Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 7/1/24**
(See policy history boxes for previous effective dates)

Title: Assisted Reproductive Techniques

Description/Background

Descriptions
In this policy the terms female and male are used to identify the sex (reproductive capacity) and not the gender identity of the individual.

The term *female* used in this policy refers to individuals with two X chromosomes (or no Y chromosome), also known as female sex. This includes individuals with gender identities other than female.

The term *male* used in this policy refers to individuals with XY chromosomes, also known as male sex. This includes individuals with gender identities other than male.

Infertility (Refer to the medical policy "Infertility Diagnosis")
Infertility can be due either to female factors (ie, pelvic adhesions, ovarian dysfunction, endometriosis), male factors (ie, abnormalities in sperm production, function or transport), a combination of male and female factors, or unknown causes. Infertility is the result of a disease (an interruption, cessation, or disorder of body functions, systems, or organs) involving the reproductive system, which prevents conception.
American Society for Reproductive Medicine (ASRM) Practice Committee (2023)[1] issued a new definition of "infertility" as follows:

"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 six months when the female partner is 35 years of age or older.

Treatment

Various reproductive techniques are available to establish a viable pregnancy; different techniques are used depending on the reason for infertility. Assisted reproductive technologies as defined by the Centers for Disease Control and Prevention and other organizations, refer to fertility treatments in which eggs or embryos are handled.[2] The American Society for Reproductive Medicine states that Assisted Reproductive Technologies are all treatments which include the handling of eggs and sperm, and/or embryos.[3] 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 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 ART 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, (ie, the laboratory procedures), which are performed on the collected oocyte and sperm. The final step is the implantation procedure.

Most Current Procedural Terminology (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 (ie, intracytoplasmic sperm injection [ICSI], assisted hatching, co-culture of embryos) and cryopreservation of reproductive tissue (ie, testicular, ovarian, oocytes) will be considered within this evidence summary.

Regulatory Status

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

Medical Policy Statement

Selected assisted reproductive techniques (ART) are established and may be considered useful therapeutic options in the treatment of infertility.

When infertility is due to an underlying medical condition (eg, chronic infection, uterine fibroids, etc.), the treatment of that disorder is medically necessary and is covered under basic medical-surgical benefits.* When no medically-correctable underlying medical condition is found (eg, low sperm count, anovulation), other options may be pursued. One option is ART – specific services that may be used to establish pregnancy. Assisted reproductive techniques are only available to members when the employer group has chosen to offer the services as additional/extra benefits, through certificate benefit language or riders.

The focus of this policy is the use of ART in individuals who are diagnosed with infertility. Assisted reproductive techniques for individuals who are not diagnosed with infertility is based on benefit coverage (the certificate of coverage or rider) and is beyond the scope of this medical policy.
*See the medical policy "Infertility Diagnosis."

Inclusionary and Exclusionary Guidelines

Assisted reproductive techniques (ARTs) are not general medical or surgical benefits. While the procedures listed in the inclusions are considered established, these services are available only as additional benefits, offered by a group or employer. The covered services and limitations are defined by the group or employer. The benefit plan, including the certificate of coverage or rider, determines the available coverage.

In order to access benefits for artificial insemination or assisted reproductive techniques, the definition of infertility* must be met. A benefit document (certificate of coverage or rider) may specify that the definition of infertility is **not** a requirement for artificial insemination or ART services; ONLY in this case is the requirement of meeting the definition of infertility waived.
**Refer to the medical policy "Infertility Diagnosis" for infertility definition and criteria.*

Inclusions:

- Artificial insemination
- Assisted Reproductive Technologies
  - in vitro fertilization (IVF)
  - gamete intrafallopian transfer (GIFT)
  - transuterine fallopian transfer (TUFT)
  - natural oocyte retrieval with intravaginal fertilization (NORIF)
  - pronuclear state tubal transfer (PROST)
  - tubal embryo transfer (TET)
  - zygote intrafallopian transfer (ZIFT)
  - embryo transfer
  - blastocyst transfer
  - intracytoplasmic sperm injection (ICSI) for male factor infertility only
  - cryopreservation of embryo(s) and sperm

