmustine, iomustine, mechlorethamine and melphalan. Radiation therapy may also have potential side effects that may affect fertility, including total body irradiation, radiation of the abdomen, pelvis, ovaries and uterus. Both the proposed anticancer therapies, as well as the type of cancer, and the overall condition of the individual may cause treatment-related gonadal failure and infertility. ASCO encourages providers to have an individualized "Discussion of fertility preservation with all females of reproductive age (and with parents or guardians of children and adolescents) if infertility is a potential risk of therapy." This discussion is recommended "As early as possible in the treatment process so as to allow for the widest array of options for fertility preservation" (Loren, 2013).

Some individuals may experience infertility not as a result of treatment for oncologic conditions, but due to inherited disorders. Genetic conditions such as mosaicism for Turner syndrome (monosomy X) and fragile X premutation predispose women to ovarian failure. Disorders (or differences) of sex development (DSD) is comprised of a group of congenital conditions associated with variations of anatomical, chromosomal, gonadal, or anatomical sex. These conditions most frequently present in the newborn period with ambiguous genitalia or in adolescence with uncharacteristic pubertal development (ACOG, 2014; Gomes, 2020).

The relationship between DSD and impaired fertility is well established, especially for one of the most common sex chromosome DSDs, Turner syndrome (45, X; monosomy X). Turner syndrome (TS) affects approximately 1:2000 girls and most (95–98%) of individuals with TS are infertile. For the majority of individuals with TS, primary ovarian failure occurs during prepuberty. Infertility results from an accelerated loss of oocytes which begins in fetal life and continues during postnatal life. Spontaneous pregnancy is uncommon, occurring only in approximately 2–5% of individuals with TS (Gomes, 2020).

Women who have the fragile X (FX) premutation gene are at increased risk for FX-associated primary ovarian insufficiency (FXPOI) and are at higher risk for having children who have FXS. FXPOI causes infertility and early menopause among adult women. Women with primary ovarian insufficiency (POI) cease having menstrual cycles and have symptoms of menopause prior to 40 years of age (CDC, 2020). Women with risk factors for POI may be candidates for fertility preservation prior to ovarian failure (ACOG, 2014).

Risk-reducing (prophylactic) salpingo-oophorectomy has been recommended to reduce the risk of ovarian cancer in selected individuals. Hereditary breast and ovarian cancer attributable to pathogenic variants in BRCA1 and BRCA 2 (BRCA1/2) significantly increases susceptibility to breast and ovarian cancer, with an unusually early onset of breast cancer, and an increased incidence of tumors of other organs, such as male breast, prostate, fallopian tubes, and pancreas. The American College of Obstetricians and Gynecologists (ACOG) has indicated that:

> The most effective ovarian cancer risk-reduction strategy for women with known BRCA mutations remains risk-reducing bilateral salpingo-oophorectomy (removal of the ovaries and fallopian tubes in their entirety). Women with BRCA mutations or who carry another actionable deleterious mutation predisposing to ovarian cancer should be offered risk-reducing bilateral salpingo-oophorectomy" (ACOG, 2017).

Similarly, the National Comprehensive Cancer Networks (NCCN) recommends that carriers (women without a personal history of cancer in whom a BRCA1/2 pathogenic variant is identified), undergo risk-reducing salpingo-oophorectomy (RRSO) beginning between 35 and 40 years of age. Because the onset of ovarian cancer tends to be later in carriers of a BRCA2 P/LP variant, the NCCN considers it "reasonable to delay RRSO for management of ovarian cancer risk until between 40 and 45 years of age, unless age at diagnosis in the family warrants earlier age for consideration of this prophylactic surgery". When considering RRSO, the NCCN also recommends that "whenever possible, patients should be referred to a gynecologic oncologist for a discussion about this surgery, and specific protocols have been recommended for pathologic review and follow-up of abnormal findings" (NCCN Genetic Familial High-Risk Assessment Breast, Ovarian and Pancreatic, 2023).

