4.02.04	Reproductive Techniques		
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Policy Statement

I. The following reproductive techniques may be considered **medically necessary** for **any** of the following:
   A. Blastocyst transfer
   B. Cryopreservation of testicular tissue in adult men with azoospermia as part of an intracytoplasmic sperm injection procedure
   C. Intracytoplasmic sperm injection for male factor infertility
   D. Cryopreservation of embryos, oocytes, ovarian tissue, sperm or testicular tissue (in post-pubertal men) when there is risk of iatrogenic sterilization from chemotherapy or similar medically necessary medical or surgical treatment when **all** of the following criteria are met:
      1. No prior elective sterilization
      2. No known infertility already present
      3. Post-pubertal and less than 45 years of age (or cryopreservation is no longer desired if younger than age 45)

II. The following reproductive techniques are considered **investigational**:
   A. Co-culture of embryos
   B. Cryopreservation of testicular tissue in prepubertal boys or ovarian tissue in prepubertal girls
   C. Intracytoplasmic sperm injection (ICSI) in the absence of male factor infertility

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Azoospermia means no sperm in the seminal fluid, either from obstruction or lack of production.

ICSI takes a single sperm and injects it directly into the ovum during the IVF process. Traditional IVF places live sperm (50,000) near the ovum in a laboratory dish and allow one of the sperm to penetrate the ovum. ICSI has only shown benefit if male factor infertility (too few, or abnormal sperm function) is present. Obtaining sperm as part of the ICSI process can involve taking some testicular tissue from which the sperm are removed. Leftover tissue can be cryopreserved in case it is needed again later.

Assisted hatching refers to mechanically disrupting the membrane around the ovum (zona pellucida) which persists after fertilization around the embryo. It usually dissolves on its own during implantation. Mechanical disruption has been proposed to help with implantation.

Co-culture refers to trying to enhance the culture medium the embryo is put into during the 2 to 3 days prior to transferring to the uterus (after the **embryo matures into a blastocyst)**. The hope is to have more embryos progress and then to have a higher implantation or pregnancy rate.

Cryopreservation of oocytes (immature eggs) is less successful than cryopreservation of a fertilized embryo. Oocytes are more fragile than embryos and more prone to damage both during freezing and thawing.

Testicular tissue from pre-pubertal boys would contain stem cells that would later create sperm. Freezing and later thawing this tissue has not yet been shown to result in usable sperm in humans. Mature, usable sperm is not available from pre-pubertal boys.

Ovarian tissue from pre-pubertal girls has been able to be used for successful conception in a few case reports. The patients best suited for this and the techniques to be used are still unclear, and success rates remain low.

Coding

The following CPT codes describe procedures that would be routinely performed in all assisted reproductive technology (ART) procedures involving in vitro fertilization (IVF):

- **58970:** Follicle puncture for oocyte retrieval, any method

Either:

- **89250:** Culture of oocyte(s)/embryo(s), less than 4 days
- **89272**: Extended culture of oocyte(s)/embryo(s), 4-7 days

Either:

- **58974:** Embryo transfer, intrauterine
- **58976:** Gamete, zygote, or embryo intrafallopian transfer, any method
- **89255:** Preparation of embryo for transfer (any method)
- **89260:** Sperm isolation; simple prep (e.g., sperm wash and swim-up) for insemination or diagnosis with semen analysis
- **89261**: Sperm isolation; complex prep (e.g., Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis
- **89268**: Insemination of oocytes
- **89280:** Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes
- **89281:** Assisted oocyte fertilization, microtechnique; greater than 10 oocytes

The following CPT codes describe procedures that would *not* be routinely performed in all ART procedures involving IVF:

- **89253:** Assisted embryo hatching, microtechniques (any method). Only performed in women over the age of 40, or in cases in which prior ART attempts resulted in failed implantation
- **89257:** Sperm identification from aspiration (other than seminal fluid). Only performed in patients with oligospermia who have undergone a prior testicular or epididymal aspiration; typically performed as a part of an intracytoplasmic sperm injection procedure (ICSI)
- **89258:** Cryopreservation; embryo(s)
- **89259:** Cryopreservation; sperm
- **89264:** Sperm identification from testis tissue, fresh or cryopreserved. Only performed in patients with oligospermia who have undergone a prior testicular biopsy; typically performed as a part of an ICSI procedure
- **89342**: Storage (per year); embryo(s)
- **89343**: Storage (per year); sperm/semen
- **89344**: Storage (per year); reproductive tissue, testicular/ovarian
- **89346**: Storage (per year); oocyte(s)
- **89352**: Thawing of cryopreserved; embryo(s)
- **89353**: Thawing of cryopreserved; sperm/semen, each aliquot
- **89354**: Thawing of cryopreserved; reproductive tissue, testicular/ovarian
- **89356**: Thawing of cryopreserved; oocytes, each aliquot

The following CPT codes describe procedures that would be routinely performed as part of an intrauterine or intracervical artificial insemination:

- **58321:** Artificial insemination; intra-cervical

- **58322:** Artificial insemination; intra-uterine
- **58323:** Sperm washing for artificial insemination

Note also that "S" codes are available (see Coding section) that describe in vitro fertilization (IVF) globally.

The following codes are available for cryopreservation of oocytes:

- **89337:** Cryopreservation, mature oocyte(s)

The following CPT code replaced 0357T:

- **89398**: Unlisted reproductive medicine laboratory procedure

Description

A variety of techniques are available to establish a viable pregnancy for couples who have been diagnosed with infertility and for whom assisted insemination has been unsuccessful.

Related Policies

- Genetic Testing: Preimplantation Genetic Testing

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

There are no medical devices or diagnostic tests related to ARTs that require U.S. Food and Drug Administration approval or clearance.

Rationale

Background

Infertility

Infertility can be due either to female factors (i.e., pelvic adhesions, ovarian dysfunction, endometriosis, prior tubal ligation), male factors (i.e., abnormalities in sperm production, function, or transport or prior vasectomy), a combination of male and female factors, or unknown causes.

Treatment

Various reproductive techniques are available to establish a viable pregnancy; different techniques are used depending on the reason for infertility. Assisted reproductive technologies (ARTs), as defined by the Centers for Disease Control and Prevention and other organizations, refer to fertility treatments in which eggs or embryos are handled.[1,] Not included in assisted reproduction is assisted

insemination (artificial insemination) using sperm from either a woman's partner or a sperm donor. In most instances, assisted reproduction will involve in vitro fertilization (IVF), a procedure in which oocytes harvested from the female are inseminated in vitro with sperm harvested from the male. Following the fertilization procedure, the zygote is cultured and ultimately transferred back into the female's uterus or fallopian tubes. In some instances, the oocyte and sperm are collected but no IVF takes place, and the gametes are reintroduced into the fallopian tubes. Examples of ARTs include, but are not limited to, gamete intrafallopian transfer, transuterine fallopian transfer, natural oocyte retrieval with intravaginal fertilization, pronuclear stage tubal transfer, tubal embryo transfer, zygote intrafallopian transfer, gamete, and embryo cryopreservation, oocyte, and embryo donation, and gestational surrogacy.

The various components of ART and implantation into the uterus can be broadly subdivided into oocyte harvesting procedures, which are performed on the female partner; sperm collection procedures, which are performed on the male partner; and the in vitro component (i.e., the laboratory procedures), which are performed on the collected oocyte and sperm. The final step is the implantation procedure.