- storage of embryo(s) and sperm
- thawing of embryo(s) and sperm
- mature oocytes: cryopreservation, with storage and thawing for up to 3 months following cryopreservation, when BOTH of the following criteria are met:
  - it is a covered IVF cycle using fresh oocyte(s) AND
  - inability to obtain viable sperm for oocyte fertilization at the time of oocyte retrieval
- assisted embryo hatching when one of the following criteria are met:
  - the individual is 38 years of age or older, OR
  - there have been 2 or more IVF failures related to failed implantation
- elective single-embryo transfer (eSET)

Sperm Retrieval procedures

- For individuals who are unable to ejaculate
  - Penile vibratory stimulation
  - Electroejaculation
- For obstructive azoospermia
  - Percutaneous Epididymal Sperm Aspiration (PESA)
  - Testicular Sperm Aspiration (TESA)
- For non-obstructive azoospermia
  - Testicular Sperm Extraction (TESE)
  - Micro-Dissection Testicular Sperm Extraction (microTESE)
- For vasal or epididymal obstruction without azoospermia
  - Microepididymal/Microsurgical Epididymal Sperm Aspiration (MESA)
- Testicular Fine Needle Aspiration (TEFNA), vasal sperm aspiration and seminal vesicle sperm aspiration

Note: sperm retrieval procedures are excluded when there has been a prior voluntary sterilization procedure (eg, vasectomy)

Exclusions:

- Co-culture of embryos
- Cryopreservation of ovarian tissue, immature oocytes or testicular tissue*
- Storage of ovarian tissue or testicular tissue*
- Thawing of ovarian tissue or testicular tissue*
- All services related to gestational surrogacy / gestational parent / gestational carrier
- Time lapse monitoring or imaging of embryos (eg, EmbryoScope®)
- Endometrial receptivity testing (eg, ERA® [Endometrial Receptivity Analysis])
- ART services are excluded when there has been a voluntary sterilization procedure (eg, tubal ligation, vasectomy), including when there has been surgical reversal of the sterilization procedure, as this is not considered treatment of disease
- Reversal of prior sterilization procedure is excluded

*Cryopreservation, storage and thawing of testicular tissue is ONLY covered in adult men with azoospermia, as these procedures are part of intracytoplasmic sperm injection.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Assisted reproductive techniques are not general medical or surgical benefits. While the following procedures are considered established for this policy, the specific coverage for each member is based on the benefit, which is defined by the group or employer.

Established codes:

54500[a]	54505[b]	54800[c]	55530	55870	
55899[d]					
55530	58321	58322	58323	58540	58672
58752	58760	58970	58974	58976	
76857	76948				
89250	89253[e]	89254	89255	89257	89258
89259	89260	89261	89264	89268	89272
89280[f]	89281[f]	89290[g]	89291[g]	89322	
89335[i]	89337[e]	89342	89343	89344[i]	89346[e]
89352	89353	89354[h]	89356[e]		
S4011	S4013	S4014	S4015	S4016	S4021
S4022	S4027	S4028	S4035	S4037	S4040
S4042	J0725				

[a] When this code represents Testicular Sperm Aspiration (TESA)

[b] When this code represents (ex micro-dissection testicular sperm extraction [microTESE], Testicular Sperm Extraction [TESE])

[c] When this code represents (Percutaneous Epididymal Sperm Aspiration)[PESA]

[d] When this code represents micro-dissection testicular sperm extraction (microTESE), Testicular Sperm Extraction (TESE),Testicular Sperm Aspiration (TESA),Percutaneous Epididymal Sperm Aspiration (PESA)

[e] ONLY when inclusion criteria are met

[f] ONLY for diagnosis of male factor infertility

[g] Refer to policy "Genetic Testing – Preimplantation"

[h] ONLY for adult men diagnosed with azoospermia, as part of the intracytoplasmic sperm injection procedure.

