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Reproductive Techniques and Immunotherapy for Recurrent Fetal Loss

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: Effective for policies issued after January 1, 2019, **Illinois** law (215 ILCS 5/356z.29) requires coverage and reimbursement for standard fertility preservation services when a necessary medical treatment may directly or indirectly cause iatrogenic infertility to a member. “Standard fertility preservation services” means procedures based upon current evidence-based standards of care established by the American Society for Reproductive Medicine, the American Society for Clinical Oncology, or other national medical associations that follow current evidence-based standards of care.

EXCEPTION: For policies issued on or after January 1, 2022, **Illinois** law (215 ILCS 5/356m; Public Act 102-0170) states infertility means a disease, condition, or status characterized by: 1) a failure to establish

a pregnancy or to carry a pregnancy to live birth after 12 months of regular, unprotected sexual intercourse if the woman is 35 years of age or younger, or after 6 months of regular, unprotected sexual intercourse if the woman is over 35 years of age; conceiving but having a miscarriage does not restart the 12-month or 6-month term for determining infertility; 2) a person's inability to reproduce either as a single individual or with a partner without medical intervention; or 3) a licensed physician's findings based on a patient's medical, sexual, and reproductive history, age, physical finding, or diagnostic testing.

EXCEPTION: For policies issued or renewed on or after January 1, 2024, **Montana** law (Senate Bill 516, Section 2-18-704) requires medically necessary coverage of standard fertility preservation services for individuals diagnosed with cancer, and the standard of care involves medical treatment that may directly or indirectly cause iatrogenic infertility. For the purposes of this mandate, iatrogenic infertility means an impairment of fertility caused directly or indirectly by surgery, chemotherapy, radiation, or other medical treatment; medical treatment that may directly or indirectly cause iatrogenic infertility means treatment with a potential side effect of impaired fertility, as established by a national association of practitioners of reproductive medicine or clinical oncology; and standard fertility preservation services means procedures consistent with established medical practices and professional guidelines published by a national association for practitioners of reproductive medicine or clinical oncology.

EXCEPTION: For policies delivered, issued for delivery or renewed on or after January 1, 2024, **Texas** law (TIC Chapter 1366, Subchapter C, §§1366.101 – 1366.103), mandates coverage of fertility preservation services to an individual who will receive a medically necessary treatment for cancer, including surgery, chemotherapy, or radiation, that the American Society of Clinical Oncology or the American Society for Reproductive Medicine has established that may directly or indirectly cause impaired fertility. The fertility preservation services as described by this mandate must be standard procedures to preserve fertility consistent with established medical practices or professional guidelines published by the American Society of Clinical Oncology or the American Society for Reproductive Medicine. For the purposes of this mandate, fertility preservation services means the collection and preservation of sperm, unfertilized oocytes and ovarian tissue, and does **NOT** include the storage of such unfertilized genetic materials.

EXCEPTION: For Oklahoma only: For policies (Fully Insured PPO/HMO, Small Group, Mid-Market, Large Group, Municipalities/Schools, State Employee Plan) offered, issued, or renewed on or after January 1, 2025, SB 1334 (Section 6060.8b of Title 36) requires coverage for standard fertility preservation services, only for individuals diagnosed with cancer and who are within reproductive age (the age range in which an individual is deemed fertile as established by the American Society of Clinical Oncology and/or the American Society for Reproductive Medicine), when a medically necessary treatment may directly or indirectly cause iatrogenic infertility. Iatrogenic infertility means an impairment of fertility caused directly or indirectly by surgery, chemotherapy, radiation, or other medical treatment with a potential side effect of impaired fertility as established by the American Society of Clinical Oncology or the American Society for Reproductive Medicine. Standard fertility preservation services mean oocyte and sperm preservation procedures, including ovarian tissue, sperm, and oocyte cryopreservation, that are consistent with established medical practices or professional guidelines published by the American Society of Clinical Oncology or the American Society for Reproductive Medicine; provided, however, standard fertility preservation services shall not include storage.

EXCEPTION: For members residing in the state of Maine, 24-A s 4320-U requires a carrier offering a health plan in this State shall provide coverage to an enrollee for fertility diagnostic care; for fertility treatment if the enrollee is a fertility patient; and for fertility preservation services. Carriers may not: use any prior diagnosis or prior fertility treatment as a basis for excluding, limiting or otherwise restricting the availability of coverage required by this section; impose any limitations on coverage for any fertility services based on an enrollee's use of donor gametes, donor embryos or surrogacy; not impose different limitations on coverage for, provide different benefits to or impose different requirements on a class of persons protected under Title 5, chapter 337 than those of other enrollees. This does not require coverage for any experimental infertility procedure; or any nonmedical costs related to donor gametes, donor embryos or surrogacy. This applies to Fully Insured Small Group, Mid-Market, Large Group, Student PPO, HMO, POS, EPO.

Coverage

NOTE 1: Carefully check the member's benefit plan, summary plan description or contract for language specific to infertility services. IF infertility services are determined to be eligible for member benefits, then the following services that are listed as medically necessary should be considered for benefit coverage.

NOTE 2: This medical policy does NOT address Gender Reassignment Services (Transgender Services). This medical policy IS NOT TO BE USED for Gender Reassignment Services. Refer to SUR717.001, Gender Assignment Surgery and Gender Reassignment Surgery with Related Services.

Reproductive Techniques
NOTE 3: The majority of procedures describing the various steps in infertility diagnosis and treatment are longstanding. Only newly emerging and/or unproven reproductive technology services will be discussed in this medical policy.