Most CPT codes describing the various steps in ART procedures are longstanding. They include codes for oocyte retrieval, sperm isolation, culture and fertilization of the oocyte, and embryo, zygote, or gamete transfer into the uterus or fallopian tubes. Only the relatively new reproductive techniques (i.e., intracytoplasmic sperm injection [ICSI], assisted hatching, co-culture of embryos) and cryopreservation of reproductive tissue (i.e., testicular, ovarian, oocytes) will be considered within this evidence summary.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Assisted Hatching

Clinical Context and Therapy Purpose

Implantation of the embryo in the uterus is a key component of success with in vitro fertilization (IVF). Although the exact steps in implantation are poorly understood, normal rupture of the surrounding zona pellucida with escape of the developing embryo (termed hatching) is crucial. Mechanical disruption of the zona pellucida (i.e., assisted hatching) has been proposed as a mechanism to improve implantation rates. The purpose of IVF with assisted hatching in individuals with infertility is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are infertile.

Interventions

The therapy being considered is IVF with assisted hatching.

Comparators

The following practice is currently being used to make decisions about infertility: IVF without assisted hatching.

Outcomes

The general outcomes of interest are live birth rates and infant abnormalities.

Follow-up is measured in weeks to confirm a successful pregnancy and months to confirm a successful birth.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A Cochrane review and meta-analysis by Carney et al (2012) identified 31 RCTs evaluating assisted hatching (N=5728).[2,] Twelve studies included women with a poor fertility prognosis, 12 studies included women with a good fertility prognosis, and the remaining 7 studies did not report this factor. Fifteen studies used a laser for assisted hatching, 11 used chemical means, and 5 used mechanical means. Live birth rates were reported in 9 studies (n=1921). A pooled analysis of data from the 9 studies did not find a statistically significant difference between the groups receiving assisted hatching and a control condition (odds ratio [OR], 1.03; 95% confidence interval [CI], 0.85 to 1.26). The rate of live birth was 313 (31%) of 995 in the assisted hatching group and 282 (30%) of 926 in the control group. All 31 trials reported clinical pregnancy rates. In a meta-analysis of all trials, assisted hatching improved the pregnancy rate, but the estimate for the odds was of marginal statistical significance (OR, 1.13; 95% CI, 1.01 to 1.27).

Randomized Controlled Trials

Two RCTs not assessed in the Cochrane review have compared laser-assisted hatching with the standard of care. Shi et al (2016) evaluated 178 patients of advanced maternal age (age range, 35 to 42 years).[3,] There were no statistically significant differences in implantation rates (32.5% in the assisted hatching group vs. 39.3% in the control group) or in clinical pregnancy rates (48.8% in the assisted hatching group vs. 50.4% in the control group; p values not reported). Kanyo et al (2016) assessed 413 women (mean age, 33 years).[4,] In the overall study population, there was no statistically significant difference in the clinical pregnancy rate between the assisted hatching group (33.3%) and the control group (27.4%; p=.08). However, in the subgroup of patients ages 38 or older, the clinical pregnancy rate was significantly higher in the assisted hatching group (18.4%) than in the control group (11.4%; p=.03). There was no significant between-group difference in the clinical pregnancy rate among women younger than 38 years old. Neither trial reported live birth rates.

Retrospective Studies

Knudtson et al (2017), in a retrospective cohort study, analyzed live birth rates in women who underwent first-cycle, autologous frozen embryo transfer.[5,] From data reported between 2004 and 2013 to the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System, 151,533 cycles were identified, 70,738 (46.7%) with assisted hatching and 80,795 (53.3%) without. Assisted hatching had a significantly lower live birth rate (34.2%) than nonassisted hatching (35.4%; p<.001). Also, older patients (age ≥38 years) who received assisted hatching were associated with lower live birth rates (p≤.05). Results were similar in a 2019 study by McLaughlin et al that analyzed Society for Assisted Reproductive Technology Clinic Outcomes Reporting System data from 2007 to 2015 comparing assisted hatching (n=48,858) with no assisted hatching (n=103,413) in women undergoing first cycle, fresh IVF. [6,] The study found assisted hatching associated with a significantly lower live birth rate than no assisted hatching (39.2% versus 43.9%; rate difference, - 4.7%, 95% CI, -0.053 to -0.040).

Kissin et al (2014) retrospectively reviewed data on assisted hatching in the U.S. from 2000 to 2010.[7,] Data were taken from the Centers for Disease Control and Prevention's National Assisted Reproductive Technology Surveillance System. The analysis of outcomes was limited to fresh autologous IVF cycles for which a transfer was performed on day 3 or 5. For the total patient population (N=536,852), rates of implantation, clinical pregnancy, and live births were significantly lower when assisted hatching was used. For example, the live birth rate was 28.3% with assisted hatching and 36.5% without (adjusted odds ratio [AOR], 0.75; 95% CI, 0.70 to 0.81). Moreover, the rate of miscarriage was significantly higher when assisted hatching was used (18.0% vs. 13.5%; AOR=1.43; 95% CI, 1.34 to 1.52).

Section Summary: Assisted Hatching

The available literature has generally not found better outcomes with assisted hatching than with standard of care. A 2012 Cochrane review of heterogeneous RCTs found that clinical pregnancy rates, but not the live birth rates, improved with assisted hatching. In subsequent RCTs, laser-assisted hatching did not improve the clinical pregnancy rate but, in 1 study, there was a higher rate of clinical pregnancy in the subgroup of women 38 years of age or older. In addition, analyses of a large national database found better outcomes (e.g., clinical pregnancy and live birth rates) when assisted hatching was not used.

Embryo Co-Culture

In routine IVF procedures, the embryo is transferred to the uterus on day 2 or 3 of development, when it has between 4 and 8 cells. Embryo co-culture techniques, used successfully in domestic animals, represent an effort to improve the culture media for embryos such that a greater proportion of embryos will reach the blastocyst stage, in an attempt to improve implantation and pregnancy rates. In addition, if co-culture results in a higher implantation rate, fewer embryos could be transferred in each cycle, decreasing the incidence of multiple pregnancies. A variety of co-culture techniques have been investigated involving the use of feeder cell layers derived from a range of tissues, including the

use of human reproductive tissues (i.e., oviducts) to nonhuman cells (i.e., fetal bovine uterine or oviduct cells) to established cell lines (i.e., Vero cells or bovine kidney cells).

Clinical Context and Therapy Purpose

The purpose of IVF with embryo co-culture in individuals with infertility is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are infertile.

Interventions

The therapy being considered is IVF with embryo co-culture.

Comparators

The following practice is currently being used to make decisions about infertility: IVF without embryo co-culture.

Outcomes

The general outcomes of interest are live birth rates and infant abnormalities. Follow-up is measured to confirm successful pregnancy up to successful birth.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

Currently, no standardized method of co-culture has emerged, and clinical trials have generally not found that co-culture is associated with improved implantation or pregnancy rates.[8,9,10,11,12,13,] For example, Wetzels et al (1998) reported on an RCT that assigned IVF treatments to co-culture with human fibroblasts or no culture.[13,] Patients in the 2 groups were stratified by age (older or younger than 36 years) and prior IVF attempts (yes vs. no). The trialists reported that fibroblast co-culture did not affect the implantation or pregnancy rates. More recently, Ohl et al (2015) reported on a novel co-culture technique involving autologous endometrial cell co-culture.[14,] In an interim analysis of 320 patients, the clinical pregnancy rate per embryo transfer was significantly higher in the co-culture group (53.4%) than in the control group (37.3%; p=.025).

