# Medical Coverage Policy

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# Infertility Services

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## Overview

This Coverage Policy addresses diagnostic testing to establish the etiology of infertility and infertility treatments.

## Coverage Policy

**Coverage of infertility diagnostic and treatment services varies across plans. Testing to determine fertility is only available under an applicable infertility benefit plan. In addition, fertility preservation services are only available under an applicable fertility preservation and/or conception benefit, unless state mandates apply. Refer to the customer's benefit plan document for coverage details.**

**In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.**

**State mandates may require coverage for some infertility-related services, including certain fertility preservation services. State mandates generally define fertility preservation services as procedures consistent with established medical practices and professional guidelines published by the American Society for Reproductive Medicine, the American Society of Clinical Oncology, or other reputable professional medical organizations. According to the American Society of Reproductive Medicine (ASRM) and American Society for Clinical Oncology (ASCO) medical practices and guidelines, fertility preservation procedures are defined as those procedures indicated for an individual facing infertility due to chemotherapy, pelvic radiotherapy, or other surgical procedures expected to render one permanently infertile (e.g., hysterectomy, oophorectomy). Please refer to the applicable state mandate for further detail.**

**When not clearly specified in the benefit plan, infertility is defined as the need for medical intervention 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. This includes, for example, the need for an individual, regardless of relationship status, sexual orientation, or gender identity, to use donor gametes or embryos in order to achieve a successful pregnancy resulting in delivery.**

**Nothing in this definition shall be construed in a manner that excludes any medical interventions on the basis of relationship status or sexual orientation.**

**Additionally, this definition does not guarantee that a particular benefit plan covers fertility services, and it does not guarantee coverage for fertility services rendered to individuals not enrolled in the applicable benefit plan, such as an individual not enrolled in a benefit plan who is acting as a surrogate.**

**In the absence of a diagnosis of infertility, in-vitro fertilization (IVF) services are considered not medically necessary.**

**Once an individual meets the definition of infertility as outlined in the benefit plan or as listed above, the following services associated with establishing the etiology of infertility are generally covered under the medical benefits of the infertility plan option when available.**

**DIAGNOSTIC TESTING TO ESTABLISH THE ETIOLOGY OF INFERTILITY**
**The following services are considered medically necessary, when performed solely to establish the underlying etiology of infertility:**

**Evaluation of the female factor:**

- history and physical examination
- laboratory tests: thyroid stimulating hormone (TSH), prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone
- ultrasound of the pelvis to assess pelvic organs/structures
- hysteroscopy
- hysterosalpingography
- sonohysterography
- diagnostic laparoscopy with or without chromotubation
- ovarian reserve testing using anti-mullerian hormone (AMH) level, cycle day 3 FSH, ultrasonography for antral follicle assessment, or clomiphene challenge test when ANY of the following criteria is met:
    - women over age 35
    - family history of early menopause
    - single ovary or history or previous ovarian surgery, chemotherapy, or pelvic radiation therapy
    - unexplained infertility
    - previous poor response to gonadotropin stimulation
    - planning treatment with assisted reproductive technologies (e.g., IVF)

**Evaluation of the male factor:**

- history and physical examination
- semen analysis: two specimens at least one month apart, to evaluate semen volume, concentration, motility, pH, fructose, leukocyte count, microbiology, and morphology
- additional laboratory tests: endocrine evaluation (including FSH, total and free testosterone, prolactin, LH, TSH), antisperm antibodies, post-ejaculatory urinalysis
- transrectal ultrasound (TRUS), scrotal ultrasound
- vasography and testicular biopsy in individuals with azoospermia
- scrotal exploration
- testicular biopsy

**TREATMENT OF INFERTILITY**
**If benefit coverage for infertility treatment is available, the following treatment services may be considered medically necessary:**

**Female infertility treatment services:**

- U.S. Food and Drug Administration (FDA)-approved ovulation induction medications
- ovulation monitoring studies such as ultrasound and endocrine evaluation
- tubal recanalization, fluoroscopic/hysteroscopic selective tube cannulation, tuboplasty, salpingostomy, fimbrioplasty, tubal anastomosis, and salpingectomy (**NOTE**: Procedures

performed to reverse female voluntary sterilization are not covered, even if benefits are available for infertility treatment.)