The following reproductive techniques for diagnosing or treating infertility **are considered experimental, investigational, and/or unproven**:

- Assisted hatching;
- Co-culture of embryos;
- Computer-assisted sperm analysis (CASA);
- Cryopreservation, storage, thawing and re-transplantation of ovarian tissue or immature oocytes and associated in vitro maturation;
- Cryopreservation, storage, thawing and re-transplantation of testicular tissue;
- Hemizona assay (HZA);
- Hyaluronan binding assay (HBA);
- Intracytoplasmic sperm injection (ICSI) in the absence of male factor infertility;
- Immune treatments (e.g., leukocyte immunization, intravenous immunoglobulins, peri-implantation glucocorticoids, anti-tumor necrosis factor agents);
- Immunological testing (e.g., an6 42tiprothrombin antibodies, circulating natural killer cell measurement, antiphospholipid antibodies);

- Inhibin B testing;
- Reactive oxygen species (ROS) test;
- Sperm acrosome reaction test;
- Sperm DNA integrity/fragmentation tests;
- Sperm penetration assays;

Immunotherapy for Recurrent Fetal Loss
Immunologic-based therapies to avoid recurrent spontaneous abortion are **considered experimental, investigational, and/or unproven**. Such therapies include, but are not limited to:

- Immunotherapy utilizing paternal leukocytes;
- Immunotherapy utilizing seminal plasma;
- Immunotherapy utilizing trophoblastic membranes; and/or
- Therapy utilizing intravenous immune globulin.

NOTE 4: Refer to Medical Policy RX504.003 for additional information on intravenous immunoglobulin use.

Policy Guidelines

NOTE: Member contract benefits may vary. **CHECK CONTRACTS FOR COVERAGE ELIGIBILITY** of services related to reproductive technologies/techniques, including but not limited to the following:

- Reversal of voluntary sterilization;
- Payment for medical services or supplies rendered to a surrogate for purposes of childbirth;
- Costs associated with cryopreservation and storage of sperm, oocytes, and embryos;
- Costs associated with the procurement of sperm, or harvesting of oocytes and embryos from a donor; and
- Living and/or travel expenses.

Description

According to a 2023 Practice Committee of the American Society for Reproductive Medicine (58), “Infertility is a disease, condition, or status characterized by any of the following:

- The inability to achieve a successful pregnancy based on a patient’s medical, sexual, and reproductive history, age, physical findings, diagnostic testing, or any combination of those factors.
- The need for medical intervention, including, but not limited to, the use of donor gametes or donor embryos in order to achieve a successful pregnancy either as an individual or with a partner.
- In patients having regular, unprotected intercourse and without any known etiology for either partner suggestive of impaired reproductive ability, evaluation should be initiated at

12 months when the female partner is under 35 years of age and at 6 months when the female partner is 35 years of age or older."

The majority of procedures describing the various steps in infertility diagnosis and treatment are longstanding. Only newly emerging and/or unproven reproductive technology services will be discussed in this medical policy.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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. RCTs 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.

The majority of procedures describing the various steps in infertility diagnosis and treatment are longstanding. Only newly emerging and/or unproven reproductive technology services will be discussed in this rationale.

Assisted Hatching

Systematic Reviews

A Cochrane review and meta-analysis by Carney et al. (2012) identified 31 randomized controlled trials (RCTs) evaluating assisted hatching (N=5728). (1) 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

Some additional 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). (2) 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). (3) 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=0.08). 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=0.03). There was no significant between group difference in clinical pregnancy rate among women younger than 38 years old. Neither trial reported live birth rates.

Curfs et al. (2023) assessed subfertile couples from the Netherlands who had either at least 2 consecutive unsuccessful in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) embryo transfers (4) Participants were randomized either to the assisted hatching arm (n=297 couples) or the control arm (IVF alone; n=295 couples), and allocation was concealed from participants and physicians and staff involved in the embryo transfer. Overall, there was no statistically significant difference in the cumulative live birth rate between assisted hatching group (77 live births; 25.9%) and the IVF only group (68 live births; 23.1%) (relative risk, 1.125; 95% CI, 0.847 to 1.494; p=.416).

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 non assisted 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% vs. 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).

Practice Guidelines and Position Statements

Updated American Society for Reproductive Medicine and Society for Assisted Reproductive Technology (ASRM) guidelines on the role of assisted hatching in IVF that were published in 2022 stated: "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 embryo transfer cycles." (8)

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 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).

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. (9-14) For example, Wetzels et al. (1998) reported on an RCT that assigned IVF treatments to co-culture with human fibroblasts or no culture. ((14) 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 a novel co-culture technique involving autologous endometrial cell co-culture. (15) 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.

Computer-Assisted Sperm Analysis (CASA)

Practice Guidelines and Position Statements

According to the American Urological Association (AUA) (2010), CASA instruments are most useful clinically for assessing sperm motility and motion parameters, such as velocity or speed and head movement, which may be important factors in determining sperm fertility potential. The AUA recommendation in regard to CASA indicates that specialized tests on semen are not required for diagnosis of male infertility. (16)

Updated AUA guidelines on the diagnosis and treatment of infertility in men that were published in conjunction with the American Society for Reproductive Medicine (ASRM) in 2020 (amended 2024), do not mention CASA. (17)

Cryopreservation, Storage, Thawing and Re-transplantation of Ovarian Tissue

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). (18) 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 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 SR1. Comparison of Trials/Studies Included in SR & M-A

Study	Ní Dhonnabháin et al. (2022) (18)
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)	●
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)	●

Table 1. SR & M-A Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Ní Dhonnabháin et al. (2022) (18)	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) (29)			
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 and a systematic review assessing the return of ovarian function using this technique. (19-21) There are also case

series and a systematic review of cohort studies and case series/case reports describing live births using cryopreserved ovarian tissue. (22-25) However, in general, the technique is not standardized and insufficiently studied to determine the success rate. (25, 26) 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. (27) 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.

