Cryopreservation of reproductive tissue, gametes, and embryos

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

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Coverage policy

Once-per-lifetime cryopreservation of gametes and embryos to preserve fertility in post-pubertal members with ovaries or testes facing infertility due to chemotherapy or other gonadotoxic therapies is clinically proven and, therefore, may be medically necessary (Brannigan, 2024 [American Urological Association]; American Cancer Society, 2025a, 2025c; National Comprehensive Cancer Network, 2024; Su, 2025 [American Society of Clinical Oncology]).

Cryopreservation of ovarian cortical tissue is clinically proven and, therefore, may be medically necessary to preserve fertility in members with ovaries who are facing infertility due to chemotherapy or other gonadotoxic therapies when (American Cancer Society, 2025b; National Comprehensive Cancer Network, 2024; Su, 2025):

- The member is either:
    - Post-pubertal, and there is insufficient time for oocyte or embryo cryopreservation prior to cancer treatment.
    - Pre-pubertal and there is a high risk of risk of future fertility problems, such as those receiving radiation to the abdomen or pelvis, high doses of certain chemotherapies, or stem cell transplants.

- No contraindications exist, such as a potential for reintroduction of malignant cells with grafting or carriers of BRCA mutations due to the increased risk for ovarian cancer.

Cryopreservation of testicular reproductive tissue is investigational/not clinically proven, therefore, not medically necessary, as the effectiveness of these procedures has not been established (Su, 2025).

Limitations

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

All other uses of cryopreservation of gametes, embryos, and cortical ovarian tissue are investigational/not clinically proven 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.
- Conservative surgical approaches or initial medical therapy for reproductive malignancies.

Background

Therapies to treat medical conditions such as cancer may compromise fertility. Surgery, chemotherapy, and radiation therapy are well-recognized for their potential to damage reproductive organs. Gonadotoxicity is particularly age-dependent in individuals with ovaries, because the number of primordial follicles making up the 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. Fertility preservation is of particular concern among children newly diagnosed with cancer, as some treatments, particularly chemotherapy and radiation, can significantly impact fertility later in life (Peterson, 2023).

Options to preserve fertility include cryopreservation of reproductive tissue. 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 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 (Peterson, 2023).

Cryopreservation of ovarian tissue has emerged in recent years as an option. Cryopreservation of ovarian tissue has several advantages over cryopreservation of embryos or oocytes. Transplanted ovarian cortical tissue can preserve hundreds of preantral follicles at once, potentially preserving both fertility and ovarian endocrine function. It requires no ovarian stimulation, thus avoiding the associated risks and delays in cancer treatment. It does not require a male partner or sperm donor, and it carries the possibility of natural conception and avoiding the burden associated with in vitro fertilization. Finally, ovarian tissue cryopreservation is the only strategy suitable for girls who have not reached reproductive maturity (Dhonnabhain, 2022).

Cryopreservation of immature testicular tissue has been proposed as an option for pre-pubertal males, but the most suitable method has not been standardized. Immature testicular tissue preservation has been demonstrated in nonhuman species, but it has not been translated to human males (Sung, 2024).

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 (Karimizadeh, 2023).

Findings

Guidelines

Fertility preservation is an important quality of life factor for many cancer survivors of reproductive age. Among guidelines, sperm, embryo, and oocyte cryopreservation are established options for fertility preservation in post-pubertal children and adults undergoing cancer treatment. Cryopreservation of ovarian cortical tissue has emerged as a recommended option for fertility preservation, and may be the only option for pre-pubertal individuals with ovaries at high risk for fertility compromise.

The National Comprehensive Cancer Network (2024) issued recommendations for cryopreservation for adolescents and young adults, defined as individuals aged 15 to 39 years at the time of initial cancer diagnosis. Ideally, fertility preservation should be initiated prior to the start of cancer treatment. For post-pubertal individuals with ovaries, cryopreservation of embryos or mature oocytes are options. Cryopreservation of ovarian cortical tissue may be considered when there is insufficient time for oocyte or embryo cryopreservation and/or the patient is pre-pubertal, and the treatment goal is to regain fertility rather than gonadal endocrine function. The procedure is not indicated if potential exists for reintroduction of malignant cells with grafting or for carriers of BRCA mutations due to the increased risk for ovarian cancer.

