

MEDICAL POLICY



SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY	EFFECTIVE DATE: 06/20/01
POLICY NUMBER: 4.01.05	REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18
CATEGORY: Contract Clarification	PAGE: 1 OF: 15
<ul style="list-style-type: none">• <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i>• <i>If a commercial product, including an Essential Plan product, covers a specific service, medical policy criteria apply to the benefit.</i>• <i>If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</i>	

Note: Refer to the section IX regarding Exclusions and Limitations for services/procedures that may be contract dependent or excluded.

POLICY STATEMENT:

- I. **Establish Infertility Diagnosis:** Based upon our criteria and review of the peer-reviewed literature, diagnostic work-up and corresponding *infertility* treatments are **medically appropriate** for the diagnosis and treatment of **correctable malformations, disease and/or dysfunction**. In cases of male infertility, the male must be covered as a member under the policy to receive any services.

Prior to initiation of infertility treatment a medical history, including history related to infertility and coexisting medical conditions should be documented. Information regarding the following may be obtained:

- A. post coital test;
- B. hysterosalpingogram, hysteroscopy, sonohysterogram;
- C. laparoscopy;
- D. prior infertility treatment;
- E. sperm count/motility; and
- F. other laboratory tests as indicated (e.g., FSH, Hba_{1c} in diabetics, Prolactin, TSH, T4, etc.).

- II. **Medical Treatment of ovulatory dysfunction:** Based upon our criteria and review of peer-reviewed literature, treatment with FDA-approved drugs has been medically proven to be effective and therefore **medically appropriate** in the *treatment of infertility* with the following limitations:

- A. Infertile, anovulatory women - once the lowest dose of clomiphene citrate required to induce ovulation is established, up to 12 cycles of clomiphene treatment will be covered. If there is no pregnancy after 6 cycles of treatment, consultation with a reproductive endocrinologist before proceeding with additional treatment cycles is indicated.
- B. Infertile, ovulatory women receiving clomiphene citrate for superovulation – appropriate for up to six cycles of treatment. Up to six cycles of intrauterine insemination will be covered in conjunction with this treatment. These superovulation cycles, with or without intrauterine insemination, should be supervised by a reproductive endocrinologist or gynecologist credentialed to provide this treatment.
- C. After clomiphene failure, or in place of clomiphene treatment, for women in late reproductive life treatment with FDA approved gonadotropin drugs is limited to:
 - 1. up to four (4) cycles per member per pregnancy as defined by a positive HCG determination; and
 - 2. prescription or administration by a reproductive endocrinologist and other physicians credentialed to provide this treatment. After two (2) successive spontaneous miscarriages, further evaluation as to the cause of the miscarriages must be performed before the use of gonadotropin drugs can be resumed.

<p>SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY</p> <p>POLICY NUMBER: 4.01.05</p> <p>CATEGORY: Contract Clarification</p>	<p>EFFECTIVE DATE: 06/20/01</p> <p>REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18</p> <p>PAGE: 2 OF: 15</p>
---	--

III. **Comprehensive services:** If the basic infertility services do not result in increased fertility, the following comprehensive infertility services are included:

- A. Ovulation induction and monitoring
- B. Pelvic ultrasound
- C. Artificial insemination
- D. Hysteroscopy;
- E. Laprosocopy;and
- F. Laparotomy.

IV. **Surgical Treatment:**

- A. Based upon our criteria, procedures to repair the anatomical structures for the purpose of conception are **medically appropriate** when no prior procedure has been performed that has purposely interrupted the function of the structure (e.g., elective sterilization, elective Essure System for permanent birth control).
- B. Based upon our criteria, assisted reproductive technologies are **not medically appropriate** when:
 1. the reversal of an elective sterilization does not restore fertility (e.g., a male member who remains azoospermic following the reversal of a prior elective sterilization), or
 2. either partner has undergone an elective sterilization in the past.

V. **Contraindications:** Clinical **contraindications** to infertility treatment with FDA-approved drugs or co-morbid conditions that include:

- A. significant bilateral tubal disease:
 1. that is uncorrectable by surgery, or
 2. with ART procedure(s) where fertilization occurs within the body, or
 3. and are contraindicated for IVF/GIFT/ZIFT;
- B. extensive pelvic adhesions;
- C. coexisting medical conditions that place the patient and/or fetus at unacceptable risk (e.g., uncontrolled diabetes mellitus, poorly controlled hypertension, morbid obesity (clinically severe obesity) with BMI>35.0, ~~or~~ usage of prescription medication detrimental to or contraindicated for pregnancy), or other uncontrolled medical conditions; or
- D. baseline (day 2-day 4) FSH greater than or equal to 15 mIU/ml.

VI. Based upon our criteria, assisted reproductive technology (ART) services that are intended to achieve conception and do not treat a correctable malformation, disease or dysfunction are **not medically appropriate** unless used in conjunction with superovulation therapy with clomiphene citrate or gonadotropins.

VII. **Sperm Washing and Artificial Insemination:** Based upon our criteria and review of the peer-reviewed literature, sperm washing and artificial insemination are **medically appropriate** in cases of low sperm count, low sperm motility, quadriplegia or paraplegia in male members, poor sperm-mucous interaction or unexplained infertility (the inability to conceive where reproductive defects have not been able to be identified).