Systematic Reviews

A systematic review by Dufour et al. (2025) evaluated the outcomes of oocyte cryopreservation in women with hematological malignancies undergoing chemotherapy, comparing these to outcomes in patients with other cancers or healthy controls. (28) The review included 22 studies (14 cohort studies, 2 case-control studies, and 6 case reports) comprising 858 women with hematological cancers and 2,676 comparators (women with other cancers or healthy controls). The primary outcome, mean number of mature oocytes that were frozen per stimulation cycle, did not significantly differ between groups (mean difference [MD], 0.11; 95% CI, -0.10 to 0.33). Data on fertilization, embryo development, and pregnancy outcomes were limited and inconsistently reported across studies.

A systematic review by Ní Dhonnabháin et al. (2022) is introduced above (see Table 1 and SR1 above). 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 versus cryopreserved embryos. Authors noted heterogeneity with regard to surgical techniques across centers.

The American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology (2013) updated their joint guidelines on mature oocyte cryopreservation. (29) 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, patients with cancer). 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. (30) 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).

Practice Guidelines and Position Statements

In 2019, the ASRM released a committee opinion on fertility preservation in patients undergoing gonadotoxic therapy. (31) The committee included several relevant opinions including that “Ovarian tissue cryopreservation is no longer considered experimental and can be used in prepubertal patients or when there is not time for ovarian stimulation.” However, “data on the efficacy, safety and reproductive outcomes after ovarian tissue cryopreservation are still limited.” Given the current body of literature, ovarian tissue cryopreservation should be considered a procedure with limited effectiveness that should only be offered to carefully selected patients.

ASRM and joint ASRM/SART opinions and recommendations on other assisted reproductive technologies are as follows:

Planned oocyte cryopreservation (OC) for preserving future reproductive potential (2018, updated 2024): The committee states that "for individuals attempting to extend their reproductive window in the face of expected reproductive aging, and for transgender men who will experience the loss of female gametes in the process of transitioning from female to male, advanced OC is ethically permissible....[and] serves an legitimate interests in reproductive

autonomy." (32) Individuals who choose planned 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. Individuals should know that this relatively new technology is still emerging and not all benefits and harms are fully understood. In 2021, ASRM developed guidelines for the efficacy of OC for donor oocyte in vitro fertilization (IVF) and planned OC. (33) 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."

Both of these guidelines on OC were endorsed by the American College of Obstetricians and Gynecologists in 2023. (34)

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.

Cryopreservation of Testicular Tissue

Adult Men with Azoospermia

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

Case Series

Testicular sperm extraction appears to be a well-established component of the overall ICSI procedure; cryopreservation of either the isolated sperm of the tissue sample eliminates the need for multiple biopsies to obtain fresh tissue in the event of a failed initial ICSI cycle. (35) However, clinical trials evaluating health outcomes after cryopreservation of testicular tissue in adult men with azoospermia were not identified.

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; the typical cryopreservation of an ejaculate is not an option in these patients.

Modeling Studies

It is 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. (36-38)

Practice Guidelines and Position Statements

In 2025, the American Society of Clinical Oncology updated its 2013 and 2018 guidelines on fertility preservation for patients with cancer. (39-41) The guidelines included the following recommendations for males.

"Recommendation 3.4. 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...."

Additionally, the ASRM released a committee opinion in 2019 on fertility preservation in patients undergoing gonadotoxic therapy. (31) The committee included several relevant opinions including that "Testicular tissue cryopreservation in prepubertal males is still considered experimental and should be conducted under research protocols when no other options are feasible."

Hemizona Assay

Practice Guidelines and Position Statements

According to the AUA (2010), sperm function can be evaluated using human zona pellucida binding tests. In some cases, these tests have detected a probable cause for low fertilization rates or failed IVF. The AUA recommendation in regard to HZA indicates that specialized tests on semen are not necessary for the routine evaluation of men with infertility. (16)

Updated AUA guidelines on the diagnosis and treatment of infertility in men that were published in conjunction with the ASRM in 2020 (amended 2024), do not mention HZA. (17)

Hyaluronan Binding Assay (HBA)

Practice Guidelines and Position Statements

The ASRM committee opinion on the evaluation of the infertile male (2015) considers the HBA test to have a very limited role in the evaluation of male infertility as it has limited clinical utility and typically does not affect treatment. (42)

Updated AUA guidelines on the diagnosis and treatment of infertility in men that were published in conjunction with the ASRM in 2020, do not mention HBA testing. (17)

Intracytoplasmic Sperm Injection (ICSI) in the Absence of Male Factor Infertility
ICSI is performed in cases of male factor infertility (MFI) when either insufficient numbers of sperm, abnormal morphology, or poor motility preclude unassisted IVF.

Case Series
The number of pregnancies per cycle and per embryo transfers, reported in relatively large series published in the mid-1990s, ranged between 45% and 50%. (43-47) At the time, those rates were very competitive with those of the standard IVF.

More recently, Borges et al. (2017) retrospectively analyzed ICSI outcomes for patients with MFI compared with isolated tubal factor infertility (TFI). (48) 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=0.34), pregnancy (MFI=46.9% vs TFI=40.9%, p=0.184), and miscarriage (MFI 10.3% vs TFI 10.6%, p=0.572); 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 Preventions' National Assisted Reproductive Technology Surveillance System from 2008 to 2012). (49) 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 male factor infertility and 64.5% of the cycles not involving male factor infertility. Among couples with male factor infertility, there was a statistically significantly lower rate of implantation after ICSI (25.5%) than after standard IVF (25.6%) (p=0.02); however, the degree of difference between groups may not be clinically significant. Rates of clinical intrauterine pregnancy and live birth did not differ significantly between ICSI and standard IVF. In couples without male factor infertility, 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. (50) 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.

