Cryopreservation of reproductive tissue, gametes, and embryos

Clinical Policy ID: CCP.1173

Recent review date: 8/2024

Next review date: 12/2025

Policy contains: Cryopreservation; embryo; gonad; gonadotoxin; onco-infertility; oocyte; sperm.

AmeriHealth Caritas Next has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Next's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of medically necessary, and the specific facts of the particular situation are considered, on a case by case basis, by AmeriHealth Caritas Next when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Next's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Next's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Next will update its clinical policies as necessary. AmeriHealth Caritas Next's clinical policies are not guarantees of payment.

Coverage policy

Once-per-lifetime cryopreservation of gametes and embryos to preserve fertility in post-pubertal men or women facing infertility due to chemotherapy or other gonadotoxic therapies is clinically proven and, therefore, may be medically necessary (American Society for Reproductive Medicine, 2019; Oktay, 2018; National Comprehensive Cancer Network, 2023; National Institute for Health and Care Excellence, 2013).

Cryopreservation of ovarian and testicular reproductive tissue is investigational/not clinically proven, as the effectiveness of these procedures has not been established (American Society for Reproductive Medicine, 2019; Corkum, 2019; Oktay, 2018).

Limitations

Cryopreservation of gametes and embryos for purposes of circumventing the reproductive aging process is investigational and, therefore, not medically necessary.

All other uses of cryopreservation of gametes and embryos are investigational and, therefore, not medically necessary.

Infertility services are always subject to legislative mandate. Some states mandate benefit coverage for certain infertility services, including cryopreservation. Where legislative mandates exist, they supersede benefit plan design.

Alternative covered services

- Reproductive endocrinology to maximize the reproductive potential of cancer patients and survivors.
- Ovarian transposition in cases where pelvic radiation is required, to minimize the damaging effects of ionizing radiation on the ovaries.
- Gonadotropin agonist injections to chemically regulate the ovaries or testes, but not to be used in place of proven fertility preservation methods (American Society for Reproductive Medicine, 2019; Oktay, 2018).
- Conservative surgical approaches or initial medical therapy for reproductive malignancies.

Background

Therapies to treat medical conditions such as cancer may compromise fertility. Chemotherapy and radiation therapy have well-recognized gonadotoxic effects. Gonadotoxicity is particularly age-dependent in females, because the number of primordial follicles making up the female ovarian reserve is nonrenewable and diminishes steadily over the years until menopause onset, whereas spermatogenesis may still continue over several years if a population of spermatogonian stem cells remain after cancer treatment (Rodriguez-Wallberg, 2014).

Radiation therapy may have potential side effects that affect fertility issues (Rodriguez-Wallberg, 2014). In females, reproductive organs may suffer damage by direct irradiation or scattered radiation even after shielding. In males, the spermatogonia are extremely sensitive to radiation regardless of age. Radical surgical procedures for cancer of the lower abdominal organs may have adverse effects on reproductive capacity and fertility. Long-term treatment of estrogen-receptor positive breast cancer also has side effects that influence fertility decisions.

Options to preserve fertility include cryopreservation of sperm, oocytes, and embryos (Rodriguez-Wallberg, 2014). Cryopreservation is the process of cooling and storing cells, tissues, or organs at very low or freezing temperatures to save them for future use. It is used to preserve sperm, semen, oocytes (eggs), embryos, ovarian tissue, or testicular tissue as an option for patients who wish to or must delay reproduction for various reasons, including the need to undergo therapies that threaten their reproductive health, such as cancer treatment.

Two cryopreservation methods are routinely used that minimize or prevent ice formation. Slow freezing occurs at a sufficiently slow rate to permit adequate cellular dehydration, while minimizing intracellular ice formation. Vitrification allows the solidification of the cell(s) and of the extracellular milieu into a glass-like state without ice formation.