VIII. **Investigational procedures:** Based upon our criteria and review of the peer-reviewed literature, the following have not been medically proven to be effective and, therefore, are considered **investigational:**

- A. Assisted hatching,
- B. Hyaluronan binding assay (HBA),
- C. Co-culture of embryos, and
- D. Sperm DNA integrity tests (e.g., sperm chromatin structure assay [SCSA®], sperm chromatin dispersion test [SCD], sperm DNA fragmentation assay [SDFATM], deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end labeling [TUNEL], single cell electrophoresis assay [COMET]).

<p>SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY</p> <p>POLICY NUMBER: 4.01.05</p> <p>CATEGORY: Contract Clarification</p>	<p>EFFECTIVE DATE: 06/20/01</p> <p>REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18</p> <p>PAGE: 3 OF: 15</p>
---	--

IX. Exclusions and Limitations:

- A. In vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT) and other forms of assisted reproductive technology: are **contract dependent**.
- B. The following services are generally excluded by contract and are **ineligible for coverage**:
 - 1. Procurement of donor sperm or ova;
 - 2. Cryopreservation of eggs, sperm or semen, embryo, oocyte, testicular or ovarian reproductive tissue.
 - 3. Monitoring and storage of cryopreserved eggs, embryo, oocyte, sperm or semen, testicular or ovarian reproductive tissue or previously frozen embryos.
 - 4. Thawing of cryopreserved eggs, embryo, oocyte, sperm or semen, testicular or ovarian reproductive tissue.
 - 5. Cloning services and procedures.
 - 6. Reversal of tubal ligations.
 - 7. Reversal of vasectomies.
 - 8. Travel expenses

All services must be provided by Providers who are qualified to provide such services in accordance with the guidelines established and adopted by the American Society for Reproductive Medicine.

Refer to the FLRx Prescription Drug Policies regarding: Infertility Medications.

POLICY GUIDELINES:

- I. **All** assisted reproductive technologies (ART), including but not limited to, in-vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), and artificial insemination, are **contract dependent**. Inclusive with ART but not limited to:
 - A. Surgical procedures, including retrieval of eggs or sperm from the Member and transfer of a fertilized egg to a female Member.
 - B. Members are eligible for In Vitro Fertilization and Assisted Reproductive Technology: when the couple has been unable to achieve a pregnancy after 12 months of unprotected intercourse, or six (6) months for Members age 35 and older; and after other reasonable, less expensive and medically appropriate infertility treatments have not resulted in a successful pregnancy.
- II. The diagnosis and treatment for infertility services must be prescribed by a physician in a plan of care.
- III. Benefits will not be provided for infertility services unless there has been a diagnosis of infertility.
- IV. ART consists of several steps over an interval of approximately 2 weeks and is considered a cycle of treatment rather than a procedure at a single point in time. The start of an ART cycle is when a woman begins taking drugs to stimulate production of ova or starts ovarian monitoring with the intent of having embryos transferred. The cycle continues through all necessary steps until after the time sperm is transferred during insemination or embryo(s) are transferred during IVF/GIFT/ZIFT.
- V. Peer-reviewed, published studies and professional society guidelines do not provide data concerning the appropriate number of cycles. Therefore, based upon specialty clinician input, when coverage is available for ART services and cycle limitations are not stipulated in the member's subscriber contract, the following will apply:
 - A. Artificial insemination is limited to a lifetime maximum of 6 cycles, and
 - B. IVF, GIFT, and/or ZIFT are limited to a lifetime maximum of 3 cycles.
- VI. All obese patients (BMI > 30 kg/2) should be counseled on lifestyle and behavioral modifications, such as appropriate diet and exercise. For counseling of morbid obesity (clinically severe obesity) as a coexisting medical conditions that places the patient and/or fetus at unacceptable risk see: <https://www.acog.org/Patients/FAQs/Obesity-and-Pregnancy#does>.

<p>SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY</p> <p>POLICY NUMBER: 4.01.05</p> <p>CATEGORY: Contract Clarification</p>	<p>EFFECTIVE DATE: 06/20/01</p> <p>REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18</p> <p>PAGE: 4 OF: 15</p>
---	--

- VII. Only a male member's primary care physician, an in-plan urologist (when required by contract), or the female member's OB/GYN or reproductive endocrinologist may perform the male member's infertility evaluation, referral for semen analysis and appropriate follow-up treatment.
- VIII. A contracted laboratory (when required by contract) must perform semen analysis in conjunction with female infertility evaluations.
- IX. Experimental, nonstandard, and/or unevaluated infertility treatments and drugs approved by the FDA that are not specifically approved to treat infertility are **ineligible for coverage**.
- According to the American Society for Reproductive Medicine (ASRM), "Procedures (including tests, treatments, or other interventions) for the diagnosis or treatment of infertility will be considered experimental or investigational until the published medical evidence regarding their risks, benefits, and overall safety and efficacy is sufficient to regard them as established medical practice."
- X. Diagnostic work-up and infertility treatments for a partner who is not a member is **ineligible for coverage**.
- XI. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION:

According to the American Society of Reproductive Medicine infertility is a disease*, defined by the failure to achieve pregnancy after 12 months or more of appropriate, timed regular unprotected intercourse or therapeutic donor insemination. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years.