Immune Treatments (e.g., leukocyte immunization, intravenous immunoglobulins) and Immunological Testing (e.g. antiprothrombin antibodies, circulating natural killer cell measurement, antiphospholipid antibodies)

Advances in reproductive medicine have increased the success of fertility treatments. Nevertheless, some women experience recurrent implantation failure (RIF) after IVF or recurrent pregnancy loss (RPL). Imbalances in the immune system and failure to achieve immune tolerance to the fetus have been implicated as potentially modifiable causes of idiopathic RIF and RPL. As such, women are increasingly being treated with immunomodulatory agents in an attempt to achieve a successful pregnancy.

Specific information related to immunoglobulin (Ig) therapy is found on medical policy RX504.003.

<u>Practice Guidelines and Position Statements</u>

In 2016, ASRM published a guideline addressing the role of immunotherapy in in-vitro fertilization (IVF)/assisted reproductive technology (ART). The guideline offered the following guidance (51):

- Corticosteroids during ovarian stimulation/ Peri-implantation corticosteroids:
    - There is good evidence to recommend against the routine use of corticosteroids during stimulation to improve the outcome of live birth in ART cycles in the general population. (From principally Level-I studies of Good quality). (Grade A).
    - There is good evidence to recommend against the routine use of corticosteroids during the implantation window to improve the outcome of live birth in ART cycles in the general population. (From principally Level-I studies of Good quality). (Grade A).
    - Additional studies are needed to determine if there are any subpopulations where benefit may exist but are not proven.
- Granulocyte Colony–stimulating Factor (G-CSF) and Granulocyte/Macrophage Colony–stimulating Factor (GM-CSF):
    - There is insufficient evidence to recommend for or against local G-CSF to improve endometrial thickness in women with thin endometrium or clinical pregnancy rates with IVF. (From principally Level-I studies of Good quality and Level-II studies of Low and Good quality with inconsistent findings). (Grade C).
    - There is insufficient evidence to recommend for or against G-CSF or GM-CSF administered locally or systemically to improve IVF outcomes. (From principally

Level-I studies of Good quality and Level-II studies of Low and Good quality with inconsistent findings). (Grade C).

- Intravenous Fat Emulsions:
    - There is insufficient evidence to routinely recommend intravenous fat emulsions for infertile women pursuing IVF. (From one Level-I study of High quality and one Level-II study of Low quality). (Grade C).
    - Additional studies are needed to identify populations where benefits may exist but are not proven.
- Intravenous Immunoglobulin (IVIG):
    - There is insufficient evidence to recommend IVIG administration as part of IVF to improve IVF outcomes. (From two Level-I, but underpowered, studies, one good quality and one Low quality). (Grade C).
    - Subpopulations that benefit from treatment may exist, but additional high-quality experimental RCTs are needed to define indications and explore risks and benefits.
- Peripheral Mononuclear Cells:
    - There is insufficient evidence to recommend intrauterine infusion of autologous peripheral mononuclear cells prior to ET to improve IVF outcome. (From one Level-I study of Low quality and one Level-II study of Low Quality. (Grade C).
- Seminal Plasma:
    - There is fair evidence that seminal plasma insemination as part of IVF improves clinical pregnancy rate (From Level-I studies of Good and High quality). (Grade B) However, there is fair evidence that it does not improve ongoing pregnancy or live-birth rates. (From underpowered Level I studies of good quality). (Grade B).
- Spermatozoa, Antibody-free Preparation:
    - There is insufficient evidence to support the recommendation either for or against antibody-free preparation of spermatozoa in improving IVF outcomes. (From one Level-I study of Low quality and one Level-II study of Low quality). (Grade C). This procedure has been rendered obsolete by the use of ICSI.
- Adalimumab (tumor necrosis factor alpha blocking antibody):
    - There is insufficient evidence to recommend adalimumab treatment to improve IVF outcome. (From Level-II studies of Low quality). (Grade C).
- Tacrolimus (an immunosuppressive drug that inhibits antigen-induced lymphocytic proliferation, cytotoxic T-cell formation, IL-2 receptor expression, and the production of IL-2 and interferon-gamma:
    - There is insufficient evidence to recommend tacrolimus to improve IVF-ET outcome. (From a single Level-II study of Low quality). (Grade C).

Based on the quality of the literature, the strength of recommendation includes the following graded recommendations:

- Grade A: There is good evidence to support the recommendations, either for or against. (From consistent Level-I studies of High quality [Grade A])
- Grade B: There is fair evidence to support the recommendations, either for or against. (From principally Level-II studies of Good quality [Grade B])

- Grade C: There is insufficient evidence to support the recommendations, either for or against. (From Level-II studies of Low quality [Grade C], or when there are conflicting data from studies of Good quality)

A 2019 joint committee opinion from the American College of Obstetricians and Gynecologists and the ASRM classify "immunologic testing" as an example of infertility testing that should not be routinely ordered. (52)

A committee opinion from the ASRM (2021) included immunologic testing as "not recommended as part of the routine infertility evaluation without other clinical indications." (53)

Inhibin B Testing

Practice Guidelines and Position Statements

The ASRM committee opinion on the evaluation of the infertile male (2015) states, "Serum inhibin B concentration has been proposed as a marker for spermatogenesis. Inhibin B levels are significantly lower in infertile men than in fertile men and correlate better than FSH levels with sperm parameters. Given the significantly greater cost of measuring inhibin B, FSH currently remains the preferred test for screening purposes." (42)

Updated AUA guidelines on the diagnosis and treatment of infertility in men that were published in conjunction with the ASRM in 2020 (amended 2024) do not mention serum inhibin B testing. (17)

A committee opinion from the ASRM (2021) concluded that inhibin B is not a helpful tool to assess ovarian reserve and therefore it is not recommended. (53)