The NCCN also recommends that bilateral salpingo-oophorectomy be considered for carriers of BRIP1, RAD51C, and RAD51D at ages 45–50 years, although individuals in this age range are not candidates for likely successful oocyte or ovarian cryopreservation based on ovarian reserve.

Individuals may also experience partial impairment to permanent loss of fertility as a result of gender-affirming therapy, which includes both hormone therapy and surgical intervention. It is recommended that individuals be counseled on fertility preservation options prior to beginning medical or surgical gender-affirming treatment. Gender-affirming hormonal therapies consist of puberty-suppressing gonadotropin-releasing hormone agonists (GnRH) and the administration of sex hormones (for example; estrogen for individuals desiring feminine secondary sex characteristics and testosterone hormone therapy for individuals desiring male secondary sex characteristics). Gender-affirming surgical procedures may include breast augmentation or mastectomy and gonadectomy. There is currently very limited clinical information and data on fertility preservation for individuals who have received gender affirming treatment. Current treatment options are generally based on protocols from fertility preservation following oncological treatments (Choi, 2022).

Impact of Aging on Female Fertility

Research has shown a direct relationship between a decline in female fecundity and advancing maternal age. In a collaborative Committee Opinion from the American Society for Reproductive Medicine (ASRM) and ACOG, the authors point out that volume of oocytes in the ovaries declines naturally and progressively through the process of atresia. The female fetus at 20 weeks gestation has a maximum complement 6–7 million oocytes. However, the number of oocytes continues to decrease to "approximately 1–2 million oocytes at birth; 300,000–500,000 at puberty; 25,000 at age 37 years; and 1,000 at age 51 years, the average age of menopause in the United States" (ACOG, 2014).

Live-birth delivery rates inversely correlate with maternal age. As the number of oocytes decreases over time, the quality of oocytes also decreases. Older women are less likely to produce live births. Declining fertility in aging women is also accompanied by significant escalations in the rates of spontaneous abortion, miscarriage, and stillbirths. The occurrence of aneuploidy also increases, with autosomal trisomy being the most frequent finding (ACOG, 2014).

As age increases, there is also an increase in the risk of other disorders that may adversely affect fertility. As mentioned above, women with a history of prior radiation therapy, chemotherapy, ovarian surgery, or a strong family history of early menopause may be at an increased risk of having a premature reduction in the size of their follicular pool and decline in fertility (ACOG, 2014).

Researchers have also attempted to determine the maximum age that is reasonable for an individual to undergo cryopreservation of oocytes. Based on a study that assessed the success of in vitro fertilization (IVF) in female subjects greater than 44 years old, the maximum age for attempting oocyte cryopreservation (OC) may be as high as 45 years. In the study results reported by Spandorfer and colleagues (2007), IVF yielded live births in individuals up to 45 years of age, but success was limited to those participants producing more than 5 oocytes in response to ovarian stimulation. Although pregnancy rates for participants 46 and 47 years of age were 17% and 9%, respectively, none of these pregnancies yielded a live birth. The authors concluded it may be reasonable to consider oocyte cryopreservation as a means for fertility preservation in individuals up to 45 years of age, provided the individual is

thoroughly counseled about the low probability of success. The ASRM recommended the women anticipating cryopreservation of oocytes be advised that “live birth rates per embryo transfer are improved when OC is performed in younger as compared to older women” and that “there are insufficient data to advise women on the optimal age to undergo planned OC” (ASRM, 2021).

The recommendation to offer risk-reducing oophorectomy prior to menopause effectively limits the fertility window of the affected woman (ACOG, 2017). Cryopreservation to preserve fertility may be an acceptable option for females who may become infertile as a result of planned gonadotoxic treatments or medical conditions, including diminished ovarian reserve; family history of premature POI; and for carriers of inherited cancer syndromes who elect to undergo cryopreservation of oocytes to reduce cancer risk. However, there are many factors such as age, cancer type, timing, and the type of treatment regimen, etc., to consider.