Section Summary: Embryo Co-Culture

There is no standardized method of co-culture, and few clinical trials have evaluated outcomes. Most have not found improved implantation or pregnancy rates after co-culture. A 2015 RCT reported on a novel co-culture method, and an interim analysis of the trial found a higher clinical pregnancy rate with co-culture than with the standard practice control group. Additional studies are needed to

evaluate this novel co-culture technique. No studies have reported on the impact of co-culture on live birth rates.

Cryopreservation of Ovarian Tissue

Clinical Context and Therapy Purpose

The purpose of cryopreservation of ovarian tissue in individuals with cancer who will undergo treatment that could precipitate infertility is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cancer who undergo treatment that could precipitate infertility.

Interventions

The therapy being considered is cryopreservation of ovarian tissue.

Comparators

The following practice is currently being used to make decisions about infertility: cryopreservation of embryos but not of ovarian tissue.

Outcomes

The general outcomes of interest are live birth rates and infant abnormalities. Follow-up is measured to confirm successful pregnancy up to successful birth.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Review

Ní Dhonnabháin et al (2022) reported on obstetric outcomes in patients who underwent oocyte, embryo, or ovarian tissue cryopreservation before gonadotoxic therapy and then attempted pregnancy using the cryopreserved cells or tissues (see Table 1 below and Table SR1 in the Appendix).[15,] A total of 39 case series were included in the final analysis, which included 550 ovarian tissue transplants, 102 embryo transfers (in 75 women), and 178 oocyte transfers (in 170 women). Results of the meta-analysis are found in Table 2. Following the transplant of cryopreserved ovarian tissue, the clinical pregnancy rate was 43.8%, the live birth rate was 32.3%, and the miscarriage rate was 7.5%. A meta-analysis found significantly fewer miscarriages with the use of cryopreserved ovarian tissue compared with cryopreserved embryos (p=.01). Authors noted heterogeneity with regard to surgical techniques across centers.

Table 1. SR & M-A Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Ní Dhonnabháin et al (2022)[15,]	Through Nov 2020	39	Patients who underwent oocyte, embryo, or ovarian tissue cryopreservation before gonadotoxic therapy and then attempted pregnancy using the cryopreserved cells or tissues	550 ovarian tissue transplants; 102 embryo transfers (in 75 women); 178 oocyte transfers (in 170 women)	Case series	Not reported

M-A: meta-analysis; SR: systematic review.

Table 2. SR & M-A Results

Study	Clinical pregnancy, %	Live birth, %	Miscarriage, %
Ní Dhonnabháin et al (2022)[15,]			
Ovarian tissue cryopreservation	43.8%	32.3%	7.5%
Oocyte cryopreservation	34.9%	25.8%	9.2%
Embryo cryopreservation	49%	35.3%	16.9%
p-value	.09	.11	oocye vs embryo; p=NS ovarian tissue vs embryo; p=.01

M-A: meta-analysis; NS: not significant; SR: systematic review.

Case Series

Cryopreservation of ovarian tissue or an entire ovary with subsequent auto- or heterotopic transplant has been investigated as a technique to sustain the reproductive function of women or children who are faced with sterilizing procedures, such as chemotherapy, radiotherapy, or surgery, frequently due to malignant diseases. There are a few case reports assessing the return of ovarian function using this technique.[16,17,] There are also case series describing live births using cryopreserved ovarian tissue.[18,19,20,] However, in general, the technique is not standardized and insufficiently studied to determine the success rate.[21,22,] Johnson and Patrizio (2011) commented on whole ovary freezing as a fertility preservation technique in women with disease or disease treatment that threaten their reproductive tract function.[23,] They concluded: "Although theoretically optimal from the point of view of maximal follicle protection and preservation, the risks and difficulties involved in whole ovary freezing limit this technique to experimental situations."

Section Summary: Cryopreservation of Ovarian Tissue

As a technique, cryopreservation of ovarian tissue has not been standardized, and there are insufficient published data that this reproductive technique is effective and safe. A systematic review of case series describing patients who underwent oocyte, embryo, or ovarian tissue cryopreservation before gonadotoxic therapy and then attempted pregnancy using the cryopreserved cells or tissue did not identify any significant differences when comparing rates of clinical pregnancy and live birth in patients who used cryopreserved ovarian tissue compared to cryopreserved embryos. However, there were fewer miscarriages with the use of cryopreserved ovarian tissue compared with cryopreserved embryos (7.5% vs 16.9%).

Cryopreservation of Oocytes

Cryopreservation of oocytes has been examined as a fertility preservation option for reproductive-age women undergoing cancer treatment. The mature oocyte is very fragile due to its large size, high water content, and chromosomal arrangement. There are 2 primary approaches to cryopreservation: a controlled-rate, slow-cooling method and a flash-freezing process known as vitrification. Vitrification, the newer method, is faster and requires a higher concentration of cryoprotectants.

Clinical Context and Therapy Purpose

The purpose of cryopreservation of oocytes in individuals with cancer who will undergo treatment that might precipitate infertility is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cancer who undergo treatment that might precipitate infertility.

Interventions

The therapy being considered is cryopreservation of oocytes.

Comparators

The following practice is currently being used to make decisions about infertility: cryopreservation of embryos but not of ovarian tissue.

Outcomes

The general outcomes of interest are live birth rates and infant abnormalities. Follow-up is measured to confirm successful pregnancy up to successful birth.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A systematic review by Ní Dhonnabháin et al (2022) is introduced above (see Table 1 above and Table SR1 in the Appendix).[15,] Included in the final analysis were data from 170 women who underwent 178 oocyte transfers. Results from the meta-analysis are found in Table 2 above. Following the transplantation of cryopreserved oocytes, the clinical pregnancy rate was 34.9%, the live birth rate was 25.8%, and the miscarriage rate was 9.2%; there were no significant differences when comparing outcomes in patients who used cryopreserved oocytes vs cryopreserved embryos. Authors noted heterogeneity with regard to surgical techniques across centers.

The American Society for Reproductive Medicine and Society for Assisted Reproductive Technology (2013) updated their joint guidelines on mature oocyte cryopreservation.[24,] A systematic review of the literature, conducted as part of guideline development, identified 4 RCTs comparing outcomes of assisted reproduction with cryopreserved and fresh oocytes. All trials were conducted in Europe and none among patients who desired to preserve fertility after medical treatment (e.g., chemotherapy). In these studies, fertilization rates ranged from 71% to 79%, and the clinical pregnancy rates per transfer ranged from 36% to 61%. The guidelines noted that the available data might not be generalizable to the U.S., to clinics with less experience with these techniques, or to other populations (e.g., older women, cancer patients). The authors stated that data from the U.S. are available only from a few clinics and report on young, highly select populations. Pregnancy outcomes and rates of congenital anomalies were not reported.