Reactive Oxygen Species (ROS) Test

Practice Guidelines and Position Statements

According to the AUA (2010), "Controversy exists regarding the best method of testing for ROS; role of excess ROS in both natural conception and assisted reproductive technology; and whether therapies are effective at reducing seminal ROS and improving fecundity. Direct ROS testing is limited by the short duration of activity of the molecules. Seminal ROS is currently assessed by indirect testing methods that measure the products of ROS. Studies correlating seminal ROS levels to pregnancy outcomes are extremely limited or contradictory. Most studies are limited by lack of controls and the lack of standardized testing methods for ROS makes comparison between studies difficult. The literature regarding ROS therapies is flawed by the paucity of randomized controlled trials and the lack of standardized type and duration of treatment. Review of the current literature reveals an inconsistent effect of therapies aimed at reducing seminal ROS upon clinical parameters/outcomes. As a result, routine clinical testing and treatment of ROS are not indicated at this time. The recommendation states: "Reactive oxygen species testing has not been shown to be predictive of pregnancy independent of routine semen parameters nor are there any proven therapies to correct an abnormal test

result. There is insufficient data to support the routine use of reactive oxygen species testing in the management of the male partner of an infertile couple." (16)

Additionally, the ASRM committee opinion on the evaluation of the infertile male (2015) considers ROS to have a "very limited role in the evaluation of male infertility." (42)

Updated AUA guidelines on the diagnosis and treatment of infertility in men that were published in conjunction with the ASRM in 2020, do not mention ROS testing. (17)

Sperm Acrosome Reaction (AR) Test

Practice Guidelines and Position Statements

According to the AUA (2010), less commonly used specialized tests such as the acrosome reaction test are important investigative tools but are not necessary for the routine evaluation of men with infertility. (16)

An ASRM committee opinion (2015) on the diagnostic evaluation for infertility in men states that sperm acrosome reaction tests have a very limited role in the evaluation of male fertility because they have limited clinical utility and typically do not affect treatment. (42)

Updated AUA guidelines on the diagnosis and treatment of infertility in men that were published in conjunction with the ASRM in 2020 (amended 2024), do not mention AR testing. (17)

Sperm DNA Integrity/Fragmentation Tests

In 2017, the Society for Translational Medicine published clinical practice guidelines for sperm DNA fragmentation testing in male infertility. The guidelines offer the following recommendation (54)

- Unexplained infertility/IUI failure/RPL
    - Sperm DNA fragmentation (SDF) testing should be offered to infertile couples with RPL or prior to initiating IUI (grade C recommendation)
    - Early IVF or ICSI may be an alternative to infertile couple with RPL or failed IUI (grade C recommendation)
- IVF and/or ICSI failure
    - SDF testing is indicated in patients with recurrent failure of assisted reproduction (grade C recommendation)
    - The use of testicular sperm rather than ejaculated sperm may be beneficial in men with oligozoospermia, high SDF and recurrent IVF failure (grade B–C recommendation)
    - Borderline abnormal (or normal) semen parameters with risk factor
- SDF testing should be offered to patients who have a modifiable lifestyle risk factor of male infertility (grade C recommendation)

Grades of recommendations according to quality of evidence include:

- Grade A, based on clinical studies of good quality and consistency with at least one randomized trial;
- Grade B, based on well-designed studies (prospective, cohort) but without good randomised clinical trials;
- Grade C, based on poorer quality studies (retrospective, case series, expert opinion).

Sperm Penetration Assays

Practice Guidelines and Position Statements

According to the American Society for Reproductive Medicine (ASRM) committee opinion on the evaluation of the infertile male (2015), sperm penetration assays may detect defects in sperm fertilizing capacity and could identify patients who would benefit from application of ICSI. However, because ICSI is routinely used during IVF for male-factor infertility couples, this test is rarely of any clinical value. (42)

Updated AUA guidelines on the diagnosis and treatment of infertility in men that were published in conjunction with the ASRM in 2020 (amended 2024) do not mention sperm penetration assays. (17)

Recurrent Pregnancy Loss (RPL)

Immunologic therapies have been suggested for individuals with recurrent pregnancy loss addressed in the following guidelines:

European Society of Human Reproduction and Embryology (ESHRE)(55)

- The ESHRE continues to not recommend human leukocyte antigen in clinical practice. (conditional coverage ++)
- There is no evidence to support sperm selection by physiological intracytoplasmic sperm injection in couples with RPL. (conditional coverage +)

Royal College of Obstetricians and Gynaecologists (RCOG) (56)

- The RCOG guideline states that women with recurrent miscarriage should not be routinely offered immunological screening (such as HLA, cytokine and natural killer cell test), infection screening or sperm DNA testing outside of context of research.
- Guidelines state that various forms of immunotherapy, including trophoblast membranes, should no longer be offered to women with unexplained recurrent miscarriage because they provide no significant benefit over placebo.
- IVIG is not recommended as a treatment for RPL (strong ++)

ASRM (American Society for Reproductive Medicine)(57)

The ASRM recurrent pregnancy loss committee offers the following guidance related to RPL:

- “Studies of human leukocyte antigen (HLA) typing, embryotoxic factors, decidual cytokine profiles, blocking or anti paternal antibody levels, HLA-G polymorphism, and other immunologic traits and factors have produced inconsistent data that generally have not been reproduced in more than one laboratory. Proposed immunomodulatory treatments

for RPL (recurrent pregnancy loss) in the setting of one or more of these findings have not been proven effective. A meta-analysis of trials on paternal white blood cell immunization concluded that it had no beneficial effect.

- Treatment with intravenous immunoglobulin (IVIG) has also been proposed for unexplained pregnancy loss. However, several trials and meta-analyses concluded that IVIG is ineffective for primary recurrent pregnancy loss; thus, this treatment is not recommended.
- Does not include immunotherapy utilizing seminal plasma as a treatment for recurrent fetal loss.