Cryopreservation of Oocytes

Cryopreservation of oocytes is less commonly performed in the setting of malignancy due to the time constraints inherent in ovarian stimulation. The mature oocyte is very fragile due to its large size, high water content and chromosomal arrangement. For example, the mature oocyte is arrested in meiosis, and may be easily damaged both in freezing and thawing. Due to these factors, survival of cryopreserved oocytes after thawing may be impacted. Vitrification is an improved technique to freeze the oocytes and reduce the negative effects of cryopreservation.

The NCCN reports that evidence suggests “that IVF with cryopreserved oocytes results in fertilization and pregnancy rates similar to that of fresh oocytes. Like embryo cryopreservation, pregnancy rates with mature oocyte cryopreservation also decline with advancing age” (NCCN AYA, 2023).

In 2013, the Practice Committees for both American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology (SART) updated the guideline for cryopreservation of mature oocytes. The guideline concluded that over the past decade, “Oocyte cryopreservation has improved dramatically, and preliminary data for safety are reassuring. Therefore, this technique should no longer be considered experimental.” ASRM and SART noted individuals receiving gonadotoxic therapies for cancer are at high risk for infertility, therefore, the option of oocyte cryopreservation with appropriate counseling is recommended (ASRM, 2013).

The ASCO guideline (Loren, 2013) addressing fertility preservation for those with cancer was updated after a systematic review of published literature from 2006 through January 2013. The guideline was modified after a review of the evidence and included the following recommendations:

> Present both embryo and oocyte cryopreservation as established fertility preservation methods.
>
> Discuss the option of ovarian transposition (oophoropexy) when pelvic radiation therapy is performed as cancer treatment.
>
> Inform patients of conservative gynecologic surgery and radiation therapy options.
>
> Cryopreservation of unfertilized oocytes: Cryopreservation of unfertilized oocytes is an option, particularly for patients who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing.
>
> Oocyte cryopreservation should be performed in centers with the necessary expertise. As of October 2012, the American Society for Reproductive Medicine no longer deems this procedure experimental. More flexible ovarian stimulation protocols for oocyte collection are now available. Timing of this procedure no longer depends on the menstrual cycle in most cases, and stimulation can be initiated with less delay compared with old protocols. Thus, oocyte harvesting for the purpose of oocyte or embryo cryopreservation is now possible on a cycle day–independent schedule.

The American College of Obstetricians and Gynecologists (ACOG) Committee on Gynecologic Practice published an opinion on oocyte cryopreservation in 2014. The committee endorsed the ASRM and SART guideline for cryopreservation of mature oocytes. The ACOG committee also noted there is “not yet sufficient data to recommend oocyte cryopreservation for the sole purpose of circumventing reproductive aging in healthy women.” ACOG most recently reaffirmed this document in 2020.

Similarly, the ASCO guidelines on Fertility Preservation in Patients with Cancer (Oktay, 2018) state that:

> Cryopreservation of unfertilized oocytes is an option and may be especially well suited to women who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing. Oocyte cryopreservation should be performed in centers with the necessary expertise. As of October 2012, the American Society for Reproductive Medicine no longer deems this procedure experimental.

The Practice Committee for ASRM (2019) published a committee opinion on fertility preservation for individuals undergoing gonadotoxic therapy or gonadectomy which includes embryo and oocyte cryopreservation as “established modalities for fertility preservation” (Ethics Committee ASRM, 2019).

The European Society of Medical Oncology (ESMO) has concluded that oocyte cryopreservation may be appropriate for women less than or equal to 40 years of age who will be exposed to gonadotoxic anticancer therapies and who would like to preserve their fertility. ESMO has cautioned that oocyte cryopreservation is not indicated in women with serious coagulation defects or high risk of infections (Lambertini, 2020).

The NCCN Clinical Practice Guidelines for Adolescent and Young Adult Oncology (2023) include oophoropexy for females receiving radiation therapy. For individuals where treatment can be delayed long enough for a cycle of oocyte stimulation, then oocyte or embryo cryopreservation via immediate (or random start) controlled ovarian stimulation should be discussed.