* Disease is "any deviation from or interruption of the normal structure or function of any part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, and prognosis may be known or unknown." (Dorland's Illustrated Medical Dictionary, 31st edition, 2007:535)

- I. There are many *causes* of infertility and these causes can be attributed to either female or male factors or both.
- A. Female factors of infertility include:
1. ovulatory dysfunctions such as: amenorrhea, oligoovulation, oligomenorrhea, or hyperprolactinemia;
 2. uterine anomalies and abnormalities such as: unicornate, septate or bicornate uteri, endometrial polyps, submucous myomas, or synechiae;
 3. peritoneal factors such as: endometriosis or pelvic/adnexal adhesions;
 4. anatomic tubal damage or disease; or
 5. cervical factors such as: abnormal cervical mucus production or poor sperm-mucous interaction.
- B. Male factors of infertility include:
1. azoospermia - the absence of spermatozoa/sperm;
 2. oligospermia - low sperm count;
 3. low sperm motility; and/or
 4. teratospermia - abnormal semen morphology.
- II. The *treatment* of infertility may include a variety of diagnostic procedures, therapeutic drugs and ART procedures. The services involved in evaluation and treatment of infertility vary and may include the following:
- A. Complex infertility work-ups;
 - B. Hormonal treatments;
 - C. Laparoscopy;
 - D. Hysteroscopy;
 - E. Endometrial biopsy;

<p>SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY</p> <p>POLICY NUMBER: 4.01.05</p> <p>CATEGORY: Contract Clarification</p>	<p>EFFECTIVE DATE: 06/20/01</p> <p>REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18</p> <p>PAGE: 5 OF: 15</p>
---	--

- F. Fallopian tube catheterization and recannulization;
 - G. Hysterosalpingogram;
 - H. Ultrasound/sonography;
 - I. Laboratory studies (e.g., Semen analysis, Hormone level studies, appropriate blood tests);
 - J. Follicular stimulation with medications (e.g., Clomid, Gonal-f);
 - K. Monitoring ovulation via ultrasound and endocrine studies;
 - L. Post coital tests;
 - M. Semen analysis;
 - N. Retrieval of ova by various methods under general or local anesthesia; and
 - O. Varicocele repair, testicular biopsy, or epididymal aspiration.
- III. ART procedures include the laboratory handling of human ova, sperm and embryos. ART procedures include, but are not limited to, the following:
- A. Procedures in which fertilization takes place within the human body:
 1. *Artificial Insemination (AI)* - a process involving the non-coital introduction of sperm into the cervical canal (intracervical) or uterine cavity (intrauterine) in order to produce conception.
 2. *Direct Intra-Peritoneal Insemination (DIPI)* - a process attempting fertilization by introducing sperm into the uterus via injection through the abdomen.
 - B. Procedures in which fertilization takes place outside the human body:
 1. *In-Vitro Fertilization (IVF)* - a process in which mature ova are removed from the ovaries by various methods, placed in a laboratory medium with sperm, and incubated for 48-72 hours. The fertilized ova are then placed into the uterus through the cervix. The fertilization procedure takes 2-3 days. The actual fertilization takes place outside the body (in-vitro).
 2. *Cryopreserved Embryo Transfer (CET)* - the transfer of fertilized embryos that were previously cryopreserved (frozen) in the laboratory, thawed and then transferred into the uterus.
 3. *Gamete Intrafallopian Transfer (GIFT)* - a process in which mature ova are aspirated from the ovary by various methods, introduced into a catheter with sperm, and immediately transferred into the fallopian tubes.
 4. *Zygote Intrafallopian Transfer (ZIFT)* - a variation of the GIFT procedure that combines sperm and ova in a laboratory medium resulting in zygote(s) which are then transferred into the fallopian tubes.
 5. *Intracytoplasmic Sperm Injection (ICSI)* - the micromanipulation of sperm performed in a laboratory, and involves injection of a single sperm directly into the cytoplasm of a mature ovum using a microinjection pipette. After fertilization, the embryo is inserted into the uterus or fallopian tube using IVF, GIFT or ZIFT procedures.
 - C. *Natural oocyte retrieval (NORIVF)* - the harvesting of ova from the ovary following natural ovulation (ovulation without hormone therapy).
- IV. Sperm may be obtained from ejaculate, including electro-ejaculate when necessary (e.g., males with spinal cord injury or peripheral neuropathy), cryopreserved specimens, or surgical procedures including, but not limited to, the following techniques:
- A. Microsurgical Epididymal Sperm Aspiration (MESA),
 - B. Microsurgical Testicular Sperm Extraction (MicroTESE),
 - C. Percutaneous Epididymal Sperm Aspiration (PESA),
 - D. Percutaneous Testicular Biopsy (PercBiopsy),
 - E. Testicular Fine Needle Aspiration (TEFNA),
 - F. Testicular Sperm Aspiration (TESA), or
 - G. Testicular Sperm Extraction (TESE).