Observational Studies

An Italian database study published subsequent to the joint guidelines compared outcomes in pregnancies achieved with fresh or frozen oocytes.[25,] The investigators identified 855 patients who had become pregnant using fresh and/or cryopreserved and thawed oocytes. The authors did not state the reasons for a desire for fertility preservation. Of a total 954 clinical pregnancies; 197 were obtained with frozen oocytes and 757 with fresh oocytes. There were 687 pregnancies from fresh cycle oocytes only, 129 pregnancies with frozen oocytes only, and 138 pregnancies from both fresh and frozen oocyte cycles. The live birth rate was 68% (134/197) from frozen and thawed oocytes and 77% (584/757) from fresh oocyte cycles. The live birth rate was significantly higher after fresh cycle oocytes (p=.008).

Section Summary: Cryopreservation of Oocytes

There are insufficient published data on the safety and efficacy of cryopreservation of oocytes, and data are only available from select clinical settings, generally outside of the U.S. Moreover, there are limited published data on success rates with cryopreserved oocytes in women who froze oocytes because they were undergoing chemotherapy. A systematic review of case series describing patients who underwent oocyte, embryo, or ovarian tissue cryopreservation before gonadotoxic therapy and then attempted pregnancy using the cryopreserved cells or tissue did not identify any significant differences when comparing rates of clinical pregnancy, live birth, and miscarriage in patients who used cryopreserved oocytes compared to cryopreserved embryos. Additional data on health outcomes (e.g., clinical pregnancy rate, live birth rate) in the population of interest are needed.

Blastocyst Transfer

The most common days for embryo transfer in the clinical IVF setting are day 3 or day 5. Embryo transfer at the blastocyst stage on day 5 continues to be less common than cleavage-stage transfer on day 3. First introduced in clinical practice in 2005, the use of blastocyst transfer is increasing in clinical practice. The rationale and reported advantages for blastocyst transfer are: higher implantation and clinical pregnancy rates, a more viable option for limiting to single embryo transfer, more appropriate endometrium-embryo synchronicity, optimization of embryo selection due to embryo development progression, and decreased potential for embryo trauma with biopsy obtained for preimplantation genetic testing. Advances in cell culture techniques and embryology assessments have facilitated increased use of blastocyst transfer and research into the technique. Critics of blastocyst transfer have raised concerns about the limitation on the number of available embryos for transfer once the cleavage-stage is passed; critics also cite concerns due to uncertainties about the effects of the culture microenvironment, as well as early indicators of a higher rate of adverse pregnancy outcomes.

Clinical Context and Therapy Purpose

The purpose of IVF with blastocyst transfer in individuals with infertility is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are infertile.

Interventions
The therapy being considered is IVF with blastocyst transfer.

Comparators
The following practice is currently being used to make decisions about infertility: IVF without cleavage-stage transfer.

Outcomes
The general outcomes of interest are live birth rates and infant abnormalities. Follow-up is measured to confirm successful pregnancy up to successful birth.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
Several systematic reviews of studies comparing outcomes associated with blastocyst-stage transfer with those of earlier stage transfer have been published. Only Cochrane reviews by Glujovsky et al (2012, 2016, 2022) included RCTs.[26,27,28,] In 2012, the authors identified 23 RCTs, 12 of which reported on the rates of live births per couple. A pooled analysis of these trials found a significantly higher live birth rate with blastocyst transfer (292/751 [39%]) than with cleavage-stage transfer (237/759 [31%]). The odds for live birth were 1.40 (95% CI, 1.13 to 1.74). There was no significant difference in the rate of multiple pregnancies between the 2 treatment groups (16 RCTs; OR, 0.92; 95% CI, 0.71 to 1.19). In addition, there was no significant difference in the miscarriage rate (14 RCTs; OR, 1.14; 95% CI, 0.84 to 1.55).

The 2016 update placed more emphasis on whether blastocyst-stage (day 5 to 6) embryo transfers improved the live birth rates, and other associated outcomes, compared with cleavage-stage (day 2 to 3) embryo transfers.[27,] Data from 4 new studies, 3 of which were published studies,[29,30,31,] resulted in a total of 27 parallel-design RCTs that included 4031 couples or women. The data from a fourth study was only available in abstract form and reported on outcomes from a multicenter trial comparing blastocyst with day 2 to 3 transfer in intracytoplasmic sperm injection (ICSI) cycles for male factor infertility (MFI). There were no exclusions from the 2012 review. The live birth rate following fresh transfer was higher in the blastocyst transfer group (OR, 1.48; 95% CI, 1.20 to 1.82; 13 RCTs, 1630 women, I^2=45%, low-quality evidence). There was no evidence of a difference between groups in rates of cumulative pregnancy per couple following fresh and frozen-thawed transfer after 1 oocyte retrieval (OR, 0.89; 95% CI, 0.64 to 1.22; 5 RCTs, 632 women, I^2=71%, very low-quality evidence). The clinical pregnancy rate was also higher in the blastocyst transfer group, following fresh transfer (OR, 1.30; 95% CI, 1.14 to 1.47; 27 RCTs, 4031 women, I^2=56%, moderate-quality evidence). Embryo freezing

rates were lower in the blastocyst transfer group (OR, 0.48; 95% CI, 0.40 to 0.57; 14 RCTs, 2292 women, I^2=84%, low-quality evidence). Failure to transfer any embryos was higher in the blastocyst transfer group (OR, 2.50; 95% CI, 1.76 to 3.55; 17 RCTs, 2577 women, I^2=36%, moderate-quality evidence). The data for rates of multiple pregnancy and miscarriage were incomplete in 70% of the trials and limit conclusions concerning the following findings. There was no evidence of a difference between the groups in rates of multiple pregnancies (OR, 1.05, 95% CI, 0.83 to 1.33; 19 RCTs, 3019 women, I^2=30%, low-quality evidence) or miscarriages (OR, 1.15, 95% CI, 0.88 to 1.50; 18 RCTs, 2917 women, I^2=0%, low-quality evidence). Reviewers reported that the main limitation of the RCTs assessed was a high-risk of bias, which was associated with failure to describe acceptable methods of randomization and unclear or high-risk of attrition bias.

The 2022 update included 32 RCTs.[28,] The live birth rate following fresh transfer was higher in the blastocyst-stage transfer group (OR, 1.27; 95% CI, 1.06 to 1.51; 15 RCTs, 2219 women, low-quality evidence). The only study (n=512) using vitrification showed evidence of a higher cumulative pregnancy rate in blastocyst transfers (OR, 2.44; 95% CI, 1.17 to 5.12; moderate-quality evidence); conversely, cumulative pregnancy rate appeared to be reduced with blastocyst transfers when slow freezing was used (OR, 0.69; 95% CI, 0.48 to 0.99; 4 RCTs, 512 women, low-quality evidence). The clinical pregnancy rate was higher in the blastocyst-stage transfer group following fresh transfer (OR, 1.25; 95% CI, 1.13 to 1.39; 32 RCTs, 5767 women, moderate-quality evidence). Embryo freezing rates were lower in the blastocyst transfer group (OR, 0.48; 95% CI,.040 to 0.57; 14 RCTs, 2292 women, low-quality evidence) and failure to transfer any embryos was higher in the blastocyst transfer group (OR, 2.50; 95% CI, 1.76 to 3.55; 17 RCTs, 2577 women, moderate-quality evidence). There were no statistically significant differences between the blastocyst-stage versus cleavage-stage embryo transfer groups in rates of multiple pregnancies (OR, 1.12; 95% CI, 0.90 to 1.38; 22 RCTs, 4208 women, low-quality evidence) or miscarriages (OR, 1.24, 95% CI, 0.98 to 1.57; 21 RCTs, 4106 women, low-quality evidence).