Ongoing and Unpublished Clinical Trials

There are multiple ongoing and unpublished trials that might influence this policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	55899, 58322, 58340, 58999, 76831, 82397, 83519, 83520, 86148, 86357, 86849, 87999, 88182, 88189, 88305, 88342, 89251, 89254, 89253, 89255, 89258, 89259, 89260, 89261, 89264, 89268, 89280, 89281, 89322, 89329, 89335, 89337, 89342, 89343, 89344, 89346, 89352, 89353, 89354, 89356, 89398, 90283, 90284, 99183, [0568T: end dated 12/31/24]
HCPCS Codes	S4024, S4030, S4031, S4040

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References

1. Carney SK, Das S, Blake D, et al. Assisted hatching on assisted conception (in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Cochrane Database Syst Rev. 2012; 12:CD001894. PMID 23235584
2. Shi W, Hongwei T, Zhang W, et al. A prospective randomized controlled study of laser-assisted hatching on the outcome of first fresh IVF-ET cycle in advanced age women. Reprod Sci. Oct 2016; 23(10):1397-1401. PMID 27071963
3. Kanyo K, Zeke J, Kriston R, et al. The impact of laser-assisted hatching on the outcome of frozen human embryo transfer cycles. Zygote. Oct 2016; 24(5):742-747. PMID 26957232
4. Curfs MHJM, Cohlen BJ, Slappendel EJ, et al. A multicentre double-blinded randomized controlled trial on the efficacy of laser-assisted hatching in patients with repeated

implantation failure undergoing IVF or ICSI. Hum Reprod. Oct 03 2023; 38(10):1952-1960. PMID 37646072
5. Knudtson, Failor C, M., Gelfond JA, et al. Assisted hatching and live births in first cycle frozen embryo transfers. Fertil Steril. Aug 30 2017; 108(4):628634. PMID 28863938
6. McLaughlin JE, Choi BY, Liu Q, et al. Does assisted hatching affect live birth in fresh, first cycle in vitro fertilization in good and poor prognosis patients? J Assist Reprod Genet. Dec 2019; 36(12):2425-2433. PMID 31713775
7. Kissin DM, Kawwass JF, Monsour M, et al. Assisted hatching: trends and pregnancy outcomes, United States, 2000-2010. Fertil Steril. Sep 2014; 102(3):795-801. PMID 25044084
8. Practice Committee of the American Society for Reproductive Medicine. The role of assisted hatching in in vitro fertilization: a guideline. Fertil Steril. Jun 2022; 117(6):1177-1182. PMID 35618358
9. Kervancioglu ME, Saridogan E, et al. Human fallopian tube epithelial cell co-culture increases fertilization rates in male factor infertility but not in tubal or unexplained infertility. Hum Reprod. 1997; 12(6):1253-1258. PMID 9222012
10. Tucker MJ, Morton PC, et al. Enhancement of outcome from intracytoplasmic sperm injection: does co-culture or assisted hatching improve implantation rates? Hum Reprod. 1996; 11(11):2434-2437. PMID 8981127
11. Veiga A, Torello MJ, et al. Use of co-culture of human embryos on Vero cells to improve clinical implantation rate. Hum Reprod. 1999; 14(supplement 2):112-120. PMID 10690807
12. Wiemer KE, Cohen J, et al. The application of co-culture in assisted reproduction: 10 years of experience with human embryos. Hum Reprod. 1998; 13(supplement 4):226-238. PMID 10091073
13. Rubio C, Simon C, et al. Clinical experience employing co-culture of human embryos with autologous human endometrial epithelial cells. Hum Reprod. 2000; 15(supplement 6):31-38. PMID 11261481
14. Wetzels AM, Bastiaans BA, et al. The effects of co-culture with human fibroblasts on human embryo development in vitro and implantation. Hum Reprod. 1998; 13(5):1325-1330. PMID 9647567
15. Ohl J, de Mouzon J, Nicollet B, et al. Increased pregnancy rate using standardized coculture on autologous endometrial cells and single blastocyst transfer: a multicentre randomized controlled trial. Cell Mol Biol (Noisy-le-grand). 2015; 61(8):79-88. PMID 26718434
16. American Urological Association. Best Practice Statement. Optimal Evaluation of the Infertile Male (2010). Available at: <https://www.auanet.org> (accessed December 22, 2025).
17. American Society for Reproductive Medicine (ASRM). Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline (Oct 2020) (amended 2024). Available at: <https://www.asrm.org> (accessed December 21, 2025).
18. Ni Dhonnabhain B, Elfaki N, Fraser K, et al. A comparison of fertility preservation outcomes in patients who froze oocytes, embryos, or ovarian tissue for medically indicated circumstances: a systematic review and meta-analysis. Fertil Steril. Jun 2022; 117(6):1266-1276. PMID 35459522