<p>SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY</p> <p>POLICY NUMBER: 4.01.05</p> <p>CATEGORY: Contract Clarification</p>	<p>EFFECTIVE DATE: 06/20/01</p> <p>REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18</p> <p>PAGE: 6 OF: 15</p>
---	--

An American Urological Association recommendation addressing the management of azoospermia states “the choice of sperm retrieval by either percutaneous or open surgery from either the testis or epididymis should be based upon local preferences and expertise since there is no evidence that the site or method of sperm retrieval affects outcome of in vitro fertilization with intracytoplasmic sperm injection for patients with obstructive azoospermia. Open surgical testicular sperm retrieval with or without microscopic magnification is recommended for patients with nonobstructive azoospermia.”

- V. Laboratory sperm testing:
- A. The *hyaluronan binding assay (HBA)* is a qualitative assay of sperm maturity in which mature sperm bind to hyaluronan. A low level of sperm binding to hyaluronan suggests there is a low proportion of mature sperm in the specimen. HBA has been proposed for standard analysis of semen to diagnose suspected male infertility and to determine if ICSI is needed as part of an ART procedure.
 - B. *Sperm DNA integrity* has emerged as a potential cause of idiopathic male infertility. Commercially available flow cytometry tests of DNA integrity include the sperm chromatin structure assay (SCSA®) and the sperm DNA fragmentation assay (SDFATM). Other laboratory tests for sperm integrity, such as the terminal deoxynucleotidyl transferase-mediated nick end-labeling (TUNEL) and single-cell gel electrophoresis (COMET) assays, require microscopic analysis and can, therefore, only assess a limited number of sperm. Tests of sperm DNA integrity have been proposed for evaluation of failed pregnancy or spontaneous abortions, in unassisted pregnancy, after failed IVF attempts or in selecting sperm samples for cryopreservation.
- VI. *Co-culture of embryos* involves an effort to improve the culture media for embryos so that a greater proportion of embryos will reach the blastocyst stage and hopefully improve the implantation and pregnancy rate. Co-culture can be referred to the procedure whereby “helper” cells are grown along with the developing embryo. A variety of co-culture techniques have been investigated, involving the use of feeder cell layers derived from a range of tissues (e.g., human oviducts, fetal bovine uterine or oviduct cells) to established cell lines.
- VII. *Assisted hatching* involves a procedure intended to thin or perforate the zona pellucida that has been investigated as a method of improving the implantation and subsequent pregnancy rates following IVF. Several techniques have been used to mechanically or chemically weaken the zona pellucida, including drilling, dissection, application of acid solutions or proteinases, and laser energy.
- VIII. New York State Insurance Laws § 3216, § 3221, § 4303 mandate the following benefits for treatment of infertility, **for persons age 21 through 44 years**, under most managed care and health insurance policies
- A. Policies that provide coverage of hospital, surgical and medical care must cover the following services:
 - 1. Services in relation to surgical and medical procedures to *correct malformation, disease or dysfunction* resulting in infertility; and
 - 2. Services in relation to diagnostic tests and procedures necessary:
 - a. to determine infertility; or
 - b. in connection with any surgical or medical treatments or prescription drug coverage included in the mandate.

These services include, but are not limited to: hysterosalpingogram, hysteroscopy, endometrial biopsy, laparoscopy, sono-hysteroqram, post coital tests, testis biopsy, semen analysis, blood tests, ultrasound.
 - B. Policies providing coverage for prescription drugs that also cover hospital or medical/surgical benefits must provide coverage for FDA approved drugs for the diagnosis and treatment of infertility.
 - C. Coverage shall be limited to those individuals who have been previously covered under the policy for a period of not less than twelve month (defined as either the date the insured was first covered under the existing policy or from the date the insured was first covered by a previously in-force converted policy, whichever is earlier).

<p>SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY</p> <p>POLICY NUMBER: 4.01.05</p> <p>CATEGORY: Contract Clarification</p>	<p>EFFECTIVE DATE: 06/20/01</p> <p>REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18</p> <p>PAGE: 7 OF: 15</p>
---	--

- D. Diagnosis and treatment of infertility in connection with: IVF, GIFT, ZIFT, reversal of elective sterilizations, sex change procedures, and cloning are excluded from this mandate.
- E. Medical or surgical services or procedures that are deemed experimental are excluded from the mandate; in accordance with the guidelines and standards of the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM) which state: “A procedure for the treatment of infertility is considered experimental until there is adequate scientific evidence of safety and efficacy from appropriately designed, peer-reviewed, published studies by different investigator groups.”
- F. The diagnosis and treatment for infertility must be prescribed by a physician in a plan of care.
- G. The determination of appropriate candidates for the treatment of infertility and the identification of the required training, experience and other standards for health care providers who wish to diagnose and treat infertility must be in accordance with the standards and guidelines adopted by ACOG and ASRM.
- H. In 1991, the National Institutes of Health defined morbid obesity as a BMI of ≥ 35 kg/m² and severe, obesity related comorbidity as a BMI of ≥ 40 kg/m².

ACOG: Being overweight is defined as having a body mass index (BMI) of 25–29.9. Obesity is defined as having a BMI of 30 or greater. Within the general category of obesity, there are three levels that reflect the increasing health risks that go along with increasing BMI:

- Lowest risk is a BMI of 30–34.9.
- Medium risk is a BMI of 35.0–39.9.
- Highest risk is a BMI of 40 or greater.