The American Society of Clinical Oncology 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 established fertility preservation options for adults and post-pubertal children (strong recommendations). Testicular tissue cryopreservation and reimplantation or grafting of human testicular tissue are considered experimental (strong recommendation). Ovarian tissue cryopreservation for the purpose of future transplantation may be offered to patients with cancer as an established fertility preservation method. It does not require ovarian stimulation and can be performed immediately in those unable to delay chemotherapy. It does not require sexual maturity and may be the only method available in pre-pubertal patients. This method may also be offered as an emerging method to restore global ovarian function. It may be used alone or adjunctively with embryo or oocyte cryopreservation (Strong recommendation) (Su, 2025).

The American Society for Reproductive Medicine (2021) cautions that individuals with ovaries considering planned oocyte cryopreservation should be fully informed of the limited published data about future pregnancy rates and neonatal outcomes. There is insufficient evidence to predict live birth rates after planned oocyte cryopreservation. Limited data suggest that ongoing and live birth rates may be improved for women who undergo planned oocyte cryopreservation at a younger versus older age. Although there are no significant differences in per transfer pregnancy rates using cryopreserved versus fresh donor oocytes, there is insufficient evidence comparing the effect of vitrified versus fresh donor oocytes on live birth rates. Neonatal outcomes appear similar with cryopreserved oocytes compared with fresh oocytes. Future studies that compare cumulative live birth rates are needed.

The American Cancer Society lists cryopreservation of eggs, embryos, and ovarian tissue as options for fertility preservation in individuals with ovaries (American Cancer Society, 2025c). Ovarian tissue cryopreservation is an

option in pre-pubertal individuals with ovaries who have a high risk of risk of fertility problems, such as those receiving radiation to the abdomen or pelvis, high doses of certain chemotherapies, or stem cell transplants (American Cancer Society, 2025a).

The American Cancer Society (2025b) 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 American Urological Association noted that gonadal dysfunction, including infertility, is a significant long-term consequence of cancer therapy. The organization recommends 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 (Brannigan, 2024).

Evidence review

The evidence supports gamete, embryo, and ovarian tissue cryopreservation as safe and feasible options for fertility preservation in individuals with cancer. All three strategies appear to have comparable clinical pregnancy rates and live birth rates, but low utilization of these procedures and lack of quality studies hamper comparisons. Patient age, cancer diagnosis, prognosis, ovarian reserve, cancer regimen, and the time requirements for cancer treatment are factors in determining recommendations for fertility preservation treatment. There is insufficient evidence supporting the safety or efficacy of cryopreservation of testicular tissue.

A meta-analysis of 38 studies reported clinical pregnancy rates of 34.9%, 49.0%, and 43.8%, live birth rates of 25.8%, 35.3%, and 32.3%, and miscarriage rates of 9.2%, 16.9%, and 7.5% 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 separate 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. Methods used to cryopreserve reproductive tissue have shown varying success rates in 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% confidence interval 0.91 to 1.31). Despite variation in methods and limited data, slow cryopreservation and vitrification appear to provide comparable outcomes of ovarian tissue quality with respect to follicle viability, the proportion of intact primordial follicles, the proportion of stromal cells, and deoxyribonucleic acid (DNA) damage in ovarian tissues (Kong, 2025).

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).

Ovarian tissue cryopreservation

Cryopreservation of ovarian tissue is an emerging option for fertility preservation with the potential to better preserve endocrine function, allowing follicles to mature and develop more effectively. Pre-pubertal females are

also potential candidates for ovarian tissue cryopreservation and transplantation procedures, but cryopreservation outcomes are mainly reported among adult patients living in high income countries (Gillipelli, 2024). Hematologic malignancies and breast cancer accounted for the majority of all indications for these procedures (Erden, 2024a; Wang, 2024).

Limited data from observational studies suggest that ovarian tissue cryopreservation with autologous transplantation are feasible options for preserving ovarian function in women with cancers, including gynecologic cancers. They appear safe, but infiltration of malignant cells into the ovarian cortex is a potential concern. The effect of chemotherapy before ovarian tissue cryopreservation required further study. Evidence of pregnancy outcomes and graft survival are mixed, and longer-term outcomes are needed, particularly among pediatric patients of all ages.

