Clinical Policy Title: Cryopreservation of sperm and embryos

Clinical Policy Number: CCP.1173

Effective Date: October 1, 2015
Initial Review Date: June 17, 2015
Most Recent Review Date: September 10, 2019
Next Review Date: December 2020

Related policies:

CCP.1239 Infertility - treatment

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’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 by Prestige Health Choice 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. Prestige Health Choice’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. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Once-per-lifetime cryopreservation of sperm and embryos in preserving fertility in post-pubertal men or women facing infertility due to chemotherapy or other gonadotoxic therapies is considered to be clinically proven and, therefore, medically necessary (Dillon, 2012; Keskinetepe; 2015; Loren, 2013, Rodriguez-Wahlberg, 2014; Slabbert, 2015; Wong, 2017).

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.

Cryopreservation of sperm and embryos for purposes of circumventing the reproductive aging process is considered to be investigational and, therefore, not medically necessary.
All other uses of cryopreservation of sperm and embryos are considered to be 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 to physically move the ovaries out of the pelvis through surgical techniques 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.

**Background**

Therapies to treat medical conditions such as cancer may compromise fertility. Chemotherapy agents linked to fertility issues include:

- Cisplatin.
- Cyclophosphamide.
- Chlorambucil.
- Busulfan.
- Procarbazine.
- Carmustine.
- Lomustine.
- Mechlorethamine.
- Melphalan.

Radiation therapy may have potential side effects that affect fertility issues:

- 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 may have adverse effects upon reproductive capacity and fertility:

- Oncologic surgery for uterine, ovarian, bladder or colon cancer in females.
- Oncologic surgery for prostate, bladder or colon cancer in men.

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 and embryos. 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 post-pubertal men and women 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.

Currently, there are no fertility preservation options available for the pre-pubertal male or female.

**Searches**

We searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

Searches were conducted on June 25, 2019, using the terms "embryo," "egg," "preservation," "freezing," "banking," "oocyte," "sperm" and "cryopreservation."

We included:
- Systematic reviews, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- Guidelines based on systematic reviews.
- Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

- A narrative review (Rodriguez-Wahlberg, 2014) addressed specifically and in depth the threat to fertility from cancer treatment and concluded, "In adult patients, cryopreservation techniques, such as sperm banking for males and embryo and oocyte banking for females, both of which are now established methods, may also be considered prior to (treatment)."
- 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. Sperm, embryo and oocyte cryopreservation are considered standard practice.

• The American Cancer Society (2013) 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 good for many years.

• The National Institute for Health and Care Excellence (2013) addresses cryopreservation issues in adults and adolescents:
  o When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos or oocytes.
  o Offer sperm cryopreservation to men and adolescent boys who are preparing for medical cancer treatment likely to make them infertile.
  o 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.
    ▪ This will not worsen their condition.
    ▪ Enough time is available before the start of their cancer treatment.

A narrative review (Dillon, 2012) concluded that, with improved survival rates for childhood cancers, long-term implications with regard to fertility were gaining importance. However, there are at present no fertility preservation measures available to pre-pubertal boys and only experimental ovarian tissue cryopreservation available to pre-pubertal girls.

Laws governing disputes about cryopreserved embryos vary by state. Some states (e.g., Tennessee) take a balance-of-interests approach. A 1992 decision argued that, in the absence of a prior agreement about the disposition of pre-embryos, the party wishing to avoid procreation should prevail if the other party had a reasonable alternative option for becoming a parent. The court ordered that the pre-embryos of a divorcing couple should be discarded, finding in favor of the former husband, who did not wish to become a father.

In the wake of this precedent-setting case, many states, such as New York and Texas, began to opt for contractual enforcement. In a 1998 dispute between a divorcing couple, the Court of Appeals in Albany, NY, followed the contract that the couple had signed with the clinic. In another approach, Iowa requires mutual consent before embryos can be disposed of or used. Massachusetts will not enforce contracts in such cases. After a 2000 divorce dispute, the Massachusetts Supreme Court ruled, “As a matter of public policy, we conclude that forced procreation is not an area amenable to judicial enforcement”

In the most recent court decision in the Szafranski-Dunston case in May 2014, Judge Sophia Hall argued that the decision should be based on a contract; but, if there is no contract, a balance of interests should be used. Hall argued that a phone conversation between Dunston and Szafranski was an oral contract. She further noted that the case was likely to be appealed, and that, were it to be considered on a balance of
interests, Dunston’s (the mother) should prevail because she could not have a genetically related child by any other means: “The Court ... finds that Karla’s desire to have a biological child in the face of the impossibility of having one without using the embryos, outweighs Jacob’s privacy concerns,” Hall wrote.