Findings

The National Comprehensive Cancer Network Clinical Practice Guidelines for Adolescent and Young Adult Oncology (2014) include oophoropexy for females receiving radiation therapy. For individuals where treatment can be delayed long enough for a cycle of oocyte stimulation, then embryo cryopreservation should be discussed.

The Practice Committees of the American Society for Reproductive Medicine (2013) published a committee opinion on fertility preservation for individuals undergoing gonadotoxic therapy or gonadectomy, which includes embryo cryopreservation as an "established modality for fertility preservation."

The American Society of Clinical Oncology (Loren, 2013) conducted a systematic review of the evidence on fertility preservation for adults and children with cancer as part of a guideline. Sperm, embryo, and oocyte cryopreservation are considered standard practice. A 2018 update to the Society’s guidelines made no major changes (Rosenberg, 2018).

The American Cancer Society (2020) considers sperm banking an effective way for men who have gone through puberty to store sperm for future use. In general, sperm collected before cancer treatment is just as likely to start a pregnancy as sperm from men without cancer. Sperm banking has resulted in thousands of pregnancies, without unusual rates of birth defects or health problems in the children. Once sperm is stored, it remains viable for many years.

The National Institute for Health and Care Excellence (2013) addresses cryopreservation issues in adults and adolescents:

- When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos, or oocytes.
- Offer sperm cryopreservation to men and adolescent boys who are preparing for medical cancer treatment likely to make them infertile.
- Offer oocyte or embryo cryopreservation, as appropriate, to women of reproductive age (including adolescent girls) preparing for medical cancer treatment likely to make them infertile if:
- They are well enough to undergo ovarian stimulation and egg collection.
- The process will not worsen their condition.
- Enough time is available before the start of their cancer treatment.

The American Urological Association noted that gonadal dysfunction, including infertility, is a significant long-term consequence of cancer therapy. The organization issued guidelines that recommended that clinicians discuss these risks with patients prior to starting treatment and strongly encourage sperm banking, which involves collecting, freezing and storing sperm before beginning gonadotoxic therapies. Banked sperm can also be used for intrauterine insemination (American Urological Association, 2020).
Systematic Reviews and Meta-Analyses:

Fertility preservation methods have shown varying success rates for cancer patients. A Cochrane review (Wong, 2017) comparing freeze-all strategies with conventional strategies found no clear difference in cumulative live birth rates (odds ratio 1.09, 95% CI 0.91 to 1.31). A meta-analysis of 38 studies reported clinical pregnancy rates of 34.9%, 49.0%, and 43.8%, and live birth rates of 25.8%, 35.3%, and 32.3% for oocyte, embryo, and ovarian tissue cryopreservation, respectively (Dhonnabhain, 2022). Another meta-analysis of 26 studies (n = 7,061) found that only 8% of women who underwent fertility preservation before cancer treatment returned to use their frozen material, with an overall live birth rate of 0.046 (Xu, 2023). A seperate analysis reported live birth rates of 41% with cryopreserved embryos, 32% with vitrified oocytes, and 21% after ovarian tissue transplantation in female cancer survivors (Fraison, 2023).

Comparing cryopreservation methods, systematic reviews by Li (2019) and Rienzi (2017) found low-to-moderate quality evidence supporting the superiority of vitrification/warming over conventional freezing/thawing for sperm, oocyte, and embryo preservation. A meta-analysis of 15 studies (n=4,643) showed that women with breast cancer who underwent controlled ovarian stimulation had a 42% reduced risk of recurrence and 46% reduced mortality compared to those who did not receive fertility preservation (Arecco, 2022).

However, caution is advised for re-cryopreservation, as a meta-analysis (n = 4,525) found it resulted in lower live birth rates (P = 0.007) and miscarriage rates (P=0.003) compared to single cryopreservation (Wang, 2023). Additionally, a meta-analysis of 42 studies (n=6,094) revealed that women with cancer had a 78% lower return of embryo transfer and a 49% lower chance of clinical pregnancy compared to women without cancer (Meernick, 2023).