RATIONALE:

Assisted hatching - has been utilized by clinicians, but this practice is not strongly supported by the evidence. An update of a 2009 Cochrane systematic review and meta-analysis on assisted hatching (AH) was undertaken to determine the effect of assisted hatching of embryos from assisted conception on live birth and multiple pregnancy rates was published in 2012 (Carney, et al). Randomised controlled trials of AH (mechanical, chemical or laser disruption of the zona pellucida prior to embryo replacement) versus no AH that reported live birth or clinical pregnancy were reviewed for quality assessments and data extraction. Thirty-one trials reported clinical pregnancy data, including 1992 clinical pregnancies in 5728 women. The authors concluded that while AH does appear to offer a significantly increased chance of achieving a clinical pregnancy, the extent to which it may do so only just reaches statistical significance; the 'take home' baby rate was still not proven to be increased by AH; and the included trials provided insufficient data to investigate the impact of AH on several important outcomes and most trials still failed to report on live birth rates. The current data do not support the use of assisted hatching as a routine practice to improve IVF outcomes.

A 2014 guideline from the **American Society of a Reproductive Medicine** that addresses assisted hatching states “There is good evidence that assisted hatching (AH) slightly improves clinical pregnancy rates, particularly in poor prognosis patients, including those with prior failed in vitro fertilization (IVF) cycles. Due to a limited number of studies, there is insufficient evidence to conclude that AH improves live-birth rates” and “AH should not be recommended routinely for all patients undergoing IVF”.

Co-culture of embryos - 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. One 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 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.

Hyaluronan binding assay -In the published 2016 study of 98 patients to evaluate the correlation of HBA with other semen parameters listed, Rashki et al concluded: The HBA is sensitive to morphological integrity, high progressive

SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY POLICY NUMBER: 4.01.05 CATEGORY: Contract Clarification	EFFECTIVE DATE: 06/20/01 REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18 PAGE: 9 OF: 15
--	---

- 89260 Sperm isolation; simple prep (e.g. sperm wash and swim up) for insemination or diagnosis with semen analysis
- 89261 complex prep (e.g. Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis
- 89264 Sperm identification from testis tissue, fresh or cryopreserved
- 89268 Insemination of oocytes
- 89272 Extended culture of oocyte(s)/embryo(s), 4-7 days
- 89280 Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes
- 89281 greater than 10 oocytes
- 89300 Semen analysis, presence and/or motility of sperm including Huhner test
- 89310 motility and count (not including Huhner test)
- 89320 volume, count, motility, and differential
- 89321 Sperm presence and motility of sperm, if performed
- 89322 volume, count, motility, and differential using strict morphologic criteria (eg, Kruger)
- 89325 Sperm antibodies
- 89329 Sperm evaluation; hamster penetration test
- 89330 cervical mucus penetration test, with or without spinnbarkeit test
- 89331 Sperm evaluation, for retrograde ejaculation, urine (sperm concentration, motility, and morphology, as indicated)

Non-covered codes:

- 0058T NCB Cryopreservation; reproductive tissue, ovarian
- 0357T NCB Cryopreservation, immature oocyte(s)
- 89251 (E/I) Culture of oocyte(s)/embryo(s), less than 4 days; with co-culture of oocyte(s)/embryos
- 89253 (E/I) Assisted embryo hatching, microtechniques (any method)
- 89258 NCB Cryopreservation; embryo
- 89259 NCB Cryopreservation; sperm
- 89335 NCB Cryopreservation, reproductive tissue, testicular
- 89337 NCB Cryopreservation, mature oocyte(s)
- 89342 NCB Storage, (per year); embryo(s)
- 89343 NCB Storage, (per year); sperm/semen
- 89344 NCB Storage, (per year); reproductive tissue, testicular/ovarian
- 89346 NCB Storage, (per year); oocyte(s)

SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY POLICY NUMBER: 4.01.05 CATEGORY: Contract Clarification	EFFECTIVE DATE: 06/20/01 REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18 PAGE: 10 OF: 15
--	--

- 89352 NCB Thawing of cryopreserved; embryo(s)
- 89353 NCB Thawing of cryopreserved; sperm/semen, each aliquot
- 89354 NCB Thawing of cryopreserved; reproductive tissue, testicular/ovarian
- 89356 NCB Thawing of cryopreserved; oocytes, each aliquot
- 89398 NCB Unlisted reproductive medicine laboratory procedure

Copyright © 2018 American Medical Association, Chicago, IL

- HCPCS:**
- S4011 In vitro fertilization; including but not limited to identification and incubation of mature oocytes, fertilization with sperm, incubation of embryo(s), and subsequent visualization for determination of development
 - S4013 Complete cycle, gamete intrafallopian transfer (GIFT), case rate
 - S4014 Complete cycle, zygote intrafallopian transfer (ZIFT), case rate
 - S4015 Complete in vitro fertilization cycle, not otherwise specified, case rate
 - S4016 Frozen in vitro fertilization cycle, case rate
 - S4017 Incomplete cycle, treatment cancelled prior to stimulation, case rate
 - S4018 Frozen embryo transfer procedure cancelled before transfer, case rate
 - S4020 In vitro fertilization procedure cancelled before aspiration, case rate
 - S4021 In vitro fertilization procedure cancelled after aspiration, case rate
 - S4022 Assisted oocyte fertilization, case rate
 - S4028 Microsurgical epididymal sperm aspiration (MESA)
 - S4035 Stimulated intrauterine insemination (IUI), case rate
 - S4037 Cryopreserved embryo transfer, case rate
 - S4042 Management of ovulation induction (interpretation of diagnostic tests and studies, non-face-to-face medical management of the patient), per cycle