Observational Studies

A retrospective cohort study by Kallen et al (2010) reported on risks associated with blastocyst transfer.[32,] Data were taken from the Swedish Medical Birth Register. There were 1311 infants born after blastocyst transfer and 12,562 born after cleavage-stage transfer. There were no significant differences in the rates of multiple births (10% after blastocyst transfer vs. 8.9% after cleavage-stage transfer). Among singleton births, the rate of preterm birth (<32 weeks) was 1.7% (18/1071) in the blastocyst transfer group and 1.35% (142/10513) in the cleavage-stage transfer group. In a multivariate analysis controlling for year of birth, maternal age, parity, smoking habits, and body mass index, the AOR was 1.44 (95% CI, 0.87 to 2.40). The rate of low birth weight singletons (<1500 g or <2500 g) did not differ significantly between the blastocyst transfer group and the cleavage-stage transfer group. There was a significantly higher rate of relatively severe congenital malformation (e.g., spina bifida, cardiovascular defects, cleft palate) after blastocyst transfer (61/1311 [4.7%]) than after cleavage-stage transfer (509/12,562 [4.1%]; AOR, 1.33; 95% CI, 1.01 to 1.75). The groups did not differ significantly in their rates of low Appearance, Pulse, Grimace, Activity and Respiration scores, intracranial hemorrhage rates, respiratory diagnoses, or cardiovascular malformations. Respiratory diagnoses were given to 94 (7.2%) of 1311 infants born after blastocyst transfer and to 774 (6.2%) of 12,562 after cleavage-stage transfer (OR, 1.15; 95% CI, 0.90 to 1.47).

Ginström Ernstad et al (2016) published another retrospective registry cohort study using data crosslinked across the Swedish Medical Birth Register, the Register of Birth Defects, and the National Patient Register.[33,] All singleton deliveries after blastocyst transfer in Sweden from 2002 through 2013 were compared with deliveries after cleavage-stage transfer and deliveries after spontaneous conception. There were 4819 singletons born after blastocyst transfer, 25,747 after cleavage-stage transfer, and 1,196,394 after spontaneous conception. Singletons born after blastocyst transfer had no increased risk of birth defects compared with singletons born after the cleavage-stage transfer (AOR, 0.94; 95% CI, 0.79 to 1.13) or spontaneous conception (AOR, 1.09; 95% CI, 0.92 to 1.28). Perinatal mortality was higher in the blastocyst group versus the cleavage-stage group (AOR, 1.61; 95% CI, 1.14

to 2.29). When comparing singletons born after blastocyst transfer with singletons born after spontaneous conception, a higher risk of preterm birth (<37 weeks) was detected (AOR, 1.17; 95% CI, 1.05 to 1.31). Singletons born after blastocyst transfer had a lower rate of low birthweight (AOR, 0.83; 95% CI, 0.71 to 0.97) than singletons born after cleavage-stage transfer. The rate of being small for gestational age was also lower in singletons born after blastocyst transfer than after both cleavage-stage conception (AOR, 0.71; 95% CI, 0.56 to 0.88) and spontaneous conception (AOR, 0.70; 95% CI, 0.57 to 0.87). The risks of placenta previa and placental abruption were higher in pregnancies after blastocyst transfer than in pregnancies after cleavage stage (AOR, 2.08; 95% CI, 1.70 to 2.55; AOR, 1.62; 95% CI, 1.15 to 2.29, respectively) and after spontaneous conception (AOR, 6.38; 95% CI, 5.31 to 7.66; AOR, 2.31; 95% CI, 1.70 to 3.13, respectively).

A 2020 study by Spangmose et al focused on the comparative obstetric and perinatal harms of blastocyst transfer versus cleavage-stage transfer.[34,] The study used combined data from Norway, Sweden, and Denmark from 56,557 singleton pregnancies. Women undergoing blastocyst transfer were significantly more likely to have placenta previa (AOR, 2.11; 95% CI, 1.76 to 2.52) and marginally more likely to have a Cesarean section (AOR, 1.09; 95% CI, 1.01 to 1.18) relative to cleavage-stage transfer. Risk of labor induction was slightly lower with blastocyst transfer (AOR, 0.91; 95% CI, 0.83 to 0.99). There were no clear differences in perinatal outcomes, apart from risk of preterm birth which was slightly higher with blastocyst transfer (AOR, 1.14; 95% CI, 1.01 to 1.29).

Section Summary: Blastocyst Transfer

An updated 2022 Cochrane review of 32 RCTs compared the effectiveness of blastocyst transfers with cleavage-stage transfers. The primary outcomes of live birth and cumulative clinical pregnancy rates were higher with fresh blastocyst transfer. There were no differences between groups in multiple pregnancies or early pregnancy loss (miscarriage). The main limitation of the RCTs evaluated in the Cochrane review was a high risk of bias associated with failure to describe acceptable methods of randomization and unclear or high risk of attrition bias. Differences in outcomes with the use of cryopreserved blastocysts and cleavage-stage embryos have been reported, and the mechanisms are not well understood. There are conflicting reports from retrospective studies on the incidence of pregnancy and neonatal adverse outcomes, including low birth weight and increased congenital anomalies.

Intracytoplasmic Sperm Injection for Male Factor Infertility

Intracytoplasmic sperm injection is performed in cases of MFI when either insufficient numbers of sperm, abnormal sperm morphology, or poor sperm motility preclude unassisted IVF. Fertilization rates represent an intermediate outcome; the final outcome is the number of pregnancies per initiated cycle or per embryo transfer.

Clinical Context and Therapy Purpose

The purpose of IVF with ICSI in individuals with MFI is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is men with MFI.

Interventions

The therapy being considered is IVF with ICSI.

Comparators

The following practice is currently being used to make decisions about infertility: IVF without ICSI.

Outcomes

The general outcomes of interest are live birth rates and infant abnormalities. Follow-up is measured in months to confirm successful birth.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Case Series

The number of pregnancies per cycle and per embryo transfer , reported in relatively large series published in the mid-1990s, ranged between 45% and 50%.[35,36,37,38,39,] At the time, those rates were very competitive with those of standard IVF.

More recently, Borges et al (2017) retrospectively analyzed ICSI outcomes for patients with MFI compared with isolated tubal factor infertility (TFI).[40,] Nine hundred twenty-two ICSI cycles (743 for MFI, 179 for TFI) performed between 2010 and 2016 were identified. No significant differences were observed between the groups for rates of implantation (MFI=35.5% vs. TFI=32%; p=.34), pregnancy (MFI=46.9% vs. TFI=40.9%; p=.184), and miscarriage (MFI 10.3% vs. TFI 10.6%, p=.572); rates remained similar even after women were stratified into groups by age (≤35 years: MFI=531 vs. TFI=112; >35 years: MFI=212 vs. TFI=67). The study was limited by its retrospective design and by the fact that MFI severity could not be determined because patients were not categorized by diagnosis.