Conditional codes: The following procedures may be appropriate for medical/surgical indications. However, the procedures are not payable when performed for the purpose of reversal of prior voluntary sterilization procedures.

54900	54901	55400	58673	58750	58770

Other codes (investigational, not medically necessary, etc.):

89251	89398[i]	0253U

[i] ***When this code represents EmbryoScope monitoring or cryopreservation of immature oocytes.***

Note: Codes may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews 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 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. 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.

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 (ie, assisted hatching) has been proposed as a mechanism to improve implantation rates.

The purpose of IVF with assisted hatching in patients 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 infertile individuals.

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 31RCTs evaluating assisted hatching (N=5728).[4] 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 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 of trials, assisted hatching improved the pregnancy rate, but the estimate for the odds ratio was marginally statistically significant (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, 35-42 years).[5] 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).[6] In the overall study population, there was no statistically significant difference in the clinical pregnancy rate in 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 clinically 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 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.[7] 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.[8] The study found assisted hatching was 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.[9] 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 heterogenous 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; however, in 1 study, there was a higher rate of clinical pregnancy in the subgroup of women 38 years or older.

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 (ie, oviducts) to nonhuman cells (ie, fetal bovine uterine or oviduct cells) to established cell lines (ie, 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 infertile individuals.

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 a successful pregnancy up to successful birth.

Study Selection Criteria

See information under the first indication.

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.[10,11,12,13,14,15] For example, Wetzels et al (1998) reported on an RCT that assigned IVF treatments to co-culture with human fibroblasts or no culture.[15] 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.[16] 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 studies 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.

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 the increase in 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 concern 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 question addressed in this evidence review is: Does IVF with blastocyst transfer treat infertility and improve the net health outcome?

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

See information under the first indication.

Review of Evidence

Systematic Reviews

Several systematic reviews of studies comparing outcomes associated with blastocyst-stage transfer compared with those of earlier stage transfer have been published. Only Cochrane reviews by Glujovsky et al (2012, 2016, 2022) included RCTs.[17,18,19] 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 5-6) embryo transfers improved the live birth rates, and other associated outcomes, compared with cleavage-stage (day 2-3) embryo transfers.[18] Data from 4 new studies, 3 of which were published studies[20,21,22] 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 2-3 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.[19] 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.[23] 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 (eg, 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 between the Swedish Medical Birth Register, the Register of Birth Defects, and the National Patient Register.[24] 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 to 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 and 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.[25] 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 individuals 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 a successful birth.

Study Selection Criteria
See information under the first indication.

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%.[,26,27,28,29,30] 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).[31] 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).[32] 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.[33] 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 (eg, 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 individuals 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 individuals 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
See information under the first indication.

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.[34] However, clinical trials evaluating health outcomes after cryopreservation of testicular tissue in adult men with azoospermia were not identified.

Meta-Analysis
Toulis et al (2010)[36] the article is a meta-analysis examining the diagnostic accuracy of inhibin B and anti-Mullerian hormone (AMH) as markers for persistent spermatogenesis in men with non-obstructive azoospermia (NOA). It evaluates several studies to determine the effectiveness of these hormone markers in predicting the presence of sperm in the testes of NOA patients. The findings suggest that both inhibin B and AMH can serve as reliable markers for persistent spermatogenesis in NOA cases, providing supportive information for clinical decision-making regarding fertility treatment options for these individuals. Serum Inh-B demonstrated a sensitivity of 0.65 (95% confidence interval [CI]: 0.56-0.74) and a specificity of 0.83 (CI: 0.64-0.93) for the prediction of the presence of sperm in TESE. When the pre-test probability of 41% was incorporated in a Fagan's nomogram, resulted in a positive post-test probability of 73% and a negative post-test probability of 23% for the presence of sperm in TESE. Serum Inh-B cannot serve as a stand-alone marker of persistent spermatogenesis in

men with NOA. Although limited, evidence on serum AMH and serum/seminal AMH do not support their diagnostic value in men with NOA.