In their recommendations on Fertility Preservation for Female Patients with Childhood, Adolescent and Young Adult Cancer, the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group includes oocyte cryopreservation as a fertility preservation option for females who have undergone bilateral oophorectomy (Mulder, 2021).

Cryopreservation of Oocytes in Transgender and Nonbinary Individuals

It has been estimated that approximately 150,000 youth (ages 13-17) and 1.4 million adults (ages 18 years and older) residing in the United States identify as transgender. While more data on the needs and experiences of the transgender community is now available, important gaps in the literature exist and additional research is needed (ACOG, 2021).

The effects of gender-affirming therapy on fertility is not yet completely understood. ACOG, ASRM and World Professional Association for Transgender Health (WPATH) support the preservation of fertility in individuals who identify as transgender.

According to ACOG:

> Fertility and parenting desires should be discussed early in the process of transition, before the initiation of hormone therapy or gender affirmation surgery. Fertility preservation options for transgender individuals are the same as for those cisgender individuals who desire preservation before gonadotoxic cancer therapy or for elective preservation. These options include sperm banking, oocyte preservation, embryo preservation, and in some cases, ovarian or testicular tissue cryopreservation (ACOG, 2021).

According to the Ethics Committee of the ASRM, fertility preservation options in transgender individuals include sperm, oocyte, embryo, and ovarian tissue (Ethics Committee ASRM, 2021a).

Cryopreservation of Ovarian Tissue

Cryopreservation of ovarian tissue with subsequent autologous or heterotopic transplantation has been researched as a technique to sustain the reproductive function of females who are faced with infertility resulting from procedures such as chemotherapy, radiation therapy or a surgical procedure to treat a malignant condition. . Ovarian tissue cryopreservation is a laparoscopic procedure that involves removing the ovarian cortical tissue prior to ovarian failure, dissecting the tissue into small fragments, and freezing it. No pretreatment is required so the process can be carried out in a short timeframe and chemotherapy can be initiated as soon as the following day, if required. In addition to increasing the possibility of pregnancy, ovarian tissue preservation has the added benefit of hormone production. Ovaries that have sustained damage as a result of gonadotoxic procedures such as radiation or chemotherapy frequently cannot produce hormones such as estrogen or progesterone, requiring the affected individual to take hormone therapy. Previously cryopreserved, healthy ovarian tissue can be reimplanted after treatment to restore natural hormone production (Donnez, 2010; Imbert, 2014; Kim, 2001; Lambertini, 2020; Practice Committee of ASRM, 2019).

As with oocyte cryopreservation, the principal factor affecting success rate is age. ESMO and the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group reported on the live birth rate following ovarian tissue cryopreservation and subsequent transplantation. According to ESMO:

> Either orthotopic or heterotopic, is currently the only method available in clinical practice to restore ovarian function and fertility using cryopreserved ovarian tissue. More than 300 women worldwide have undergone the procedure and ovarian function restoration was achieved in 95% of cases within 4-9 months. To date, more than 180 babies have been born using this procedure. Approximately 85% of the women receiving ovarian transplants were cancer survivors. The live birth rate per patient was 40%, half of which were from natural conceptions, thus avoiding the need for further medical intervention. As with oocyte and embryo cryopreservation, the main factor affecting success rate is age: women of younger age at ovarian tissue cryopreservation have better fertility outcomes after ovarian tissue transplantation than older women, with only a few pregnancies achieved in women over 36 years of age (Lambertini, 2020).

The PanCareLIFE Consortium in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group published a clinical practice guideline addressing fertility preservation in female patients who were diagnosed with childhood, adolescent, and young adult (CAYA) cancer. In this guideline the authors reported on the rate of successful pregnancies and live births following cryopreservation, thawing, and implantation of ovarian tissue.