Non-covered codes (See Contract Rider):

- S4023 (NCB) Donor egg cycle, incomplete, case rate
- S4025 (NCB) Donor services for in vitro fertilization (sperm or embryo), case rate
- S4026 (NCB) Procurement of donor sperm from sperm bank
- S4027 (NCB) Storage of previously frozen embryo
- S4030 (NCB) Sperm procurement and cryopreservation services; initial visit
- S4031 (NCB) Sperm procurement and cryopreservation services; subsequent visit
- S4040 (NCB) Monitoring and storage of cryopreserved embryos, per 30 days

- ICD10:**
- E23.0 Hypopituitarism
 - N46.01-N46.9 Male infertility (code range)

SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY POLICY NUMBER: 4.01.05 CATEGORY: Contract Clarification	EFFECTIVE DATE: 06/20/01 REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18 PAGE: 11 OF: 15
--	--

N97.0-N97.9 Female infertility (code range)

REFERENCES:

*Agency for Healthcare Research and Quality. Effectiveness of assisted reproductive technology. Evidence report Publication No. 08-E012. 2008 May [<http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/evidence-based-reports/infertil-evidence-report.pdf>] accessed 9/13/18.

Al-Inany HG, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev 2016 Apr;4:CD001750.

American College of Obstetricians and Gynecologists Committee on Gynecologic Practice; Practice Committee of the American Society for Reproductive Medicine. Committee Opinion No. 589: Female age-related fertility decline. Obstet Gynecol 2014 Mar;123(3):719-21. Reaffirmed 2016.

American College of Obstetricians and Gynecologists Committee on Gynecologic Practice; Obesity and Pregnancy [<https://www.acog.org/Patients/FAQs/Obesity-and-Pregnancy>] accessed 9/13/18.

American Society for Reproductive Medicine [<http://www.asrm.org/news-and-publications/practice-committee-documents/>] accessed 9/13/18.

- ASRM standard embryo transfer protocol template: a committee opinion. 2017 Apr.
- Blastocyst culture and transfer in clinical-assisted reproduction. 2013 Mar.
- Criteria for number of embryos to transfer. 2013 Jan.
- Definition of experimental procedures. 2013 Apr.
- Definitions of infertility and recurrent pregnancy loss. 2013 Jan.
- Diagnostic evaluation of the infertile female. 2015 Jun.
- Diagnostic evaluation of the infertile male. 2015 Mar.
- *Effectiveness and treatment for unexplained infertility. 2006 Nov.
- Elective single-embryo transfer. 2012.
- *Evaluation of the azoospermic male. 2008 Nov.
- Female age-related fertility decline. 2014 Mar.
- Guidance on the limits to the number of embryos to transfer: a committee opinion. 2017 Apr.
- Intracytoplasmic sperm injection (ICSI) for non-male factor infertility. 2012 Dec.
- In vitro maturation. 2013 Mar.
- Optimizing natural fertility. 2013 Sep.
- Revised minimum standards for practices offering assisted reproductive technologies. 2014 Sep.
- Role of assisted hatching in in vitro fertilization: a guideline. 2014 May.
- *Round spermatid nucleus injection (ROSNI). 2008 Jun.
- *Sperm retrieval for obstructive azospermia. 2008 Nov.
- The clinical utility of sperm DNA integrity testing. 2013 Mar.
- *The management of infertility due to obstructive azospermia. 2008 Aug.
- Use of clomiphene citrate in women. 2013 Aug.

*American Urological Association. The optimal evaluation of the infertile male: AUA best practice statement. Reviewed 2011 [[https://www.auanet.org/guidelines/male-infertility-optimal-evaluation-\(reviewed-and-validity-confirmed-2011\)](https://www.auanet.org/guidelines/male-infertility-optimal-evaluation-(reviewed-and-validity-confirmed-2011))] accessed 9/13/18.

*American Urological Association. The management of obstructive azospermia: AUA best practice statement. Reviewed 2011 [[https://www.auanet.org/guidelines/male-infertility-management-of-obstructive-azoospermia-\(reviewed-and-validity-confirmed-2011\)](https://www.auanet.org/guidelines/male-infertility-management-of-obstructive-azoospermia-(reviewed-and-validity-confirmed-2011))] accessed 9/13/18.

<p>SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY</p> <p>POLICY NUMBER: 4.01.05</p> <p>CATEGORY: Contract Clarification</p>	<p>EFFECTIVE DATE: 06/20/01</p> <p>REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18</p> <p>PAGE: 12 OF: 15</p>
---	---

*Badawy A, et al. Clomiphene citrate or aromatase inhibitors for superovulation in women with unexplained infertility undergoing intrauterine insemination: a prospective randomized trial. Fertil Steril 2009 Oct;92(4):1355-9.