A systematic review/meta-analysis of 19 studies identified a significantly higher proportion of intact stromal cells in vitrified tissue compared with slow-frozen tissue (Behl, 2023).

Other Evidence:

A narrative review (Dillon, 2012) highlighted the growing importance of fertility preservation in childhood cancer survivors, noting the lack of options for pre-pubertal patients. Ovarian tissue cryopreservation has emerged as a potential option for this group, as summarized by the American Pediatric Surgical Cancer Committee (Corkum, 2019) in a review of 23 observational studies involving 1,019 participants aged 0.4 to 20.4 years, with 298 under 13 years old.

A literature review of 30 studies concluded that there is insufficient evidence to predict live birth rates after planned oocyte cryopreservation or to assess if live birth rates are similar after vitrified versus fresh donor oocytes (American Society of Reproductive Medicine, 2021). Additionally, a systematic review of whole ovary cryopreservation and transplantation (Hossay, 2020) found results consistent with previous findings.

In 2024, we rewrote and condensed the findings section and added a 2020 guideline from The American Urological Association. No policy changes are warranted no additional studies were added.

References

On July 11, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "cryopreservation" (MeSH), “spermatazoa” (MeSH), “oocytes” (MeSH), and “fertility preservation.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

American Cancer Society. Preserving fertility in males with cancer. https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fertility-and-sexual-side-effects/fertility-and-men-with-cancer/preserving-fertility-in-men.html. Last revised February 6, 2020.

American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: A Committee opinion. *Fertil Steril.* 2019;112(6):1022-1033. Doi: 10.1016/j.fertnstert.2019.09.013.

American Society for Reproductive Medicine, Practice Committees of, Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: A guideline. *Fertil Steril.* 2013;99(1):37-43. Doi: 10.1016/j.fertnstert.2012.09.028.

American Society for Reproductive Medicine. Evidence-based outcomes after oocyte cryopreservation for donor oocyte in vitro fertilization and planned oocyte cryopreservation: A guideline. *Fertil Steril*. 2021;116(1):36-47. Doi: 10.1016/j.fertnstert.2021.02.024.

American Urological Association. Diagnosis and treatment of infertility in men: AUA/ASRM guideline; 2020. Published October 2020. Accessed July 2024. https://www.auanet.org/guidelines-and-quality/guidelines/male-infertility.

Arecco L, Blondeaux E, Bruzzone M, et al. Safety of fertility preservation techniques before and after anticancer treatments in young women with breast cancer: A systematic review and meta-analysis. *Hum Reprod*. 2022;37(5):954-968. Doi: 10.1093/humrep/deac035.

Behl S, Joshi VB, Larson NB, et al. Vitrification versus slow freezing of human ovarian tissue: A systematic review and meta-analysis of histological outcomes. *J Assist Reprod Genet*. 2023;40(3):455-464. Doi: 10.1007/s10815-022-02692-w.

Corkum KS, Rhee DS, Wafford QE, et al. Fertility and hormone preservation and restoration for female children and adolescents receiving gonadotoxic cancer treatments: A systematic review. *J Pediatr Surg.* 2019; pii: S0022-3468(18)30886-8. Doi: 10.1016/j.jpedsurg.2018.12.021.

Dhonnabhain BN, Elfaki N, Fraser K, et al. A comparison of fertility preservation outcomes in patients who froze oocytes, embryos, or ovarian tissue for medically indicated circumstances: A systematic review and meta-analysis. *Fertil Steril*. 2022;117(6)1266-1276. Doi: 10.1016/j.fertnstert.2022.03.004.

Dillon K, Gracia R. Pediatric and young adult patients and oncofertility. *Curr Treat Options Oncol.* 2012;13(2):161-173. Doi: 10.1007/s11864-012-0183-7.