Retrospective Clinical Study

Turek et al. (1999)[37] A retrospective clinical study explores a technique called testis sperm extraction (TESE) guided by fine-needle aspiration mapping in patients with nonobstructive azoospermia, a condition where sperm production is impaired. The aim is to improve the success of intracytoplasmic sperm injection (ICSI) by identifying areas in the testes where sperm may be present. This approach could potentially offer new options for fertility treatment in such patients.

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.

POTENTIAL ADVERSE EVENTS TO OFFSPRING CONCEIVED VIA ASSISTED REPRODUCTION

Several systematic reviews have addressed the risk of birth defects.[,38,39,40,41] The review with the most data is that by Hansen et al (2013).[39] 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 (RR, 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 that were conducted in the U.S. or Canada (RR, 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 ART.[40] 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 (eg, maternal age, parity, maternal ethnicity, maternal smoking during pregnancy, and 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.[41] 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).

SUMMARY OF EVIDENCE

For individuals who have infertility who receive in vitro fertilization (IVF) with assisted hatching, the evidence includes randomized controlled trials (RCTs), a systematic review, and retrospective studies. The 2012 Cochrane review of heterogenous RCTs found that clinical pregnancy rates improved with assisted hatching. In subsequent RCTs, one study found a higher rate of clinical pregnancy in the subgroup of women 38 years or older following laser-assisted hatching. The evidence is sufficient to determine that the technology improves pregnancy rates in an identified population.

For individuals who have infertility and receive IVF with embryo co-culture, the evidence includes RCTs and case series. Most clinical trials have not found improved implantation or pregnancy rates after co-culture, and studies have not reported live birth rates. Moreover, co-culture techniques have not been standardized. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have infertility and receive IVF with blastocyst transfer, the evidence includes RCTs and meta-analyses. The RCTs and meta-analyses have found that blastocyst transfer is associated with higher live birth rates than cleavage-stage transfer. One retrospective cohort study reported a significantly higher rate of preterm birth after blastocyst-stage versus cleavage-stage transfer but did not find increased risks of other outcomes such as low birth rate or perinatal mortality. A retrospective registry review of a similar population reported different findings. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have male factor infertility who receive IVF with intracytoplasmic sperm injection (ICSI), the evidence includes observational studies and a systematic review. The evidence includes observational studies that found similar rates of clinical pregnancy and live birth after ICSI and standard IVF, and a meta-analysis of observational studies found a higher rate of genitourinary malformations in children born after ICSI (but only when lower quality studies were included in the analysis). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have azoospermia who receive cryopreservation of testicular tissue as part of ICSI, the evidence includes no clinical trials. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Endometrial Receptivity

Normal endometrial receptivity allows embryo attachment, implantation, invasion and development of the placenta. Causes of defective endometrial receptivity and biomarkers for evaluation of endometrial receptivity are being investigated.[42] There is no evidence in the peer reviewed medical literature that endometrial receptivity analysis by gene testing has validity or clinical utility.

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 Received Through 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 from the Blue Cross Blue Shield Association, input was received from 4 physician specialty societies and 2 academic medical centers while their policy was under review in 2012. There was general agreement that ICSI and cryopreservation of testicular

tissue in adult men with azoospermia as part of an ICSI 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 with the statement that cryopreservation of ovarian tissue or oocytes is investigational. The other 3 reviewers 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
ASRM and joint ASRM/Society for Assisted Reproductive Technology (SART) opinions and recommendations are as follows:

- American Society for Reproductive Medicine (ASRM) Practice Committee (2023)[1] issued a new definition of "infertility" as follows:

  "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 six months when the female partner is 35 years of age or older.
- Nothing in this definition shall be used to deny or delay treatment to any individual, regardless of relationship status or sexual orientation.