Members with concerns regarding cryopreservation maintenance after insurance benefit is terminated or exhausted may be referred to support and advocacy groups as a resource for their needs. The organization Stupid Cancer (https://stupidcancer.org) maintains a list of several resources for young people living with cancer.

Prestige Health Choice members may also find the clinical trials ongoing in regards to onco-infertility to be of benefit.

Policy updates:

There was no further information identified in a search of the literature since our last policy update for material advances or findings with regard to cryopreservation of sperm and embryos.

A Cochrane review (Wong, 2017) compared a freeze-all strategy with a conventional strategy which includes fresh transfer of embryos in women. Included were four randomized clinical trials analyzing data from a total of 1892 women. The evidence was of moderate to low quality due to serious risk of bias and (for some outcomes) serious imprecision. There was no clear evidence of a difference in cumulative live birth rate between the freeze-all strategy and the conventional strategy (odds ratio 1.09, 95 percent confidence interval 0.91 to 1.31; 4 trials; 1892 women; I2 = 0 percent; moderate-quality evidence). Time to pregnancy was not reported, but it can be assumed to be shorter using a conventional strategy in the case of similar cumulative live birth rates, as embryo transfer is delayed in a freeze-all strategy.

A retrospective study (Slabbert, 2015) compared cryoprotectant-free vitrification to conventional cryopreservation protocols. Cryoprotectant-free vitrification is a simple and cost-effective method for the storage of human spermatozoa without the use of conventional cryoprotectants, by plunging the sperm suspension directly into liquid nitrogen. As a result, solidification of living cells without the formation of ice crystals is achieved during cooling. Semen samples (n = 35) were processed using a discontinuous density-gradient centrifugation method, and washed samples were split into two aliquots and cryopreserved either by means of cryoprotectant-free vitrification (sucrose + 1 percent albumin) or conventional slow freezing (TEST-yolk buffer). TEST-yolk buffer is a semen extender and cryobuffer that can be paired with glycerol to achieve high sperm motility and viability. No significant differences were observed in the sperm motility parameters (p > 0.05). Lower percentages of deoxyribonucleic acid fragmentation (2.79 percent ± 1.017 percent versus 3.86 percent ± 1.38 percent; P < 0.01) were also observed when comparing cryoprotectant-free vitrification to conventional cryopreservation. The authors concluded that cryoprotectant-free vitrification was promising as a rapid alternative to conventional methods of gamete cryopreservation.

In a narrative review, Keskintepe (2015) considered long-term preservation of mammalian sperm at suprazoero temperatures by the freeze-drying of sperm samples. Although freeze-drying results in immotile and membrane-compromised sperm, intracytoplasmic sperm injection can be used to introduce such an
immotile sperm into an oocyte and thus start the fertilization process. The authors noted that improved freeze-drying protocols preserve chromosomal integrity and oocyte-activating factor(s) at 4 °C for several years and at ambient temperature for approximately 1 month, which permits shipping freeze-dried samples at ambient temperature. The authors presented a protocol for simple freeze-drying of mammalian sperm in order to facilitate adoption of their methods.

In 2019, we added one guideline/other reference and two peer-reviewed articles to the policy. The policy ID changed from 12.03.05 to CCP.1173.

References

Professional society guidelines/other:


Peer-reviewed references:


Centers for Medicare & Medicaid Services National Coverage Determinations:

No National Coverage Determinations for cryopreservation to preserve fertility in adult cancer survivors were identified on the Centers for Medicare & Medicaid Services website. However, Medicare does cover reasonable and necessary services associated with treatment for infertility:

Local Coverage Determinations:

No Local Coverage Determinations were identified at this time.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

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