- surgical laparoscopy, therapeutic hysteroscopy, cervical recanalization, lysis of adhesions, myomectomy, removal of tumors and cysts, septate uterus repair, ovarian wedge resection, ovarian drilling
- in vitro fertilization with embryo transfer (IVF-ET), in vitro with elective single embryo transfer (eSET), tubal embryo transfer (TET), low tubal ovum transfer (LTOT), pronuclear stage transfer (PROST), or natural cycle IVF, and associated services, including the following: ovulation induction, oocyte retrieval, sperm preparation and washing, associated laboratory tests and ultrasounds, mock embryo transfer/uterine sounding, embryo assessment and transfer, and embryologist services
- assisted embryo hatching for women with **ANY** of the following criteria:
  - individuals 38 years of age or older
  - elevated day-3 FSH
  - increased zona thickness on microscopy
  - three or more IVF-attempt failures related to failed implantation
- intracytoplasmic sperm injection (ICSI) and associated services, including sperm extraction and retrieval procedures

**Male infertility treatment services:**

- pharmacologic treatment of endocrinopathies including hypogonadotropic hypogonadism with FDA-approved drugs such as human chorionic gonadotropins, human menopausal gonadotropin or pulsatile gonadotropin-releasing hormone, corticosteroids, and androgens
- surgical/microsurgical reconstruction or repair of the vas and/or epididymis or other epididymis surgery, such as vasovasostomy, epididymovasostomy, and epididymectomy (**NOTE**: Procedures performed to reverse voluntary male sterilization are not covered, even if benefits are available for infertility treatment.)
- transurethral resection of the ejaculatory ducts (TURED) for the treatment of ejaculatory duct obstruction
- repair of varicocele, excision of tumors (e.g., epididymal), testicular biopsy, orchiopexy, spermatic vein ligation, and excision of spermatocele
- seminal tract washout
- sperm extraction and retrieval procedures such as: electroejaculation, microsurgical epididymal sperm aspiration (MESA), testicular sperm aspiration (TESA), testicular fine needle aspiration (TEFNA), testicular sperm extraction (TESE), microscopic-TESE, percutaneous epididymal sperm aspiration (PESA), vasal sperm aspiration, and seminal vesicle sperm aspiration

**CRYOPRESERVATION SERVICES**

**Coverage of cryopreservation services varies across plans and may be governed by state mandates.**

**If benefit coverage for cryopreservation and/or related services are available and there is no state mandate requiring coverage of more extensive fertility preservation services, the following apply:**

**Cryopreservation, storage and thawing of EITHER of the following is considered medically necessary:**

- embryos, only while the individual is currently under covered active infertility treatment
- mature oocyte(s), only while the individual is currently under covered active infertility treatment and when **BOTH** of the following criteria are met:

- a covered IVF cycle using fresh oocyte(s) for fertilization
- an inability to obtain viable sperm for oocyte fertilization at the time of oocyte retrieval

**Each of the following is considered experimental, investigational or unproven:**

- Cryopreservation of immature oocytes, including in vitro maturation
- Retrieval, cryopreservation, storage, thawing, and re-transplantation of testicular reproductive tissue
- Retrieval, cryopreservation, storage, thawing, and re-transplantation of ovarian reproductive tissue (Unless applicable state mandate requires coverage for fertility preservation.)

**Many benefit plans exclude cryopreservation, storage, and thawing of the following, even when benefits are available for infertility treatment. In addition, these services are considered not medically necessary:**

- embryos when not undergoing covered active infertility treatment
- sperm
- oocytes for any indication other than listed above