Among patients with gynecological cancers, a systematic review and meta-analysis of 23 studies concluded ovarian tissue cryopreservation and autologous transplantation are feasible options for preserving ovarian function. In total, 27.3% had at least one child, and ovarian endocrine function was restored in 78.1% after autologous transplantation. The median graft longevity was 32 months, and no graft-site cancer recurrence was reported, but longer-term outcomes of autologous transplantation are needed (Erden, 2024a).

Results of a pooled analysis of 122 women suggest autologous cryopreserved ovarian tissue transplantation is feasible. In all, 83.6% of the women had a malignant disease, and 51.0% were exposed to some form of chemotherapy before ovarian tissue cryopreservation. Of the 162 childbirths, 108 (66.7%) were conceived naturally, and 54 (33.3%) were conceived through assisted reproductive techniques. Perinatal complication rates were comparable between women who underwent autologous cryopreserved ovarian tissue transplantation and the general pregnant population, except for preeclampsia outcomes. Not receiving chemotherapy before ovarian tissue cryopreservation (odds ratio = 0.23; 95% confidence interval, 0.07 to 0.72; *P* = .012) and natural conception (odds ratio = 0.29; 95% confidence interval, 0.09 to 0.92; *P* = .035) were associated with a lower perinatal complication rate (Erden, 2024b).

A meta-analysis (n = 722) examined pregnancy outcomes following ovarian tissue transplantation among women with hematological diseases (53% of diagnoses), breast cancer (25%), and gynecologic malignancy (8%). A subgroup analysis examined fertility outcomes of patients with hematological diseases after ovarian tissue cryopreservation. The overall ovarian function recovery rate, live birth rate, and miscarriage rate were 93%, 35%, and 28%, respectively. The pregnancy rate was higher among those with only hematological diseases (54% versus 44%), was higher among patients younger than 35 years, and was not affected by chemotherapy use before ovarian tissue cryopreservation. Limited data from 26 participants with leukemia found no relapse of disease, suggesting no malignant cell infiltration after ovarian tissue transplantation (Wang, 2024).

In patients with childhood cancer, the American Pediatric Surgical Cancer Committee summarized the results of 23 observational studies involving 1,019 participants. Ages ranged from 0.4 to 20.4 years, with 298 under 13 years of age. The median age at the time of ovarian tissue cryopreservation was 19 years. Eighteen individuals underwent auto-transplantation of thawed cortical tissue, 17 of whom achieved restoration of reproductive endocrine hormone function. Sixteen patients had autologous ovarian tissue transplantation for the purpose of restoring fertility, of whom 11 were able to achieve pregnancy and nine resulted in a live birth. Three patients were pre-pubertal at the time of cryopreservation and one went on to have autologous ovarian tissue transplantation and a successful live birth (Corkum, 2019).

A systematic review of 12 studies analyzed the outcomes of 612 pediatric and adolescent patients with malignant disease. The most common cancer diagnoses were hematological malignancies (81%), central nervous system tumors (56%), and sarcomas (39%). Ovarian tissue cryopreservation was undertaken in 501 patients, of whom 30 (5.9%) underwent ovarian tissue transplantation. Following autologous transplantation, 27 patients desired pregnancy, and nine (33%) became pregnant. Six of these nine patients had live births. Reproductive hormone

function was restored in all participants, although at varying lengths of graft duration. The authors stressed the need for longitudinal studies in this population (Gillipelli, 2024).

Testicular tissue cryopreservation

For cryopreservation of immature testicular tissue, a systematic review of 11 studies found variations in cryopreservation protocols in freezing rate and cryoprotectant media. The optimum combination that preserves tissue integrity and function and the method most likely to induce spermatogenesis have not been determined (Dhonnabhain, 2021).

In 2024, we rewrote and condensed the findings section and updated the guideline section. No policy changes are warranted no additional studies were added.

In 2025, we updated the references and several guidelines and added medical necessity criteria for ovarian tissue cryopreservation that align with recent guideline recommendations.

References

On June 5, 2025, 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) 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.

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Policy updates

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

8/2016: Policy references updated.

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