19. Tryde SKL, Yding AC, Starup J, et al. Orthotopic autotransplantation of cryopreserved ovarian tissue to a woman cured of cancer – follicular growth, steroid production and oocyte retrieval. Reprod BioMed Online. 2004; 8(4):448-453. PMID 15149569
20. Oktay K, Buyuk E, Veeck L,et al. Embryo development after heterotopic transplantation of cryopreserved ovarian tissue. Lancet. (2004) 363:837-840. PMID 15031026
21. Erden M, Gayete-Lafuente S, Vural NA, et al. Utility and Outcomes of Ovarian Tissue Cryopreservation and Transplantation for Gynecologic Cancers: A Systematic Review and Meta-analysis. Obstet Gynecol. Oct 01 2024; 144(4): 481-492. PMID 39173181
22. Meirow D, Levron J, Eldar-Geva T, et al. Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med. Jan 3 2005; 353:318-321. PMID 15983020
23. Siegel-Itzkovich J. Woman gives birth after receiving transplant of her own ovarian tissue. BMJ. 2005; 331(7508):70. PMID 16002876
24. Donnez J, Dolmans MM, Demylle D, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet. 2004; 364(9443):1405-1410. PMID 15488215
25. Kim SS, Battaglia DE, Soules MR. The future of human ovarian cryopreservation and transplantation: fertility and beyond. Fertil Steril. 2001; 75(6):1049-1056. PMID 11384626
26. Lobo RA. Potential options for preservation of fertility in women. N Engl J Med. 2005; 353(1):64-73. PMID 16000356
27. Johnson J, Patrizio P. Ovarian cryopreservation strategies and the fine control of ovarian follicle development in vitro. Ann N Y Acad Sci. 2011; 1221:40-46. PMID 21401628
28. Dufour S, Gagné SA, Jackson A, et al. Oocyte Cryopreservation Outcomes in Women With Hematological Malignancies Undergoing Chemotherapy-A Systematic Review and Meta-Analysis. J Obstet Gynaecol Can. Jun 2025; 47(6): 102824. PMID 40157648
29. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril. Jan 2013; 99(1):37-43. PMID 23083924
30. Levi Setti PE, Albani E, Morenghi E, et al. Comparative analysis of fetal and neonatal outcomes of pregnancies from fresh and cryopreserved/thawed oocytes in the same group of patients. Fertil Steril. Aug 2013; 100(2):396-401. PMID 23608156
31. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. Dec 2019; 112(6): 1022-1033. PMID 31843073
32. Ethics Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Planned oocyte cryopreservation to preserve future reproductive potential: an Ethics Committee opinion. Fertil Steril. Apr 2024; 121(4): 604-612. PMID 38430080
33. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Evidence-based outcomes after oocyte cryopreservation for donor oocyte in vitro fertilization and planned oocyte cryopreservation: a guideline. Fertil Steril. Jul 2021; 116(1):36-47. PMID 34148587
34. American College of Obstetricians and Gynecologists. ACOG endorsed. Available at <https://www.acog.org> (accessed June 26, 2024).

35. Dafopoulos K, Griesinge G, Schultze-Mosgau A, et al. Cumulative pregnancy rate after ICSI with cryopreserved testicular tissue in non-obstructive azoospermia. Reprod BioMed Online. Apr 2005; 10(4):461-466. PMID 15901452
36. Hovatta O. Cryobiology of ovarian and testicular tissue. Best Pract Res Clin Obstet Gynaecol. Apr 2003; 17(2):331-342. PMID 12758103
37. Tournaye H, Goossens E, et al. Preserving the reproductive potential of men and boys with cancer: current concepts and future prospects. Hum Reprod Update. Nov-Dec 2004; 10(6):525-532. PMID 15319377
38. Dhonnabhain BN, Getreu N. Freezing protocols for the cryopreservation of immature testicular tissue - a systematic review. Cryo Letters. Jul-Aug 2021; 42(4):188-201. PMID 35363838
39. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. Jul 01 2013; 31(19):2500-2510. PMID 23715580
40. Oktay K, Harvey BE, Partridge AH, et al. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. Apr 05 2018; 36(19):19942001. PMID 29620997
41. Su HI, Lacchetti C, Letourneau J, et al. Fertility Preservation in People With Cancer: ASCO Guideline Update. J Clin Oncol. Apr 20 2025; 43(12): 1488-1515. PMID 40106739
42. American Society for Reproductive Medicine (ASRM). A Practice Committee Opinion. Diagnostic evaluation of the infertile male: a committee opinion (2015). Available at: <https://www.asrm.org> (accessed December 24, 2025).
43. Van Steirteghem AC, Liu J, Joris H, et al. Higher success rate by intracytoplasmic sperm injection than by subzonal insemination. Report of a second series of 300 consecutive treatment cycles. Hum Reprod. Jul 1993; 8(7):1055-1060. PMID 8408486
44. Palermo G, Joris H, Devroey P, et al. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet. Jul 4 1992; 340(8810):17-18. PMID 1351601
45. Palermo G, Joris H, Derde MP, et al. Sperm characteristics and outcome of human assisted fertilization by subzonal insemination and intracytoplasmic sperm injection. Fertil Steril. Apr 1993; 59(4):826-835. PMID 8458504
46. Van Steirteghem AC, Nagy Z, Joris H, et al. High fertilization and implantation rates after intracytoplasmic sperm injection. Hum Reprod. Jul 1993; 8(7): 1061-6. PMID 8408487
47. Fishel S, Timson J, Lisi F, et al. Micro-assisted fertilization in patients who have failed subzonal insemination. Hum Reprod. Mar 1994; 9(3):501-505. PMID 8006142
48. Borges Jr E, Zanetti BF, Braga DPAF, et al. Overcoming male factor infertility with intracytoplasmic sperm injection. Rev Assoc Med Bras (1992). 2017; 63(8):697703. PMID 28977108
49. Boulet SL, Mehta A, Kissin DM, et al. Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection. JAMA. Jan 20 2015; 313(3):255-263. PMID 25602996
50. Massaro PA, MacLellan DL, Anderson PA, et al. Does intracytoplasmic sperm injection pose an increased risk of genitourinary congenital malformations in offspring compared to in vitro fertilization? A systematic review and meta-analysis. J Urol. May 2015; 193(5 Suppl):1837-1842. PMID 25813561