Boulet et al (2015) published a large retrospective analysis of the outcomes following ICSI versus standard IVF (data captured from the Centers for Disease Control and Prevention's National Assisted Reproductive Technology Surveillance System from 2008 to 2012).[41,] During that time, there were data on 494,907 fresh IVF cycles. A total of 74.6% of cycles used ICSI, with 92.9% of the cycles involving MFI and 64.5% of the cycles not. Among couples with MFI, there was a statistically significantly lower rate of implantation after ICSI (25.5%) than after standard IVF (25.6%; p=.02); however, this difference between groups was not clinically significant. Rates of clinical intrauterine pregnancy and live birth did not differ significantly between ICSI and standard IVF. In couples without MFI, implantation, clinical pregnancy, and live birth rates were all significantly higher with standard IVF than with ICSI.

Adverse Events

A systematic review and meta-analysis by Massaro et al (2015) examined adverse events related to ICSI and standard IVF without ICSI.[42,] Twenty-two observational studies were included; no RCTs were identified. A meta-analysis of 12 studies found a significantly increased odds of congenital genitourinary malformations in children conceived using ICSI versus standard IVF (pooled OR, 1.27; 95% CI, 1.02 to 1.58; p=.04; I^2=0). Five studies in this analysis were considered at high-risk of bias, and a pooled analysis of the 4 studies considered at low-risk of bias did not determine whether ICSI was associated with a statistically increased odds of genitourinary malformations.

Section Summary: Intracytoplasmic Sperm Injection for Male Factor Infertility

There is a lack of RCTs comparing ICSI with standard IVF. Observational studies have found similar rates of clinical pregnancy and live births after ICSI and standard IVF but those observational studies are subject to limitations (e.g., selection bias). A 2015 meta-analysis of observational studies found a

significantly higher rate of congenital genitourinary malformations in children born after ICSI versus IVF, but there was no significant difference when only studies with low-risk of bias were analyzed. Randomized controlled trials comparing health outcomes after ICSI for MFI with standard IVF would strengthen the evidence base.

Cryopreservation of Testicular Tissue in Adult Men With Azoospermia

Testicular sperm extraction refers to the collection of sperm from testicular tissue in men with azoospermia. Extraction of testicular sperm may be performed during or subsequent to a diagnostic biopsy, specifically for the collection of spermatozoa. Spermatozoa may be isolated immediately and a portion used for an ICSI procedure during oocyte retrieval from the partner, with the remainder cryopreserved. Alternatively, the entire tissue sample can be cryopreserved with portion thawed and sperm isolation performed at subsequent ICSI cycles.

Clinical Context and Therapy Purpose

The purpose of the cryopreservation of testicular tissue as part of ICSI in patients with azoospermia is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is men who are infertile.

Interventions

The therapy being considered is cryopreservation of testicular tissue as part of ICSI.

Comparators

The following practice is currently being used to make decisions about infertility: IVF without cryopreservation of testicular tissue.

Outcomes

The general outcomes of interest are live birth rates and infant abnormalities. Follow-up is measured in months to confirm successful birth.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Case Series

Testicular tissue extraction appears to be a well-established component of the overall ICSI procedure; cryopreservation of either the isolated sperm or the tissue sample eliminates the need for multiple biopsies to obtain fresh tissue in the event of a failed initial ICSI cycle.[43,] However, clinical trials evaluating health outcomes after cryopreservation of testicular tissue in adult men with azoospermia were not identified.

Section Summary: Cryopreservation of Testicular Tissue in Adult Men With Azoospermia

While cryopreservation of testicular tissue in adult men with azoospermia is a well-established component of the ICSI procedure, there is a lack of clinical trials to support this treatment.

Cryopreservation of Testicular Tissue in Prepubertal Boys With Cancer

A potential application of cryopreservation of testicular tissue is its potential to preserve the reproductive capacity in prepubertal boys undergoing cancer chemotherapy; cryopreservation of ejaculate is not an option in these patients.

Clinical Context and Therapy Purpose

The purpose of the cryopreservation of testicular tissue in prepubertal boys with cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is prepubertal boys with cancer.

Interventions

The therapy being considered is the cryopreservation of testicular tissue.

Comparators

The following practice is currently being used to make decisions about infertility: no cryopreservation of testicular tissue.

Outcomes

The general outcomes of interest are live birth rates and infant abnormalities. Follow-up is measured in months to confirm successful birth.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Modeling Studies

It has been hypothesized that reimplantation of the frozen-thawed testicular stem cells will reinitiate spermatogenesis or, alternatively, spermatogenesis could be attempted in vitro, using frozen-thaw spermatogonia. While these strategies have been explored in animals, there are inadequate human studies.[44,45,46,]

Section Summary: Cryopreservation of Testicular Tissue in Prepubertal Boys With Cancer

No clinical trials were identified evaluating the safety and efficacy of cryopreservation of testicular tissue in prepubertal boys undergoing cancer therapy.

Potential Adverse Events to Offspring Conceived Via Assisted Reproduction

Several systematic reviews have addressed the risk of birth defects.[47,48,49,50,] The review with the most data is that by Hansen et al (2013).[49,] They examined 45 cohort studies with outcomes in 92,671 infants born following assisted reproduction and 3,870,760 naturally conceived infants. In a pooled analysis, there was a higher risk of birth defects in infants born using reproductive techniques (relative risk, 1.32; 95% CI, 1.24 to 1.42). The risk of birth defects was also elevated when the analysis was limited to the 6 studies conducted in the U.S. or Canada (relative risk, 1.38; 95% CI, 1.16 to 1.64). Another review, published by Davies et al (2012), included data on 308,974 live births in Australia, 6163 of which used assisted reproductive technologies (ARTs).[50,] There was a higher rate of birth defects after assisted conception (8.3%) compared with births to fertile women who did not use assisted reproduction (5.8%; unadjusted OR, 1.47; 95% CI, 1.33 to 1.62). The risk of birth defects was still significantly elevated but was lower in an analysis that adjusted for other factors that might increase risk (e.g., maternal age, parity, maternal ethnicity, maternal smoking during pregnancy, socioeconomic status; OR, 1.28; 95% CI, 1.16 to 1.41). A more recent review by Elias et al (2020) identified 14 cohort studies examining neonatal outcomes in ART.[51,] The risk of preterm birth was significantly increased among both those undergoing fresh embryo transfer (OR, 1.64; 95% CI, 1.46 to 1.84) and frozen embryo transfer (OR, 1.39; 95% CI, 1.34 to 1.44) compared with spontaneous conceptions. Fresh embryo transfer was also associated with low birth weight (OR, 1.67; 95% CI, 1.52 to 1.85) and small for gestational age (OR, 1.46; 95% CI, 1.11 to 1.92) compared with standard conception while frozen embryo transfer increased the risk of large for gestational age (OR, 1.57; 95% CI, 1.48 to 1.68).