  Built upon the clinical reality of the disease of infertility, this definition also reflects the fact that challenges in reproduction can have a myriad of causes, all of which deserve to be taken seriously and treated.

  ASRM has a longstanding tradition of data-driven, clinically sound positions. This definition builds on that while also responding to the needs of a diverse patient population. This new and inclusive definition is driven by the clinical needs of patients who come from different places and with different treatment needs.

- 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 embryo transfer cycles."[43]
- Blastocyst transfer (2013; reaffirmed in 2018): "Evidence supports blastocyst transfer in 'good prognosis' patients."[44,45]

In 2021, ASRM/SART published an updated committee opinion on guidance on the limits to the number of embryos to transfer.[46] Recommendations included:

- Transfer of a euploid embryo should be limited to one, regardless of patient age
- Patients <35 years of age should be strongly encouraged to receive a single-embryo transfer, regardless of the embryo stage
- For patients between 35 and 37 years of age, strong consideration should be made for a single-embryo transfer

In 2020, ASRM developed joint guidelines with the American Urological Association (AUA) for male infertility diagnosis and treatment including recommendations for intracytoplasmic sperm injection.[47,48] Based on expert opinion, patients with low total motile sperm count should be advised to consider IVF with intracytoplasmic sperm injection.[45]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Blastocyst transfer			
NA			
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 2021 (completed)
NCT04128904	In Vitro Fertilization Versus Intracytoplasmic Sperm Injection in Patients Without Severe Male Factor Infertility (INVICSI): a Randomised, Controlled, Multicentre Trial	824	Dec 2024 (active, Not recruiting)
Unpublished			
NCT03152643	Cumulative Live Birth Rates After Cleavage-stage Versus Blastocyst-stage Embryo Transfer: A Multicenter, Prospective, Randomized Controlled Trial	992	Feb 2022 (completed)
NCT03764865	Day 3 vs Day 5 Embryo Transfer for Patients With Low Embryo Numbers Going Through in Vitro Fertilization	10	Feb 2022 (completed)

NCT: national clinical trial

Government Regulations

National:

There is no National Coverage Determination (NCD) on this topic.

Local:

There is no Local Coverage Determination (LCD) on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing-Preimplantation
- Infertility Diagnosis
- Infertility Related to Cancer Treatment
- Sperm Penetration Assay (Retired)

References

1. Practice Committee of the American Society for Reproductive Medicine, American Society for Reproductive Medicine, (2023 by American Society for Reproductive Medicine.) FNS_ASRM_Reviewers_proof 1..1 assessed 2/29/24
2. Centers for Disease Control. What is Assisted Reproductive Technology? https://www.cdc.gov/art/whatis.html#:~:text=According%20to%20this%20definition%2C%20ART,donating%20them%20to%20another%20woman Accessed 2/29/24.
3. American Society for Reproductive Medicine. Topics. Search | American Society for Reproductive Medicine | ASRM Accessed 2/29/24.
4. 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 Dec 12 2012; 12:CD001894. PMID23235584
5. 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):1397-401. PMID 27071963
6. 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):742-7. PMID 26957232
7. Knudtson JF, Failor CM, Gelfond JA, et al. Assisted hatching and live births in first-cycle frozen embryo transfers. Fertil Steril. Oct 2017;108(4):628-634. PMID 28863938
8. 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