**Experimental/Investigational/Unproven**

**Each of the following infertility services or tests are considered experimental, investigational, or unproven:**

- acupuncture
- hyperbaric oxygen therapy for IVF and/ or treatment of male factor infertility
- intravaginal culture of oocytes (e.g., INVOcell)
- immunological testing (e.g., antiprothrombin antibodies, embryotoxicity assay, circulating natural killer cell measurement, antiphospholipid antibodies, reproductive immunophenotype [RIP], T1 and T2 Helper ratios)
- immune treatments (e.g., peri-implantation glucocorticoids, anti-tumor necrosis factor agents, leukocyte immunization, IV immunoglobulins)
- co-culturing of embryos/oocytes (i.e., culture of oocyte(s), embryo(s), less than 4 days with co-culture)
- computer-assisted sperm motion analysis
- direct intraperitoneal insemination, intrafollicular insemination, fallopian tube sperm transfusion
- endometrial receptivity testing (e.g., Endometrial Function Test™ [EFT®], integrin testing, Beta-3 integrin test, E-tegrity®, endometrial receptivity array [ERA])
- fine needle aspiration mapping
- hemizona test
- hyaluronan binding assay (HBA)
- serum inhibin B
- sperm viability test (e.g., hypo-osmotic swelling test), when performed as a diagnostic test
- the use of sperm precursors (i.e., round or elongated spermatid nuclei, immature sperm) in the treatment of infertility
- sperm-capacitation assessment (e.g., Cap-Score™ Assay [Androvia LifeSciences, Mountainside, New Jersey])
- manual soft tissue therapy for the treatment of pelvic adhesions (WURN Technique®, Clear Passage Therapy)
- laser-assisted necrotic blastomere removal from cryopreserved embryos

- reactive oxygen species testing (ROS)
- time-lapse monitoring/imaging of embryos (e.g., EmbryoScope, Eeva™ Test )
- vaginal microbiome testing (e.g., SmartJane™ screening test [Biome, Inc])
- uterine transplantation
- saline-air infused sono-hysterosalpingogram (e.g., femVue® [Femasys, Inc.])

**Many benefit plans exclude the following services even when benefits are available for infertility treatment. In addition, all of these services are not covered or reimbursable:**

- services associated with the reversal of voluntary sterilization
- infertility services when the infertility is caused by or related to voluntary sterilization
- donor charges, fees and services, including services associated with donor sperm and donor oocytes
- infertility services rendered to a surrogate and surrogate fees
- commercially available over-the-counter home ovulation prediction test kits
- home pregnancy test kits

## Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

Black and Hispanic/Latinx women face significant disparities in seeking care for infertility compared with White women. Studies have shown that Black women are half as likely to be evaluated for infertility. Compared with White women, Black and Hispanic/Latinx women had been attempting to conceive 20 months longer before receiving care. The underlying causes of these inequities are not well understood but likely involve factors such as limited fertility knowledge, misconceptions, and mistrust of the health care system among Black women; these underlying causes can be compounded by physician bias based on longstanding stereotypes. Black and Hispanic/Latinx women have reported difficulties in finding physicians with whom they feel comfortable, sharing that they have felt judged by fertility clinicians based on their racial characteristics or physical appearance. Black women who meet the criteria for infertility are less likely to undergo a preliminary evaluation compared with White women. One study found that only 8.7% of women in the sample sought fertility services and that Black women and American Indian or Alaska Native women had a lower prevalence of receiving treatment compared with other racial and ethnic groups. Similarly, in a retrospective cohort study involving 554,995 live births associated with fertility treatment, Black and Hispanic/Latinx women were approximately 70% less likely to receive any form of infertility treatment compared with White women. White women accounted for the majority of live births associated with any type of infertility treatment (53.8%), whereas Black and Hispanic/Latinx women were the least represented groups (4.0% and 7.6%, respectively) (Weiss, 2023).

Disparities in infertility and access to infertility treatments, such as assisted reproductive technology (ART), by race/ethnicity, have been reported. The ASRM Ethics Committee Opinion (2021) indicates that many factors, such as economic, racial, ethnic, geographic, and other

disparities affect both access to fertility treatments and treatment outcomes. More specifically, both social and cultural factors, including individual or systemic discrimination that disadvantages certain people because of their race, ethnicity, sexual orientation, or gender identity contribute to disparities. Within this report the authors note a publication by Armstrong and Plowdan (2012) a group of authors using the Society for Assisted Reproductive Technologies Clinical Outcome Reporting System (SARTCORS) data to compare outcomes between cycles from Black -non-Hispanic/Latinx women and White non-Hispanic/Latinx women found race to be a strong independent predictor of live birth outcomes in ART cycles. Moreover, when African-American, Asian, and Hispanic/Latinx women attain access to ART, they experience lower success rates compared with non-Hispanic/Latinx White women. The findings include evidence of lower implantation and clinical-pregnancy rates as well as increased miscarriage rates among underrepresented women. The ASRM concluded disparity in infertility and access to treatment along with differences in treatment success are concerning, the results are not well understood, and require additional evaluation (ASRM, 2021).