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input

In response to requests, input was received from 4 physician specialty societies and 2 academic medical centers while this policy was under review in 2012. There was general agreement that intracytoplasmic sperm injection and cryopreservation of testicular tissue in adult men with azoospermia as part of an intracytoplasmic sperm injection procedure may be considered medically necessary. Three of 5 reviewers who responded agreed that co-culture of embryos is considered investigational. In addition, 4 of 5 reviewers did not agree that blastocyst transfer is investigational; these reviewers considered blastocyst transfer to be medically necessary to decrease multiple gestations. Three of 6 reviewers agreed that cryopreservation of ovarian tissue or oocytes is investigational. The other 3 thought that cryopreservation of oocytes, but not ovarian tissue, is medically necessary. Clinical input on other policy statements was more variable.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Reproductive Medicine and Society for Assisted Reproductive Technology

In 2019, the American Society for Reproductive Medicine (ASRM) released a 2019 committee opinion on fertility preservation in patients undergoing gonadotoxic therapy.[52,] The committee included several relevant opinions:

- Embryo, oocyte, and ejaculated or testicular sperm cryopreservation remain the principle established modalities for fertility preservation.
- Ovarian tissue cryopreservation is no longer considered experimental and can be used in prepubertal patients or when there is not time for ovarian stimulation.
- Testicular tissue cryopreservation in prepubertal males is still considered experimental and should be conducted under research protocols when no other options are feasible.

ASRM and joint ASRM/Society for Assisted Reproductive Technology (SART) opinions and recommendations on other assisted reproductive technologies are as follows:

- Planned oocyte cryopreservation (OC) for preserving future reproductive potential (2018): The committee states the process is ethical and "serves women's legitimate interests in reproductive autonomy." Women who choose OC should be informed of its efficacy, safety, benefits, and risks, and possible long-term health effects on the child. Providers should also provide their clinic's statistics for successful freeze-thaw and live birth. Women should know that this relatively new technology is still emerging and not all benefits and harms are fully understood.[53,] In 2021, ASRM developed guidelines for the efficacy of OC for donor oocyte in vitro fertilization (IVF) and planned OC.[54,] The following statements were made in the guideline:
  - "There is insufficient evidence to predict live birth rates after planned OC. On the basis of limited data, ongoing and live birth rates appear to be higher for women who undergo planned OC at younger versus older ages. There are no significant differences in per transfer pregnancy rates with cryopreserved versus fresh donor oocytes. Neonatal outcomes appear similar with cryopreserved oocytes. There is a pressing need for additional data about long-term outcomes and cumulative live birth rates with cryopreserved oocytes, after planned OC and use of cryopreserved donor eggs."
- Assisted hatching (2022): "There is moderate evidence that assisted hatching does not significantly improve live birth rates in fresh assisted reproductive technology cycles and insufficient evidence for the benefit of assisted hatching in patients with poor prognosis or undergoing frozen embroyo transfer cycles."[55,]
- Blastocyst transfer (2013; reaffirmed in 2018): "Evidence supports blastocyst transfer in 'good prognosis' patients."[56,53,]

In 2020, ASRM developed joint guidelines with the American Urological Association (AUA) for male infertility diagnosis and treatment including recommendations for intracytoplasmic sperm injection (ICSI).[57,58,] Based on expert opinion, patients with low total motile sperm count should be advised to consider IVF with ICSI.

American College of Obstetricians and Gynecologists

In 2014, the American College of Obstetricians and Gynecologists endorsed the 2013 ASRM-SART joint guidelines on mature OC.[59,] The endorsement was affirmed in 2020.

American Society of Clinical Oncology

In 2018, the American Society of Clinical Oncology updated its 2013 guidelines (with no changes to its recommendations) on fertility preservation for patients with cancer.[60,61,] The guidelines included the following recommendations for males and females, respectively.

- "Recommendation 2.1. Sperm cryopreservation: Sperm cryopreservation is effective, and health care providers should discuss sperm banking with postpubertal males receiving cancer treatment.
- Recommendation 2.2. Hormonal gonad protection: Hormonal therapy in men is not successful in preserving fertility. It is not recommended.

- Recommendation 2.3. Other methods to preserve male fertility: Other methods, such as testicular tissue cryopreservation and reimplantation or grafting of human testicular tissue, should be performed only as part of clinical trials or approved experimental protocols..."
- "Recommendation 3.1. Embryo cryopreservation: Embryo cryopreservation is an established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization.
- Recommendation 3.2. 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..."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Ovarian tissue cryopreservation			
NCT02646384	Ovarian Tissue Freezing For Fertility Preservation In Girls Facing A Fertility Threatening Medical Diagnosis Or Treatment Regimen	100	Jan 2026
NCT02846064	Development of Ovarian Tissue Autograft in Order to Restore Ovarian Function	50	Oct 2022
Intracytoplasmic Sperm Injection			
NCT03298633	Intracytoplasmic Sperm Injection (ICSI) Versus Conventional in Vitro Fertilization (IVF) in Couples With Non-severe Male Infertility: a Randomized Controlled Trial	2346	Jul 2022
NCT04128904	In Vitro Fertilisation Versus Intracytoplasmic Sperm Injection in Patients Without Severe Male Factor Infertility (INVICSI): a Randomised, Controlled, Multicentre Trial	824	Dec 2024
Testicular tissue cryopreservation			
NCT02872532	Testicular Tissue Cryopreservation for Fertility Preservation in Males Facing Fertility Threatening Diagnoses or Treatment Regimens	100	Dec 2025
NCT02972801	Testicular Tissue Cryopreservation for Fertility Preservation in Patients Facing Infertility-causing Diseases or Treatment Regimens	1000	Jan 2025
Unpublished	In Vitro Fertilisation Versus Intracytoplasmic Sperm Injection in Patients Without Severe Male Factor Infertility (INVICSI): a Randomised, Controlled, Multicentre Trial	784	Dec 2024
Blastocyst transfer			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03152643	Cumulative Live Birth Rates After Cleavage-stage Versus Blastocyst-stage Embryo Transfer: A Multicenter, Prospective, Randomized Controlled Trial	992	Feb 2022
NCT03764865	Day 3 vs Day 5 Embryo Transfer for Patients With Low Embryo Numbers Going Through in Vitro Fertilization	10	Feb 2022
Oocyte cryopreservation			
NCT04616417	Investigational Oocyte Cryopreservation for Medical and Non Medical Indications	50	Jul 2030

NCT: national clinical trial.

Appendix 1

Table SR1. Comparison of Trials/Studies Included in SR & M-A

Study	Ní Dhonnabháin et al (2022)[15],
Embryo cryopreservation	
Alvarez and Ramanathan (2018)	●
Babb (2012)	●
Barcroft (2013)	●
Dolmans (2015)	●
Johnson (2013)	●
Moravek (2018)	●
Nordan (2020)	●
Oktay (2015)	●
Robertson (2011)	●
Oocyte cryopreservation	
Alvarez and Ramanathan (2018)	●
Cobo (2018)	●
Diaz-Garcia (2018)	●
Druckenmiller (2016)	●
Garcia-Velasco (2013)	●
Khiat (2020)	●
Martinez (2014)	●
Specchia (2019)	●
Ovarian tissue cryopreservation	
Biasin (2015)	●
Diaz-Garcia (2018)	●
Dittrich (2015)	●
Dolmans (2013)	●

Study	Ní Dhonnabháin et al (2022)[15,]
Donnez (2013)	●
Dueholm Hjorth (2013)	●
Fabbri (2014)	●
Fabregues (2017)	●
Hoekman (2020)	●
Hulsbosch (2018)	●
Imbert (2014)	●
Jadoul (2017)	●
Jensen (2015)	●
Meirow (2016)	●
Oktay (2016)	●
Oktay and Oktem (2010)	●
Poirot (2019)	●
Pretalli (2019)	●
Ruan (2020)	●
Schmidt (2011)	●
Shapira (2020)	●
Silber (2018)	●
Tanbo (2015)	●
Van der Ven (2016)	●