9. 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
10. Kervancioglu ME, Saridogan E, Atasu T, 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. Jun 1997; 12(6):1253-8. PMID 9222012
11. Tucker MJ, Morton PC, Wright G, et al. Enhancement of outcome from intracytoplasmic sperm injection: does co-culture or assisted hatching improve implantation rates? Hum Reprod. Nov 1996; 11(11):2434-7. PMID 8981127
12. Veiga A, Torello MJ, Menezo Y, et al. Use of co-culture of human embryos on Vero cells to improve clinical implantation rate. Hum Reprod. Dec 1999; 14 Suppl 2:112-20. PMID 10690807
13. Wiemer KE, Cohen J, Tucker MJ, et al. The application of co-culture in assisted reproduction: 10 years of experience with human embryos. Hum Reprod. Dec 1998; 13 Suppl 4:226-38. PMID 10091073
14. Rubio C, Simon C, Mercader A, et al. Clinical experience employing co-culture of human embryos with autologous human endometrial epithelial cells. Hum Reprod. Dec 2000; 15 Suppl 6:31-8. PMID 11261481
15. Wetzels AM, Bastiaans BA, Hendriks JC, et al. The effects of co-culture with human fibroblasts on human embryo development in vitro and implantation. Hum Reprod. May 1998; 13(5):1325-30. PMID 9647567
16. 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). Dec 24 2015;61(8):79-88. PMID 26718434
17. Glujovsky D, Blake D, Farquhar C, et al. Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology. Cochrane Database Syst Rev. Jul 11 2012; (7): CD002118. PMID 22786480
18. Glujovsky D, Farquhar C, Quinteiro Retamar AM, et al. Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology. Cochrane Database Syst Rev. Jun 30 2016(6):Cd002118. PMID 27357126
19. Glujovsky D, Quinteiro Retamar AM, Alvarez Sedo CR, et al. Cleavage-stage versus blastocyst-stage embryo transfer in assisted reproductive technology. Cochrane Database Syst Rev. May 19 2022; 5: CD002118. PMID 35588094
20. Aziminekoo E, Mohseni Salehi MS, Kalantari V, et al. Pregnancy outcome after blastocyst stage transfer comparing to early cleavage stage embryo transfer. Gynecol Endocrinol. 2015;31(11):880-884. PMID 26437606
21. Fernandez-Shaw S, Cercas R, Brana C, et al. Ongoing and cumulative pregnancy rate after cleavage-stage versus blastocyst-stage embryo transfer using vitrification for cryopreservation: impact of age on the results. J Assist Reprod Genet. Feb 2015;32(2):177-184. PMID 25403438
22. Kaur P, Swarankar ML, Maheshwari M, et al. A comparative study between cleavage stage embryo transfer at day 3 and blastocyst stage transfer at day 5 in in-vitro fertilization/intra-cytoplasmic sperm injection on clinical pregnancy rates. J Hum Reprod Sci. Jul 2014;7(3):194-197. PMID 25395745
23. Kallen B, Finnstrom O, Lindam A, et al. Blastocyst versus cleavage stage transfer in in vitro fertilization: differences in neonatal outcome? Fertil Steril. Oct 2010; 94(5):1680-3. PMID 20137785