## General Background

Infertility is a disease, condition or status characterized by the need for medical intervention 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. This includes, for example, the need for an individual, regardless of relationship status, sexual orientation, or gender identity, to use donor gametes or embryos in order to achieve a successful pregnancy resulting in delivery. (American Society of Reproductive Medicine [ASRM], 2023). Evaluation and treatment may be warranted based on medical history and physical findings and is reasonable after six months for women over the age of 35 years (ASRM, 2021; ACOG, 2019; American Urological Association/ASRM, 2020). For woman over the age of 40 more immediate evaluation and treatment may be considered (ASRM, 2021). In addition, the inability of a woman to achieve conception after six trials of medically supervised artificial insemination over a one-year period may necessitate evaluation for infertility.

Infertility can affect one or both reproductive partners. Some underlying factors are reversible through medical intervention; the major underlying causes of infertility include: ovulatory, tubal, cervical, uterine/endometrial, and male partner factors.

**Diagnostic Testing To Establish the Etiology of Infertility**

Formal evaluation of infertility is generally initiated in women attempting pregnancy who fail to conceive after one year or more of regular, unprotected intercourse. However, there are an increasing number of women over the age of 35 who are seeking infertility services. Since reproductive potential decreases in the early to mid-thirties, for this age group formal evaluation typically begins earlier. For couples over 35 it is generally recommended that infertility testing begins after 6 months of unsuccessful attempts at conception (ASRM, 2023; ACOG, 2022; Williams, Elam, 2007; Institute for Clinical Systems Improvement [ICSI], 2004). In some cases, an evaluation may be warranted prior to one year if there is a known male infertility risk factor such as bilateral cryptorchidism or known female risk factor (AUA, 2021).

The preliminary approach to infertility typically begins with the evaluation of ovulatory, tubal, and male factors, and involves physical examination, laboratory studies and diagnostic testing. Other potential contributing causes that may be explored include genetic factors and immunological factors.

The female infertility diagnostic workup to determine the underlying etiology includes basic evaluation of ovulatory dysfunction including basal body temperature recordings, laboratory

studies and hormone levels, Additional studies are performed when the initial workup fails to provide definitive information (ASRM, 2021). Tests may include:

- ultrasound
- hysteroscopy
- hysterosalpingography
- diagnostic laparoscopy with or without chromotubation
- sonohysterography
- ovarian reserve testing

Conventional hysterosalpingogram (HSG) is an x-ray procedure where contrast medium is injected through the cervix into the uterine cavity to assess the inner size and shape of the uterus and patency of the fallopian tubes. Sonohysterography is an ultrasound procedure performed to visualize the inside of the uterine cavity and involves the installation of fluid into the uterus. Sonohysterography can be performed in an office setting, hospital or clinic. If the fallopian tubes are evaluated a fluid containing bubbles of air are instilled through a catheter, bubbles make the fluid easier to see when assessing patency of the tubes (ACOG, 2021). Tubal patency is determined by observing the saline and air contrast flowing into or out of each fallopian tube. There is a paucity of evidence evaluating sono-air HSG in the peer reviewed literature. One systematic review with meta-analysis evaluating the use of sono-HSG for evaluation of tubal occlusion was published in 2014, (Maheuz-Lacroix, et al., 2014). The authors assessed the accuracy of sono-HSG for diagnosing tubal occlusion in subfertile women. Although authors concluded that they observed high diagnostic accuracy of sono-HSG for tubal occlusion with overall sensitivity of 0.92 (95% CI: 0.82–0.96) and specificity of 0.95 (95% CI: 0.90–0.97) and also noted they found that the diagnostic accuracy of sono-HSG and HSG was comparable with no significant difference in performance of the two tests, all 28 studies included in this systematic used a flexible or rigid catheter for instillation of contrast and no study evaluated the use of the devices specifically indicated for sono-air HSG (e.g., femVue® [Femasys, Inc.]). Of note, only 6 studies included in the review evaluated saline +air as the contrast media, each study has small sample populations ranging from 31 subjects to 129 subjects. Of these 6 studies that utilized saline +air as the contrast media, three studies were a comparison of sono-HSG with the gold standard test for evaluation of tubal pregnancy, HSG. At present the evidence is insufficient to support the clinical utility of sono-air HSG.