M-A: meta-analysis; SR: systematic review.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Reason for cryopreservation if applicable (e.g., cancer with plans for radiation or chemotherapy)
  - Previous history of fertility/infertility
  - Previous treatment plan and response
  - Previous procedures to address infertility
  - Request for procedure per ongoing treatment plan
- Laboratory report including: specific name and test requested

Post Service (in addition to the above, please include the following):

- Operative/procedure notes (if applicable)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0255U	Andrology (infertility), sperm-capacitation assessment of ganglioside GM1 distribution patterns, fluorescence microscopy, fresh or frozen specimen, reported as percentage of capacitated sperm and probability of generating a pregnancy score
	54500	Biopsy of testis, needle (separate procedure)
	54505	Biopsy of testis, incisional (separate procedure)
	54800	Biopsy of epididymis, needle
	55400	Vasovasostomy, vasovasorrhaphy
	55870	Electroejaculation
	58321	Artificial insemination; intra-cervical
	58322	Artificial insemination; intra-uterine
	58323	Sperm washing for artificial insemination
	58970	Follicle puncture for oocyte retrieval, any method
	58974	Embryo transfer, intrauterine
	58976	Gamete, zygote, or embryo intrafallopian transfer, any method
	89240	Unlisted miscellaneous pathology test
	89250	Culture of oocyte(s)/embryo(s), less than 4 days;
	89251	Culture of oocyte(s)/embryo(s), less than 4 days; with co-culture of oocyte(s)/embryos
	89253	Assisted embryo hatching, microtechniques (any method)
	89254	Oocyte identification from follicular fluid
	89255	Preparation of embryo for transfer (any method)
	89257	Sperm identification from aspiration (other than seminal fluid)
	89258	Cryopreservation; embryo(s)
	89259	Cryopreservation; sperm
	89260	Sperm isolation; simple prep (e.g., sperm wash and swim-up) for insemination or diagnosis with semen analysis
	89261	Sperm isolation; complex prep (e.g., Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis
	89264	Sperm identification from testis tissue, fresh or cryopreserved
	89268	Insemination of oocytes
	89272	Extended culture of oocyte(s)/embryo(s), 4-7 days

Type	Code	Description
	89280	Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes
	89281	Assisted oocyte fertilization, microtechnique; greater than 10 oocytes
	89335	Cryopreservation, reproductive tissue, testicular
	89337	Cryopreservation, mature oocyte(s)
	89342	Storage (per year); embryo(s)
	89343	Storage (per year); sperm/semen
	89344	Storage (per year); reproductive tissue, testicular/ovarian
	89346	Storage (per year); oocyte(s)
	89352	Thawing of cryopreserved; embryo(s)
	89353	Thawing of cryopreserved; sperm/semen, each aliquot
	89354	Thawing of cryopreserved; reproductive tissue, testicular/ovarian
	89356	Thawing of cryopreserved; oocytes, each aliquot
	89398	Unlisted reproductive medicine laboratory procedure
HCPCS	S4011	In vitro fertilization; including but not limited to identification and incubation of mature oocytes, fertilization with sperm, incubation of embryo(s), and subsequent visualization for determination of development
	S4013	Complete cycle, gamete intrafallopian transfer (GIFT), case rate
	S4014	Complete cycle, zygote intrafallopian transfer (ZIFT), case rate
	S4015	Complete in vitro fertilization cycle, not otherwise specified, case rate
	S4016	Frozen in vitro fertilization cycle, case rate
	S4017	Incomplete cycle, treatment cancelled prior to stimulation, case rate
	S4018	Frozen embryo transfer procedure cancelled before transfer, case rate
	S4020	In vitro fertilization procedure cancelled before aspiration, case rate
	S4021	In vitro fertilization procedure cancelled after aspiration, case rate
	S4022	Assisted oocyte fertilization, case rate
	S4023	Donor egg cycle, incomplete, case rate
	S4025	Donor services for in vitro fertilization (sperm or embryo), case rate
	S4026	Procurement of donor sperm from sperm bank
	S4027	Storage of previously frozen embryos
	S4028	Microsurgical epididymal sperm aspiration (MESA)
	S4030	Sperm procurement and cryopreservation services; initial visit
	S4031	Sperm procurement and cryopreservation services; subsequent visit
	S4035	Stimulated intrauterine insemination (IUI), case rate
	S4037	Cryopreserved embryo transfer, case rate
	S4040	Monitoring and storage of cryopreserved embryos, per 30 days
	S4042	Management of ovulation induction (interpretation of diagnostic tests and studies, nonface-to-face medical management of the patient), per cycle

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
08/31/2015	BCBSA Medical Policy adoption
11/01/2016	Policy revision without position change
10/01/2017	Policy revision without position change

Effective Date	Action
10/01/2018	Policy revision without position change
12/01/2019	Policy revision without position change
03/01/2020	Coding update
11/01/2020	Annual review. No change to policy statement. Literature review updated.
01/01/2021	Coding update
11/01/2021	Annual review. No change to policy statement. Literature review updated.
11/01/2022	Annual review. No change to policy statement. Policy guidelines and literature review updated.
10/01/2023	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Reproductive Techniques 4.02.04 **Policy Statement:** I. The following reproductive techniques may be considered **medically necessary** for **any** of the following: A. Blastocyst transfer B. Cryopreservation of testicular tissue in adult men with azoospermia as part of an intracytoplasmic sperm injection procedure C. Intracytoplasmic sperm injection for male factor infertility D. Cryopreservation of embryos, oocytes, ovarian tissue, sperm or testicular tissue (in post-pubertal men) when there is risk of iatrogenic sterilization from chemotherapy or similar medically necessary medical or surgical treatment when **all** of the following criteria are met: 1. No prior elective sterilization 2. No known infertility already present 3. Post-pubertal and less than 45 years of age (or cryopreservation is no longer desired if younger than age 45) II. The following reproductive techniques are considered **investigational**: A. Co-culture of embryos B. Cryopreservation of testicular tissue in prepubertal boys or ovarian tissue in prepubertal girls C. Intracytoplasmic sperm injection (ICSI) in the absence of male factor infertility	**Reproductive Techniques 4.02.04** **Policy Statement:** I. The following reproductive techniques may be considered **medically necessary** for **any** of the following: A. Blastocyst transfer B. Cryopreservation of testicular tissue in adult men with azoospermia as part of an intracytoplasmic sperm injection procedure C. Intracytoplasmic sperm injection for male factor infertility D. Cryopreservation of embryos, oocytes, ovarian tissue, sperm or testicular tissue (in post-pubertal men) when there is risk of iatrogenic sterilization from chemotherapy or similar medically necessary medical or surgical treatment when **all** of the following criteria are met: 1. No prior elective sterilization 2. No known infertility already present 3. Post-pubertal and less than 45 years of age (or cryopreservation is no longer desired if younger than age 45) II. The following reproductive techniques are considered **investigational**: A. Co-culture of embryos B. Cryopreservation of testicular tissue in prepubertal boys or ovarian tissue in prepubertal girls C. Intracytoplasmic sperm injection (ICSI) in the absence of male factor infertility