> We identified seven studies that reported ovarian tissue cryopreservation in patients who were diagnosed with a malignant cancer at age 25 years or younger. Although livebirths have been reported after ovarian tissue cryopreservation (with an approximate success rate of 45%), it is unclear whether these successes were all from patients who were diagnosed with cancer at age 25 years or younger because age of patients who had livebirths was not reported. At least nine women who were diagnosed with cancer at a young age (ie, ≤25 years) successfully gave birth to 14 healthy babies after transplantation of cryopreserved tissue. Systematic reviews, including patients with CAYA and adult cancer and patients without cancer, reported 86 livebirths after ovarian tissue cryopreservation, with a corresponding pregnancy rate of 23–37%. As of 2017, an estimated 130 livebirths have been achieved. We identified no cohort studies reporting livebirths after prepuberty ovarian tissue cryopreservation and reimplantation (Mulder, 2021).

Several medical societies have published guidelines or recommendations addressing cryopreservation of ovarian tissue.

The 2018 ASCO guidelines on Fertility Preservation in Patients with Cancer (Oktay, 2018) provide the following information on ovarian tissue cryopreservation and transplantation:

> Ovarian tissue cryopreservation for the purpose of future transplantation does not require ovarian stimulation and can be performed immediately. In addition, it does not require sexual maturity and, hence, may be the only method available in children. Finally, this method may also restore global ovarian function. However, it should be noted that further investigation is needed to confirm whether it is safe in patients with leukemias.

These guidelines also go on to provide the following qualifying statement:

> As of the time of this publication, ovarian tissue cryopreservation remains experimental. However, emerging data may prompt reconsideration of this designation in the future (this technique is already considered nonexperimental in some countries, and its experimental status is undergoing evaluation in the United States) (Oktay, 2018).

The ASRM's 2019 updated Practice Committee Opinion on Fertility Preservation and Reproduction in Patients Undergoing Gonadotoxic Therapy or Gonadectomy removed the experimental designation it had assigned to ovarian tissue cryopreservation. According to the updated document:

> Ovarian tissue banking is an acceptable fertility-preservation technique and is no longer considered experimental. Ovarian tissue banking is the only method to preserve fertility for prepubertal girls since ovarian stimulation and IVF are not options. Cryopreservation of ovarian cortical tissue theoretically represents an efficient way of preserving thousands of ovarian follicles at one time. This technique has been proposed principally for prepubertal females and for those who cannot delay cancer treatment in order to undergo ovarian stimulation and oocyte retrieval (Practice Committee of ASRM, 2019).

ESMO provides the following recommendations for ovarian tissue cryopreservation.

> Ovarian tissue cryopreservation is appropriate when the time available before starting anticancer treatments is too short for ovarian stimulation and oocyte or embryo cryopreservation. Although there is no clear consensus on the maximum age for ovarian tissue cryopreservation, it is usually recommended to offer this procedure only to women 36 years of age. Ovarian tissue cryopreservation can also be carried out after an initial, low-intensity gonadotoxic treatment regimen in order to reduce the risk of neoplastic cells being present in the ovary (i.e. in leukaemia

> patients) or when the patient's initial health condition contraindicates an immediate procedure. Although the procedure has recently been carried out with success in a patient affected by acute myeloid leukaemia, the risk of tissue contamination remains a major concern in such patients and there is a need for very careful evaluation in each individual case. While normal oocytes can develop from cryopreserved ovarian tissue after ChT administration, there are no robust data regarding the impact of different regimens and time interval between last treatment dose and ovarian tissue cryopreservation on the subsequent reproductive outcomes (Lambertini, 2020).

The PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group states:

> Female patients with CAYA cancer who will be treated with alkylating agents, ovarian radiotherapy, HSCT, cranial radiotherapy, unilateral oophorectomy, or a combination of these treatments, are at potential risk for infertility and should be counselled about options for fertility preservation. Recommendations for specific methods for fertility preservation vary by treatment exposure. Patients who will be treated with bilateral oophorectomy will, by definition, become infertile and are therefore qualified for any of the options for fertility preservation…
>
> Because the research surrounding the use of ovarian tissue cryopreservation is evolving and the lag time between collection of ovarian tissue and its use for fertility is so long, particularly in prepubertal patients, the panel made a clear distinction between collection and transplantation of ovarian tissue. The panel agreed that the technical risks for the resection of ovarian tissue are small and are risks that are associated with any laparoscopic technique (ie, infection, bleeding, perforation of bowel, bladder, or blood vessel) and undergoing anaesthesia. However, these risks were balanced against the fact that the procedure can be done concurrently with other surgical procedures and that ovarian tissue cryopreservation is the only method for fertility preservation that is available for prepubertal and peripubertal girls and postpubertal women who are unable to undergo oocyte cryopreservation.
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> Fertility preservation for prepubertal girls is ethically complex because there is a scarcity of evidence about the efficacy of ovarian tissue cryopreservation for this age group. The panel agreed that collection of ovarian tissue is ethically justifiable in most circumstances and does not require additional governance. The panel concurred that the benefits of harvesting ovarian tissue probably outweigh the potential harms in this population, who are at high risk of infertility, due to the possible future desire of the patient to have biological offspring. Therefore, we moderately recommend offering ovarian tissue harvesting for cryopreservation and storage to prepubertal and postpubertal patients as standard care (very low-quality evidence and evidence cited in existing guidelines). Depending on the age of the patient and their disease ensuring that patients and their families understand the limitations that are associated with future use of the tissue that is preserved is important.
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> Because there is a potential risk of premature ovarian insufficiency when removing ovarian tissue, the panel agreed that the potential harms outweigh the benefits for patients who will be treated with low-dose alkylating agents or cranial radiotherapy. Therefore, we do not recommend offering ovarian tissue cryopreservation to these patients (very low-quality evidence and evidence cited in existing guidelines (Mulder, 2021).

The NCCN Clinical Practice Guidelines for Adolescent and Young Adult Oncology (2023) provide the following guidance with regards to cryopreservation of ovarian tissue:

> Cryopreservation of ovarian cortical tissue is a promising strategy for female fertility preservation when there is insufficient time for oocyte or embryo cryopreservation and/or the patient is prepubertal. This technique does not require hormonal stimulation, so there is no long delay in initiation of treatment. This procedure would not be appropriate for certain women with cancer if potential exists for reintroduction of malignant cells with grafting. It is also not recommended for carriers of BRCA mutations due to the increased risk of ovarian cancer… While ovarian tissue cryopreservation is still considered investigational at some institutions, it may be discussed as an option for fertility preservation, if available.

Cryopreservation of Ovarian Tissue in Transgender and Nonbinary Individuals

It is recommended that prior to transition, all transgender individuals should be counseled regarding fertility preservation and reproductive options, as well as on the effects of transition on their fertility. Similar to the options available to men and women undergoing gonadotoxic cancer therapies, fertility preservation options for transgender men include oocyte cryopreservation, embryo cryopreservation, and ovarian tissue cryopreservation with in vitro maturation (IVM) (Choi, 2022).

Gender-affirming therapy impacts fertility and, depending on the treatment modality chosen, may cause a partial, temporary, or permanent loss of fertility. Oophorectomy and hysterectomy result in irreversible infertility, but the long-term effect of testosterone therapy on the ovaries and future fertility is unclear. Gender-affirming therapy may include both hormone therapy and surgical intervention (removal of gonads). Transgender individuals should be counseled on their fertility preservation options prior to proceeding with medical and surgical gender transition. There is relatively limited clinical information and data regarding fertility preservation for transgender individuals. Current treatment regimens are based on recommendations for fertility preservation following oncological treatments (Choi, 2022).

In 2019, the ASRM announced that ovarian tissue cryopreservation with IVM is no longer considered experimental (Practice Committee of ASRM, 2019). Ovarian tissue cryopreservation may be performed during gender-affirming surgery and does not require hormonal stimulation which may help avoid gender dysphoria. In transmen with a male partner, ovarian tissue may serve as a potential source for IVM with mature oocytes fertilized by partner sperm along with a gestational carrier. For transmen with a female partner, IVM can be carried out using mature oocytes fertilized with donor sperm and with the embryo being transferred to the partner's uterus (Choi, 2022).