Within recommendations published by the ASRM for fertility evaluation of infertile women, the ASRM notes that although post coital testing is often performed to evaluate cervical factor infertility, it is not recommended as part of the routine evaluation of an infertile female (ASRM, 2021). The practice committee concluded "the test is subjective, has poor reproducibility, typically does not impact clinical management, and does not predict inability to conceive." Similarly, endometrial biopsy has been used to evaluate secretory development of the endometrium, dating, and to assess the quality of luteal function (e.g., luteal phase deficiency). However, this test is no longer recommended by the ASRM as it is not considered a valid diagnostic tool; the test lacks accuracy and precision and cannot distinguish between fertile and infertile women (ASRM, 2021). According to the ASRM recommendations, its' use should be reserved for conditions where endometrial pathology is strongly suspected.

Following the physical examination, evaluation of the male begins with the semen analysis, considered the primary screening test for male factor infertility. Semen analysis is generally done through the examination of or more semen analyses , ideally two specimens at least one month apart (AUA/ASRM, 2024), and generally precedes invasive testing of the female partner. The semen analysis provides detailed information on semen volume, sperm concentration, motility, pH, fructose, leukocytes, and morphology. Depending on the clinical situation, repeat semen analyses may be performed every one to three months, up to a total of five. Other laboratory

studies include an endocrine evaluation, antisperm antibodies, post-ejaculatory urinalysis, urine culture and semen culture. Additional testing includes:

- transrectal ultrasound in individuals with azoospermia or oligospermia
- scrotal ultrasound for individuals in whom testicular mass is suspected or for whom physical exam is difficult/inconclusive
- vasography or testicular biopsy in individuals with azoospermia
- scrotal exploration

Genetic testing for cystic fibrosis is performed in males with congenital absence of vas deferens or for males with azoospermia or severe oligospermia (i.e., < 5 million sperm/millimeter) with palpable vas deferens. Karyotyping for chromosomal abnormalities and Y-chromosome deletion testing may be done in individuals with nonobstructive azoospermia or severe oligospermia.

Immunological factors may adversely affect fertility. As a result, various testing and treatment modalities have been proposed including, but not limited to, natural killer cell testing, antiphospholipid antibodies, antiprothrombin antibodies, embryotoxicity assay, and immune treatments such as pre-implantation glucocorticoids, anti-tumor necrosis factor agents (infliximab, etanercept), leukocyte immunization and IV immunoglobulin therapy. Nonetheless, scientific literature is insufficient to support improved individual clinical outcomes (Royal College of Obstetricians and Gynaecologists [RCOG], 2003; RCOG, 2008).

Categories of other immunological tests such as immunophenotype measuring are also under investigation. Reproductive immunophenotype identifies the percentage of lymphocyte types in the blood. Analysis of subsets of lymphocyte types, such as CD-3, CD-4, CD-8, CD-19, CD-5, CD56, CD16 may be recommended for women with unexplained infertility or who fail to conceive after IVF. In theory, disturbances in the proportions of lymphocyte types may be related to reproductive failure. Evidence in the published scientific literature, however evaluating the immunophenotype measurements is insufficient and the predictive value these tests are not clearly established (Baczkowski, et al., 2007; Ghazeeri and Kutteh, 2001).

T1 and T2 Helper cell ratios have been investigated as a cause of infertility and recurrent pregnancy loss, however evidence in the peer-reviewed published scientific literature supporting clinical utility for T1:T2 Helper ratio testing is lacking (Ozkan, et al, 2014; Kwak Kim, et al., 2005).

Methods of predicting fertility potential continue to be researched. Oocyte quality and number decrease with age and determining ovarian reserve may add prognostic value for couples seeking assisted reproductive technologies. Early follicular phase FSH remains the most commonly used marker for determining ovarian reserve, other tests such as antral follicle count, and clomid challenge tests are well-established. Serum inhibin B is an enzyme immunoassay being investigated as a method of evaluating function of the antral follicles of the ovaries in women or the Sertoli cells of the testes in men. However, it has been reported in the literature that there is no international assay standard, and both follicular and recombinant standards are used, and that testing is not readily available (Creus, et al., 2000). The role of inhibin B for predicting pregnancy is unclear. At present, there is insufficient evidence in the published literature to support serum inhibin B testing as a predictive marker of ovarian response (ASRM, 2021; Lukaszuk, et al., 2013; RCOG, 2004; Creus, et al., 2000; Corson et al., 1999).