Benkhalifa M, et al. Autologous embryo-cumulus cells co-culture and blastocyst transfer in repeated implantation failures: a collaborative prospective randomized study. Zygote 2012 May;20(2):173-80.

Assisted reproductive technologies for male subfertility. Cochrane Database Syst Rev. 2016 Feb 26;2:CD000360. Updated.

*Besselink DE, et al. Cervical insemination versus intra-uterine insemination of donor sperm for subfertility. Cochrane Database Syst Rev 2008;(2):CD000317.

BlueCross BlueShield Association. Reproductive technologies. Medical Policy Reference Manual Policy #4.02.04. 2015 Apr 23.

*BlueCross BlueShield Association. Laboratory tests of sperm maturity, function, and DNA integrity - archived. Medical Policy Reference Manual Policy #4.02.01. 2009 Sep 10.

*Boomsma CM, et al. Semen preparation techniques for intrauterine insemination. Cochrane Database Syst Rev 2007;(4):CD004507.

*Cantineau AEP and Cohlen BJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. Cochrane Database Syst Rev 2007;(2):CD005356.

Carney SK, et al. Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI)). Cochrane Database Syst Rev 2012;(12):CD001894.

Centers for Disease Control and Prevention. Assisted reproductive technology. Last updated 2017 November 28 [<http://www.cdc.gov/ART/index.html>] accessed 9/13/18.

Cissen M, et al. Assisted reproductive technologies for male subfertility. Cochrane Database Syst Rev 2016 Feb;2:CD000360.

*Collins JA, et al. Do sperm DNA integrity tests predict pregnancy with in vitro fertilization? Fertil Steril 2008 Apr;89(4):823-31.

*Custers IM, et al. Intrauterine insemination: how many cycles should we perform? Hum Reprod 2008 Apr;23(4):885-8.

Das S, et al. Assisted hatching on assisted conception (IVF and ICSI). Cochrane Database of Systematic Reviews 2012;(12):CD001894.

*Donoso P, et al. Which is the best sperm retrieval technique for non-obstructive azoospermia? A systematic review. Hum Reprod Update 2007 Nov-Dec;13(6):539-49.

*ESHRE Capri Workshop Group. Intrauterine insemination. Hum Reprod Update 2009 May-Jun;15(3):265-77.

Farquhar C, et al. Assisted reproductive technology: an overview of Cochrane reviews. Cochrane Database Syst Rev 2015 Jul;7:CD010537.

*Ghobara T and Vandekerckhove P. Cycle regimens for frozen-thawed embryo transfer. Cochrane Database Syst Rev 2008;(1):CD003414.

Glujovsky D, et al. Cleavage stage versus blastocyst stage embryo transfer in assisted conception. Cochrane Database Syst Rev 2012;(7):CD002118.

Hansen M, et al. Assisted reproductive technology and birth defects: a systematic review and meta-analysis. Hum Reprod Update 2013 Jul-Aug;19(4):330-53.

<p>SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY</p> <p>POLICY NUMBER: 4.01.05</p> <p>CATEGORY: Contract Clarification</p>	<p>EFFECTIVE DATE: 06/20/01</p> <p>REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18</p> <p>PAGE: 13 OF: 15</p>
---	---

Huang Z, et al. Brief co-incubation of sperm and oocytes for in vitro fertilization techniques. *Cochrane Database Syst Rev* 2013 Apr 30;4:CD009391.

Johnson LN, et al. Does intracytoplasmic sperm injection improve the fertilization rate and decrease the total fertilization failure rate in couples with well-defined unexplained infertility? A systematic review and meta-analysis. *Fertil Steril* 2013 Sep;100(3):704-11.

*Joint SOGC-CFAS. Guidelines for the number of embryos to transfer following in vitro fertilization No. 182, 2006 Sep. *Int J Gynaecol Obstet* 2008 Aug;102(2):203-16.

Jungwirth A, et al; European Association of Urology Working Group on Male Infertility. European Association of Urology guidelines on Male Infertility: the 2012 update. *Eur Urol* 2012 Aug;62(2):324-32.

Junsheng L, et al. The impact of surgical sperm retrieval on the in vitro fertilization outcomes of infertile patients with temporary ejaculation failure on their oocyte retrieval day. *Fertil Steril* 2013 Feb;99(2):362-6.

Kanyo K, Zeke J, Kriston R, et al. The impact of laser-assisted hatching on the outcome of frozen human embryo transfer cycles. *Zygote*. Mar 9 2016:1-6. PMID 26957232

*Kwan I, et al. Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI). *Cochrane Database Syst Rev* 2008;(2):CD005289.

Leanza V, et al. Ovulation induction with clomiphene citrate for infertile couple. *Minerva Ginecol* 2014 Jun;66(3):309-12.

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.

Martins WP, et al. Assisted hatching of human embryos: a systematic review and meta-analysis of randomized controlled trials. *Human Repro Update* (2013) 19 (2): 207.

*Martins WP, et al. Assisted hatching of human embryos: a systematic review and meta-analysis of randomized controlled trials. *Hum Reprod Update* 2011 Jul-Aug;17(4):438-53.