With regard to fertility preservation (FP) in the transgender population, WPATH offers the following recommendations and cautions:

> We recommend health care professionals counsel pre- or early-pubertal transgender and gender diverse youth seeking gender-affirming therapy and their families that currently evidence-based/established fertility preservation options are limited.
>
> For prepubertal and early-pubertal children, FP options are limited to the storage of gonadal tissue. Although this option is available for TGD children in the same way that it is available for cisgender prepubertal and early-pubertal oncological patients, there is no literature describing the utilization of this approach in the transgender population …. Although the recent American Society for Reproductive Medicine guideline has lifted the experimental label from ovarian tissue cryopreservation (Practice Committee of the American Society for Reproductive Medicine, 2019), there are very few case reports describing a successful pregnancy in a woman following the transplantation of ovarian tissue cryopreserved before puberty.
>
> Currently, the only future clinical application for storing ovarian tissue is autotransplantation, which might be

undesirable in a transgender man (due to the potentially undesirable effects of estrogen). A laboratory procedure that would make it possible to mature oocytes in vitro starting with ovarian tissue would be the ideal future application of stored ovarian tissue for transgender people, but this technique is currently only being investigated and optimized in basic science research settings (Coleman, 2022).

As mentioned above, although the effects of gender-affirming therapy on fertility is not yet completely understood, several medical societies include cryopreservation of ovarian tissue as a possible method of fertility preservation in individuals who seek fertility preservation (ACOG, 2021; Ethics Committee ASRM, 2021a; and Coleman, 2022).

Summary

Several professional medical societies (ACOG, ASCO, ASRM, ESMO, NCCN, PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group), and WPATH consider the use of cryopreserved mature oocytes an effective method for preserving fertility in select individuals facing anticipated infertility as a result of treatment of a disease with gonadotoxic therapies or bilateral oophorectomy.

While the data on the efficacy, safety, and reproductive outcomes after ovarian tissue cryopreservation are still limited, the reported cases of safe and successful fertility restoration and live births following cryopreservation of ovarian tissue continue to grow. Currently, ovarian tissue cryopreservation is the only method of fertility preservation that is available for prepubertal and peripubertal girls and postpubertal women who are unable to undergo oocyte cryopreservation. Given the current body of literature, ovarian tissue cryopreservation should be considered an established fertility preserving procedure that is appropriate for individuals who are unable to undergo oocyte cryopreservation (that is, prepubertal girls and individuals who require immediate gonadotoxic treatment).

Cryopreservation of oocytes and ovarian tissue may be considered medically necessary when certain criteria are met in accordance with generally accepted standards of medical practice and when cryopreservation is being done to preserve fertility in an individual undergoing non-elective sterilization (treatment of an illness, injury or disease which will potentially leave them infertile). However, anticipated infertility as a result of elective sterilization services (for example, salpingectomy and tubal occlusion procedures), when they are performed as a contraceptive method of choice, or to circumvent normal reproductive aging is not considered treatment of an illness, injury or disease or its symptoms.

Definitions

Atresia: The deterioration of ovarian follicles which do not ovulate during the menstrual cycle.

Cisgender: A term used to describe an individual whose gender identity matches the sex assigned to them at birth.

Cryopreservation: The process of preserving and storing living systems in a viable condition at low temperatures for future use.

Disorders (or differences) of sex development (DSD): A group of various congenital conditions associated with variations of anatomical, chromosomal, or gonadal, or anatomical sex. This diverse group of conditions most frequently present in the newborn period with ambiguous genitalia or in adolescence with uncharacteristic pubertal development.

Fecundity: The ability to produce offspring; fertility.

Gender dysphoria: A sense of unease caused by the feeling that one's biological sex does not match one's gender identity.