24. Ginström Ernstad E, Bergh C, Khatibi A, et al. Neonatal and maternal outcome after blastocyst transfer: a population-based registry study. Am J Obstet Gynecol. Mar 2016; 214(3): 378.e371-378.e310. PMID 26928152
25. Spangmose AL, Ginstrom Ernstad E, Malchau S, et al. Obstetric and perinatal risks in 4601 singletons and 884 twins conceived after fresh blastocyst transfers: a Nordic study from the CoNARTaS group. Hum Reprod. Apr 282020; 35(4): 805-815. PMID 32294185
26. 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):1055-60. PMID 8408486
27. Palermo G, Joris H, Devroey P, et al. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet. Jul 04 1992; 340(8810):17-8. PMID 1351601
28. 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-Jan):826-35. PMID 8458504
29. Van Steirteghem A. C., Nagy Z., Jori H, et al. High fertilization and implantation rates after intracytoplasmic sperm injection. Hum Reprod. Jul 1993; 8(7):1061-6. PMID 28977108
30. Fishel S, Timson J, Lisi F, et al. Micro-assisted fertilization in patients who have failed subzonal insemination. Hum Reprod. Mar 1994; 9(3):501-5. PMID 8006142
31. Borges Jr E, Zanetti BF, Braga DPAF, et al. Overcoming male factor infertility with intracytoplasmic sperm injection. Rev Assoc Med Bras (1992). Aug 2017 63(8):697-703. PMID 28977108
32. 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
33. 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
34. Dafopoulos K, Griesinger 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):461-6. PMID 15901452
35. Kettner LO, Henriksen TB, Bay B, et al. Assisted reproductive technology and somatic morbidity in childhood: a systematic review. Fertil Steril. Mar 2015; 103(3): 707-19. PMID 25624193
36. Toulis KA, Iliadou PK, Venetis CA, et al. Inhibin B and anti-Mullerian hormone as markers of persistent spermatogenesis in men with non-obstructive azoospermia: A meta-analysis of diagnostic accuracy studies. Hum Reprod Update. 2010;16(6):713-724.
37. Turek PJ, Givens CR, Schriock ED, Meng MV, Pedersen RA, Conaghan J. Testis sperm extraction and intracytoplasmic sperm injection guided by prior fine-needle aspiration mapping in patients with nonobstructive azoospermia. Fertil Steril. 1999 Mar;71(3):552-7.
38. Farhi A, Reichman B, Boyko V, et al. Congenital malformations in infants conceived following Assisted Reproductive Technology in comparison with spontaneously conceived infants. J Matern Fetal Neonatal Med. Aug 2013; 26(12): 1171-9. PMID 23451839
39. Hansen M, Kurinczuk JJ, Milne E, et al. Assisted reproductive technology and birth defects: a systematic review and meta-analysis. Hum Reprod Update. Jul-Aug 2013; 19(4): 330-53. PMID 23449641
40. Davies MJ, Moore VM, Willson KJ, et al. Reproductive technologies and the risk of birth defects. N Engl J Med. May 10 2012; 366(19):1803-13. PMID 22559061
41. Elias FTS, Weber-Adrian D, Pudwell J, et al. Neonatal outcomes in singleton pregnancies conceived by fresh or frozen embryo transfer compared to spontaneous conceptions: a

systematic review and meta-analysis. Arch Gynecol Obstet. Jul 2020; 302(1): 31-45. PMID 32445067
42. Tulandi T, AL-Fozan HM. Recurrent pregnancy loss: definition and etiology. Last updated April 6, 2022. https://www.uptodate.com/contents/recurrent-pregnancy-loss-definition-and-etiology?search=endometrial%20receptivitry&source=search_result&selectedTitle=2~16&usage_type=default&display_rank=2#H12 Accessed 2/29/24
43. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. The role of assisted hatching in in vitro fertilization: a guideline. Fertil Steril. Jun 2022; 117(6): 1177-1182. PMID 35618358
44. Practice Committee of the American Society for Reproductive Medicine and Practice Committee of the Society of Assisted Reproductive Technology. Blastocyst culture and transfer in a clinically assisted reproduction: a committee opinion. Fertil Steril. 2018;110(7):1246-1252.
45. Practice Committee of American Society for Reproductive Medicine. Blastocyst culture and transfer in clinical-assisted reproduction. Fertil Steril. Nov 2008;90(5 Suppl):S174-177. PMID 19007621
46. Penzias A, Assis R, Bedickson K, et al. Guidance on the limits to the number of embryos to transfer: a committee opinion. Practice Committee of the American Society for Reproductive Medicine and the Practice Committee for the Society for Assisted Reproductive Technologies. Fertil Steril 2021;116:651-54
47. Schlegel PN, Sigman M, Collura B, et al. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline Part I. J Urol. Jan 2021; 205(1):36-43. PMID 33295257
48. Schlegel PN, Sigman M, Collura B, et al. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline PART II. J Urol. Jan 2021; 205(1):44-51. PMID 33295258
49. James M. Dupree, R. Matthew Coward, Tung-Chin Hsieh, Cigdem Tanrikut, Paul Shin, Akanksha Mehta, James M. Hotaling, Alexander W. Pastuszak, Daniel Williams, Joseph Alukal, Larry I. Lipshultz, Peter Schlegel, Thomas J. Walsh, Michael L. Eisenberg, David Shin, Stan Honig, Harris M. Nagler, Mary Samplaski, Ajay K. Nangia, Jay Sandlow, James F. Smith,The Impact of Physician Productivity Models on Access to Subspecialty Care: A White Paper From the Society for the Study of Male Reproduction and the Society for Male Reproduction and Urology,Urology,Volume 153,2021,Pages 28-34,ISSN 0090-4295, https://doi.org/10.1016/j.urology.2021.01.016
https://www.sciencedirect.com/topics/medicine-and-dentistry/general-urology