McDowell S, et al. Advanced sperm selection techniques for assisted reproduction. *Cochrane Database Syst Rev* 2014 Oct 28;10:CD010461.

*National Institutes of Health Consensus Development Program: Overweight and Obesity. [<https://consensus.nih.gov/1991/1991GISurgeryObesity084html.htm>] accessed 9/13/18.

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.

Ohlander S, et al. Impact of fresh versus cryopreserved testicular sperm upon intracytoplasmic sperm injection pregnancy outcomes in men with azoospermia due to spermatogenic dysfunction: a meta-analysis. *Fertil Steril* 2014 Feb;101(2):344-9

Ombelet W, et al. Semen quality and prediction of IUI success in male subfertility: a systematic review. *Reprod Biomed Online* 2014 Mar;28(3):300-9.

*Pandian Z, et al. Number of embryos for transfer after IVF and ICSI: a Cochrane review. *Hum Reprod* 2005 Oct;20(10):2681-7.

*Pandian Z, et al. In vitro fertilisation for unexplained subfertility. *Cochrane Database Syst Rev* 2012;(4):CD003357.

<p>SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY</p> <p>POLICY NUMBER: 4.01.05</p> <p>CATEGORY: Contract Clarification</p>	<p>EFFECTIVE DATE: 06/20/01</p> <p>REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18</p> <p>PAGE: 14 OF: 15</p>
---	---

Rashki GL, et al. Hyaluronic Acid Binding Assay Is Highly Sensitive to Select Human Spermatozoa with Good Progressive Motility, Morphology, and Nuclear Maturity. Gynecol Obstet Invest. 2016;81(3):244-50.

Ray A, et al, Unexplained infertility: an update and review of practice. Reprod Biomed Online 2012 Jun;24(6):591-602.

Ren X, et al. Effect of the site of assisted hatching on vitrified-warmed blastocyst transfer cycles: a prospective randomized study. J Assist Reprod Genet 2013 Jun;30(5):691-7.

Reproductive Endocrinology and Infertility Committee, et al. Advanced reproductive age and fertility. J Obstet Gynaecol Can 2011 Nov;33(11):1165-75.

Rimm AA, et al. A meta-analysis of the impact of IVF and ICSI on major malformations after adjusting for the effect of subfertility. J Assist Reprod Genet 2011 Aug;28(8):699-705.

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. 2016 Oct;23(10):1397-401.

Sinawat S, et al. Long versus short course treatment with Metformin and Clomiphene Citrate for ovulation induction in women with PCOS. Cochrane Database Syst Rev 2012;(10):CD006226.

Society of Obstetricians and Gynaecologists of Canada, Okun N and Sierra S. Pregnancy outcomes after assisted human reproduction. J Obstet Gynaecol Can 2014 Jan;36(1):64-83.

Teixeira DM, et al. Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction. Cochrane Database Syst Rev 2013 Jul 25;7:CD010167.

van der Linden M, et al. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev 2011 Oct 5;(10):CD009154.

van Hoogenhuijze, et al. Endometrial scratching in women with implantation failure after a first IVF/ICSI cycle; does it lead to a higher live birth rate? The SCRaTCH study: a randomized control trial (NTR 5342) BMC Womens Health. 2017 Jul 21. Epub ahead of print.

*Van Peperstraten A, et al. Techniques for surgical retrieval of sperm prior to intra-cytoplasmic sperm injection (ICSI) for azoospermia. Cochrane Database Syst Rev 2008;(2):CD002807.

Veltman-Verhulst SM, et al. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev 2012;(9):CD001838.

Zhao J, et al. Whether sperm deoxyribonucleic acid fragmentation has an effect on pregnancy and miscarriage after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis. Fertil Steril 2014 Oct;102(4):998-1005.e8.

*key articles

KEY WORDS:

Artificial insemination, COMET assay, Direct intra-peritoneal insemination (DIPI), Gamete intrafallopian transfer (GIFT), Hyaluronan binding assay (HBA), Infertility, Intracytoplasmic sperm injection (ICSI), In-vitro fertilization (IVF), Microsurgical epididymal sperm aspiration (MESA), Microsurgical Testicular Sperm Extraction (MicroTESE), Sperm chromatin dispersion test [SCD], Sperm DNA integrity, Sperm chromatin structure assay (SCSA®), Sperm DNA fragmentation assay (SDFATM), Testicular sperm extraction (TESE), TUNEL assay, Zygote intrafallopian transfer (ZIFT).

SUBJECT: ASSISTED REPRODUCTIVE TECHNOLOGIES FOR INFERTILITY	EFFECTIVE DATE: 06/20/01
POLICY NUMBER: 4.01.05	REVISED DATE: 07/02/01, 08/22/02, 07/24/03, 06/24/04, 08/25/05, 08/31/06, 08/23/07, 08/28/08, 04/23/09, 06/24/10, 06/24/11, 06/28/12, 06/27/13, 06/26/14, 06/25/15, 06/22/16, 10/26/17, 10/25/18
CATEGORY: Contract Clarification	PAGE: 15 OF: 15

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based on our review, Assisted Reproductive Technologies for Infertility is not addressed in National or Local CMS coverage determinations or policies.