51. American Society for Reproductive Medicine. The role of immunotherapy in vitro fertilization: A guideline. 2018. Available at: <https://www.asrm.org> (accessed December 24, 2025).
52. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 781. Infertility workup for the women's health specialist (2019; reaffirmed 2020). Obstet Gynecol 2019 Jun;133(6):1294-1295.PMID: 31135761
53. American Society for Reproductive Medicine (ASRM). Fertility evaluation of infertile women: a committee opinion (Nov 2021). Available at: <https://www.asrm.org> (accessed December 24, 2025).
54. Agarwal, A, Cho C, Majzoub A, et al. The Society for Translational Medicine: clinical practice guidelines for sperm DNA fragmentation testing in male infertility. Translational andrology and urology. 2017; 6(4):S720-S733. PMID 29082206
55. Bender R, Christiansen2OB, Elson J, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022; Human Reproduction Open. Available at <https://academic.oup.com> (accessed December 26, 2025).
56. Royal College of Obstetricians and Gynaecologists. Recurrent Miscarriage Green-top Guideline No. 17. Available at <https://obgyn.onlinelibrary.wiley.com> (accessed December 26. 2025).
57. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. The Practice Committee of the American Society for Reproductive Medicine. Available at: <https://www.asrm.org> (accessed December 22, 2025).
58. American Society for Reproductive Medicine (ASRM). Definition of infertility: a committee opinion (2023). Available at: <https://www.asrm.org> (accessed December 22, 2025).

Centers for Medicare and Medicaid Services (CMS)

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The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/01/2026	Document updated. Coverage significantly revised: 1) Added peri-implantation glucocorticoids and anti-tumor necrosis factor agents as examples of immune treatments; and 2) Removed multiple conditions from coverage section. Added references 21, 28, 41, 51, 54-57; others removed and/or updated.

05/15/2025	Document updated with literature review. The following changes were made to Coverage: 1) Modified coverage content to address only newly emerging and/or unproven reproductive technology services; and 2) Added new experimental, investigational and/or unproven indication of "sperm DNA integrity/fragmentation tests". Added references 5, 6, 10, 25, 26, 38, 39, 41-43, 65, 82, 85, 97, 105, 106, and 108-113. Title changed from: Services for Infertility and Recurrent Fetal Loss.
02/01/2024	Reviewed. No changes.
05/01/2023	Document updated with literature review. The following changes were made to Coverage: 1) Added "Sperm capacitation assessment (e.g., Cap-Score™ Test)" to the list of experimental, investigational and/or unproven services performed for establishing the diagnosis and/or underlying etiology of infertility, and 2) Added "Intrauterine injection/infusion of platelet rich plasma" to the list of experimental, investigational and/or unproven services for the treatment of infertility. Added/updated the following references: 2, 6, 8, 11, 16-18, 22, 24, 25, 30-33, 38, 45, 62, 67, 78, 79, 82, 83, 94, 95, 97, and 99.
01/15/2022	Reviewed. No changes.
05/01/2021	Document updated with literature review. The following changes were made to Coverage: 1) Added uterine and endometrial receptivity testing to the list of experimental, investigational and/or unproven services performed for establishing the diagnosis and/or underlying etiology of infertility, 2) Added "(with or without cumulus cell removal)" to the medical necessity statement on intracytoplasmic sperm injection, and 3) Modified NOTEs. Added/updated the following references: 1, 31, and 49.
01/01/2020	Document updated with literature review. Coverage extensively modified in regard to infertility evaluation and treatment. Added the following references: 1-27, 31, 48-50, 55-66, 72, and 77. Title changed from: Reproductive Technologies or Techniques and Related Services.
01/01/2019	Document updated with literature review. The following changes were made to Coverage: 1) Added language on Illinois-specific law for fertility preservation, 2) Modified "oocytes" to "immature oocytes" in list of reproductive techniques or services that are considered experimental, investigational and/or unproven, 3) Modified "eggs" to "oocytes" in list of services related to reproductive technologies/techniques that are considered not medically necessary. No new references added.
10/01/2018	Document updated with literature review. The following changes were made to Coverage Section: 1) Removed NOTE: Cryopreservation of testicular tissue may be considered medically necessary in adult men with azoospermia as a part of an ICSI procedure. (Check all contract benefits as cryopreservation may be a contract exclusion); 2) removed AI or IUI from Therapeutic drugs coverage statement; 3) removed "of prepubertal boys as a method of preserving fertility" from EIU reproductive techniques stating

	Cryopreservation of testicular tissue of prepubertal boys as a method of preserving fertility; and 4) added uterine transplant to the list of EIU reproductive techniques. References 7, 9-13, 15, 42-43, 50, 72-78, 83-84 added.
10/01/2016	Reviewed. No changes.
11/01/2015	Document updated with literature review. The following was added to the reproductive techniques or services experimental, investigational and/or unproven coverage statement, "Intracytoplasmic sperm injections (ICSI) in the absence of male factor infertility."
07/01/2014	Document updated with literature review. The following changes were made: 1.) For determination if intracytoplasmic injections (ICSI) should be a part of in vitro fertilization (IVF); determination of sperm maturation; and/or sperm selection as added to sperm penetration assay testing and/or hyaluronan binding assay testing medically necessary criteria; 2.) "for male factor infertility" was added to the medically necessary intracytoplasmic injection criteria; 3.) "blastocyst transfer was added to the medically necessary embryo transfer criteria; and, 4.) Tests of sperm DNA integrity, including but not limited to, sperm chromatin assays and sperm DNA fragmentation assays were added to the experimental, investigational and/or unproven coverage listing. Clarification made to the definition of infertility within the Description section, changing from couples with infertility, to an individual who has been suspected of and/or diagnosed with infertility due to a dysfunction of the reproductive system. The remainder of the infertility definition remains unchanged. Title changed from Assisted Reproductive Technologies and Related Services. Rationale substantially revised.
05/15/2010	Revised/updated entire document. Coverage remains conditional when benefit contract does not exclude assisted reproductive technology and/or related therapy services. Added recent Illinois Insurance Code mandate amendment information. This policy is no longer scheduled for routine literature review and update.
01/01/2007	Revised/updated entire document
07/01/1999	New medical document