Gender identity: Our sense of how we see and describe ourselves (for example: male or female).

Gonad: A reproductive cell-producing gland, such as an ovary.

Gonadotoxic: Having a deleterious effect on the gonads, such as chemotherapy or radiation therapy.

Infertility: A condition that is clinically defined in women and men who cannot achieve a successful pregnancy following 12 or more months of appropriate, timed unprotected intercourse or 6 cycles of therapeutic donor insemination. The diagnosis of female or male infertility requires evaluation of the couple versus a single individual.

Institutional review board (IRB): An institutional review board is a group that has been formally designated to approve, monitor and review biomedical and behavioral research involving humans with the aim to protect the rights and welfare of the subjects. The Food and Drug Administration and the Office of Protection from Research Risks (part of the National Institutes of Health) set the guidelines and regulations governing human subject research and IRBs.

Nonbinary: A term used by some individuals whose gender identity is neither man/boy nor woman/girl.

Oocyte: The egg cell produced in the ovaries; also called the ovum or gamete.

Oophoropexy (ovarian transposition): A surgical procedure that involves moving the ovaries to another place in the body, away from where radiation therapy will be directed.

Ovarian: Having to do with the ovaries, the female reproductive glands in which the ova (eggs) are formed. The ovaries are located in the pelvis, one on each side of the uterus.

Ovarian failure: A condition in which the ovaries stop functioning and results in symptoms of menopause.

Ovarian tissue banking: The process of freezing ovarian tissue to preserve fertility. A portion or all of an ovary is removed, and the tissue that contains the eggs is sliced into thin sections and frozen. The tissue may later be thawed and placed back into the woman's body, typically on the remaining ovary.

Primary gonadal failure: A term that encompasses testicular insufficiency in 46,XY males (including, but not limited to Klinefelter syndrome) and ovarian insufficiency in 46,XX females (including, but not limited to Turner syndrome); also refers to DSD which result in gender assignment that disagrees with the genotype and gonadal type.

Salpingo-oophorectomy: Surgical removal of the fallopian tubes and ovaries.

Transgender: Adjective to describe a diverse group of individuals who cross or transcend culturally defined categories of gender. The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth (Coleman, 2022).

Vitrification: Ultra-rapid freezing process resulting in a glass-like solid that is free of any crystal formation.

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Revised	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. MN criteria for cryopreservation of mature oocytes revised to include: (1) medical and surgical treatment, gonadotoxic therapy and bilateral oophorectomy as possible causes of anticipated infertility; (2) Criterion which states “individual is a candidate based on ovarian reserve and likelihood for successful oocyte cryopreservation (for example, age 45 years or less)”. Revised criteria so cryopreservation of ovarian tissue is considered MN when criteria are met. Updated Discussion/General Information, Definitions, Coding, References, Websites for Additional Information, Index and History sections.
Reviewed	08/11/2022	MPTAC review. Updated review date, Description, Discussion/General Information, Definitions References, Websites for Additional Information and History sections.
Reviewed	08/12/2021	MPTAC review. Updated review date, Websites for Additional Information and History sections.
	12/16/2020	Updated Coding section with 01/01/2021 CPT changes; 0058T deleted 12/31/2020.
Reviewed	08/13/2020	MPTAC review. Updated review date, Discussion/General Information, References, Websites for Additional Information and History sections. Reformatted Coding section.
	12/31/2019	Updated Coding section with 01/01/2020 CPT changes; added 89398 replacing 0357T deleted 12/31/2019.
Reviewed	08/22/2019	MPTAC review. Updated review date, Discussion/General Information, References, Websites for Additional Information and History sections.

Reviewed	09/13/2018	MPTAC review. Updated review date, Rationale, References, Websites for Additional Information and History sections.
New	11/02/2017	MPTAC review. Initial document development.
New	11/01/2017	Hematology/Oncology Subcommittee review. Initial document development. Moved content of MED.00080 to new clinical utilization management guideline document with the same title.