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 02/29/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/08	11/26/07	1/1/08	Joint policy established
3/1/09	12/9/08	12/21/08	Routine maintenance
3/1/12	12/13/11	12/21/11	Routine maintenance
7/1/13	4/16/13	4/22/13	Routine maintenance, policy title changed from Infertility Treatment to Reproductive Techniques
9/1/14	6/17/14	6/30/14	Routine maintenance
5/1/16	2/16/16	3/28/16	• Routine maintenance • Code Updates – multiple deletions/additions • Updated Inclusions and Exclusions • Updated Rationale, Practice Guidelines/Position Statements & References
5/1/17	2/21/17	2/21/17	• Routine maintenance
3/1/18	12/12/17	12/12/17	• Routine maintenance
3/1/19	12/11/18		• Routine maintenance
3/1/20	12/17/19		• Routine maintenance
3/1/21	12/15/20		Routine maintenance Ref 5, 32 added
1/1/22	10/19/21		Routine maintenance. Code 0058T was deleted 1/1/21. Code 0357T was deleted 1/1/20. Code 76857 added as est. Codes 89398, 0253U added as inv. Added cryopreservation for those facing iatrogenic infertility. Ref added: 1,49,53,54,59 Codes added to INV table: 54900, 54901, 55400, 58673, 58750, 58770
3/1/22	12/20/22		Routine maintenance Title change: “Assisted” added Revision of MPS
5/1/22	3/9/22		Review of certificate / rider language.

			Changes to inclusions/exclusions: coverage of cryopreservation, storage and thawing of oocytes; coverage of assisted hatching. New code table for conditional services.
9/1/22	6/21/22		Routine maintenance. Removed references to fertility preservation. Added eSET as covered. 89251 from EST to INV 89253 suprascript added 58673 from INV to Conditional 89335, 89344, 89354 to EST with suprascript instructions.
3/1/23	12/20/22		Routine maintenance. ls Background section edited. Medical policy statement revised. Exclusions edited. Removed sections: Cryopreservation of ovarian tissue and Cryopreservation of testicular tissue in prepubertal boys with cancer. Ref 2,18 added
3/1/24	12/19/23		Routine maintenance (jf) Vendor Managed: NA
7/1/24	4/16/24		Routine maintenance (jf) Vendor Managed: NA Added the following codes as EST: Added the following sperm retrieval codes as EST: 54500,54505,54800,55870,and 55899 -Added all inclusive Infertility language into the description of the policy. -Ref added: 1,36,37,49 -Edits to the inclusions and exclusions - Superscripts added to represent sperm retrieval procedures.

Next Review Date: 2nd QTR, 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: 4/10/97	Revised: 6/1/07
BCBSM: N/A	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ASSISTED REPRODUCTIVE TECHNIQUES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Refer to the member's certificate for specific coverage information.
BCNA (Medicare Advantage)	Refer to the member's Evidence of Coverage.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.