Clinical UM Guideline

Subject:	Cryopreservation of Oocytes or Ovarian Tissue		
Guideline #:	CG-MED-66	**Publish Date:**	10/05/2022
Status:	Reviewed	**Last Review Date:**	08/11/2022

Description

This document addresses oocyte and ovarian tissue cryopreservation which are alternative techniques to embryo cryopreservation for individuals who are at risk of infertility due to 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:

Cryopreservation of mature oocytes is considered **medically necessary** in post-pubertal individuals facing anticipated infertility resulting from chemotherapy or radiation therapy.

Not Medically Necessary:

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

Cryopreservation of ovarian tissue is considered **not medically necessary** as treatment for anticipated infertility.

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.

Mature oocytes
When services may be Medically Necessary when criteria are met:

CPT	
89337	Cryopreservation, mature oocyte(s)
89346	Storage (per year); oocyte(s)

89356	Thawing of cryopreserved; oocytes, each aliquot

ICD-10 Diagnosis

All diagnoses

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

Immature oocytes, ovarian tissue
When services are Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure designated in the Clinical Indications section as not medically necessary.

CPT

89344	Storage, (per year); reproductive tissue, testicular/ovarian [when specified as ovarian tissue]
89354	Thawing of cryopreserved; reproductive tissue, testicular/ovarian [when specified as ovarian tissue]
89398	Unlisted reproductive medicine laboratory procedure [when specified as cryopreservation of immature oocyte(s) or ovarian tissue]

ICD-10 Diagnosis

All diagnoses

Discussion/General Information

Therapies to treat medical conditions, such as cancer, may compromise fertility for females. 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. 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).

Options to preserve fertility for females who may become infertile as a result of planned gonadotoxic treatments include cryopreservation of oocyte and ovarian tissue. 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.

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 National Comprehensive Cancer Network® (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 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 surgery that are frequently utilized to treat malignant diseases. A variety of articles have focused on the technical feasibility of these options, and there are retrospective case reports of successful pregnancies using this technique. However, in general, the technique is not standardized, and there is ongoing investigation of the following unresolved issues (Donnez, 2010; Imbert, 2014; Kim, 2001):

- Optimization and standardization of a freeze-thaw method;
- Metabolic injury;
- Ischemia-reperfusion injury (that is, after autotransplant);
- The optimal graft site;
- The quality of oocytes matured in a graft;
- The efficacy of frozen-thaw grafts for fertility restoration and hormonal function;

- Safety issues, particularly regarding the risk of reseeding residual cancer cells within a graft.

The ASRM Practice Committee updated a 2008 committee opinion on ovarian tissue cryopreservation. Based on the established criteria of ASRM, "Ovarian tissue cryopreservation and transplantation is experimental." The committee also noted:

> Ovarian tissue cryopreservation is an option for patients who require immediate gonadotoxic treatment and is the only option available for prepubertal girls...Ovarian tissue cryopreservation and subsequent transplant may be offered to carefully selected patients as an experimental protocol.

In addition, the Practice Committee for ASRM (2013) published a committee opinion on fertility preservation for individuals undergoing gonadotoxic therapy or gonadectomy, noting ovarian tissue cryopreservation "should be viewed as investigational."

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).
The NCCN Clinical Practice Guidelines for Adolescent and Young Adult Oncology (2020) provide the following guidance with regards to cryopreservation of ovarian tissue:

> Ovarian tissue cryopreservation is a promising, but less well-studied 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. While evidence supporting the effectiveness and safety of ovarian tissue cryopreservation is scarce, a few systematic review have supported its use for fertility preservation in patients with cancer. This procedure would not be appropriate for some women with cancer when there is a potential for reintroduction of malignant cells that could occur with grafting. While ovarian tissue cryopreservation is still considered investigational at some institutions, it may be discussed as an option for fertility preservation, if available.

There are recruiting and ongoing clinical trials studying ovarian tissue cryopreservation as well as cryopreservation and use of immature oocytes. However, to date, results from these studies have not been published. Although there have been case reports of successful live births after cryopreservation, thawing, and implantation of ovarian tissue, there are still many unanswered questions about this technology. Data from prospective, randomized, long-term studies are needed to determine the safety and efficacy of ovarian tissue cryopreservation as a method to preserve fertility.

Definitions

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

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.

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.

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

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Websites for Additional Information

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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
Reviewed	08/11/2022	Medical Policy & Technology Assessment Committee (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.