Fraison E, Huberlant S, Labrune E, et al. Live birth rate after female fertility preservation for cancer or haematopoietic stem cell transplantation: A systematic review and meta-analysis of the three main techniques: embryo, oocyte, and ovarian tissue. *Hum Reprod*. 2023;38(3):489-502. Doi: 10.1093/humrep/deac249.

Hossay C, Donnez J, Dolmans MM. Whole ovary cryopreservation and transplantation: A systematic review of challenges and research developments in animal experiments and humans. *J Clin Med.* 2020;9(10). Doi: 10.3390/jcm9103196.

Lambertini M, Peccatori FA, Demeestere I, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO clinical practice guidelines. *Ann Oncol.* 2020;31(12):1664-1678. Doi: 10.1016/j.annonc.2020.09.006.

Li YX, Zhou L, Lv MQ, et al. Vitrification and conventional freezing methods in sperm cryopreservation: A systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol.* 2019;233:84-92. Doi: 10.1016/j.ejogrb.2018.11.028.

Loren A, Mangu P, Beck L, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013;31(19):2500-2510. Doi: 10.1200/JCO.2013.49.2678.

Meernick C, Poole C, Engel SM, Rauh-Hain JA, Luke B, Nichols HB. Outcomes after assisted reproductive technology in women with cancer: A systematic review and meta-analysis. *Hum Reprod*. 2023;38(1):30-45. Doi: 10.1093/humrep/deac235.

National Comprehensive Cancer Network. NCCN Guidelines Version 2.2022. Adolescent and young adult (AYA) oncology. www.nccn.org. Updated January 9, 2023.

National Institute for Health and Care Excellence. Fertility problems: Assessment and treatment. https://www.nice.org.uk/guidance/cg156. Published February 2013. Updated September 2017.

Rienzi L, Gracia C, Maggiulli R, et al. Oocyte, embryo, and blastocyst cryopreservation in art: Systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. *Hum Reprod Update.* 2017;23(2):139-155. Doi: 10.1093/humupd/dmw038.

Rodriguez-Wallberg K and Oktay K. Fertility preservation during cancer treatment: Clinical guidelines. *Cancer Manag Res.* 2014;6:105-117. Doi: 10.2147/CMAR.S32380.

Rosenberg J. 2018 ASCO Guideline Update: Fertility Preservation in Patients with Cancer. https://www.ajmc.com/view/2018-asco-guideline-update-fertility-preservation-in-patients-with-cancer. Published April 12, 2018.

Shandley LM, McKenzie LJ. Recent advances in fertility preservation and counseling for reproductive-aged women with colorectal cancer: A systematic review. *Dis Colon Rectum.* 2019;62(6):762-771. Doi: 10.1097/DCR.0000000000001351.

Wang X, Mao R, Wang M, Long R, Jin L, Zhu L. The effect of re-cryopreservation on embryo viability and in vitro fertilizatin outcomes: A systematic review and meta-analysis. *Fertil Steril*. 2023;S0015-0282(23)00208-X. Doi: 10.1016/j.fertnstert.2023.03.001.

Wong KM, van Wely M, Mol F, Repping S, Mastenbroek S. Fresh versus frozen embryo transfers in assisted reproduction. *Cochrane Database Syst Rev*. 2017 Mar 28;3:CD011184. Doi: 10.1002/14651858.CD011184.pub2.

Xu Z, Ibrahim S, Burdett S, Rydzewska L, Al Wattar BH, Davies MC. Long term pregnancy outcomes of women with cancer following fertility preservation: A systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2023;281:41-48. Doi: 10.1016/j.ejogrb.2022.12.016.

Policy updates

6/2015: initial review date and clinical policy effective date: 10/2015

8/2016: Policy references updated.

8/2017: Policy references updated.

8/2018: Policy references updated.

8/2019: Policy references updated. Policy ID changed.

8/2020: Policy references updated. Policy title changed. Coverage modified.

8/2021: Policy references updated.

8/2022: Policy references updated.

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