Anti-mullerian hormone (AMH), produced by granulosa cells from preantral and early antral follicles, has also been evaluated as a predictor of ovarian reserve (Lukaszuk, et al., 2013; Brodin, et al., 2013; Ankaert, et al., 2012; Kunt, et al., 2011; A La Marca, et al., 2011; Steiner, et al, 2011; Tremellen, et al., 2010; Kini, et al., 2010; Steiner, 2009; Kaya, et al., 2010; Guerif, et al.,

2009). Authors generally agree that the decline of ovarian reserve with aging is associated with a decrease in anti-mullerian hormone levels. Nonetheless there appears to be little consensus regarding a specific value of serum anti-mullerian hormone for defining those women who may respond poorly to assisted reproductive technologies such as in vitro fertilization. According to the ASRM (2020) serum concentrations of anti-mullerian hormone remain consistent within and between menstrual cycles in both young ovulating and infertile women and levels can be obtained on any day of the menstrual cycle. Levels lower than 1 ng/ml have been associated with less than optimal responses to stimulation of the ovaries, poor embryo quality and poor pregnancy outcomes in IVF (ASRM, 2020). Evidence supporting improved clinical outcomes as a result of testing is mixed; some authors have reported strong predictive value, sensitivity and specificity, while others have not. According to the ASRM (2020) there is evidence to support that low levels of AMH have high specificity for poor ovarian response, therefore testing may help predict response to ovarian stimulation. However evidence to support use for screening of a woman's ability to conceive is lacking. Serum AMH testing is recommended for select woman at increased risk of ovarian reserve, including any of the following:

- women over age 35
- family history of early menopause
- women with a single ovary or history of previous ovarian surgery, chemotherapy, or pelvic radiation therapy, woman who have unexplained infertility
- women who have had a poor response to gonadotropin stimulation
- women who are planning treatment with assisted reproductive technologies (e.g., IVF).

Endometrial receptivity and the relationship to infertility, particularly for IVF cycles, is another area that is being investigated. Traditionally, researchers have used the endometrial biopsy as a method of assessing components of the endometrium. Researchers have evaluated a series of markers that can potentially be used to assess the functional state of the endometrium. The endometrial receptivity array (ERA), a genomic diagnostic tool based on microarray technology, is under investigation as an endometrial receptivity marker (Diaz-Gimeno, et al., 2011). Cyclin E and p27 have been identified as markers of endometrial receptivity and predictors of successful implantation (Dubowy, et al., 2003; Kliman, et al., 2000). A test recently developed that can assess the expression of cyclin E and p27 is the Endometrial Function Test™ (EFT®) (Yale University School of Medicine, New Haven, CT). While some authors contend these tests may have a role in evaluating the endometrial receptivity, studies are limited, and the benefits of endometrial function testing in predicting pregnancy outcomes have not been established. Expression of integrins has been studied by some authors and may be associated with endometriosis and unexplained infertility; although the data is limited, it is not conclusive, and further study is needed (Thomas, et al, 2003, Bourgain and Devroey, 2003).

Vaginal microbiome testing is a method of testing under evaluation and investigation. Imbalances of vaginal flora may lead to vaginal/pelvic infection and possibly reproductive complications. One vaginal microbiome test, SmartJane™ (uBiome, Inc.) is a sequencing based screening test purported by the manufacturer that genotypes 14 high-risk HPV strains, 5 low-risk HPV strains, 4 common sexually transmitted diseases (STIs) (i.e., chlamydia, gonorrhea, syphilis, mycoplasma genitalium) and measures 23 other vaginal flora. Once the test is ordered by a physician, a sample is collected in the home which is then mailed to a uBiome laboratory where it is processed. Results are subsequently made available to the patient and their physician electronically and may potentially contribute to diagnosis, treatment and monitoring of conditions that can affect vaginal health. Published evidence in the medical literature is insufficient to support the validity, clinical utility, and improvement of net health outcomes for vaginal microbiome testing at this time and the implication of testing in infertility requires additional research to support its use.

The clinical utility of the tests noted below has not been demonstrated in the medical literature. These tests have been proposed for a select subset of patients to identify a male factor

contributing to unexplained infertility or in the treatment of infertility to select specific interventions. In general, they are reserved for those individuals for whom identification of the underlying cause of male infertility will direct specific treatment modalities.

- Sperm viability test (hypo-osmotic swelling test): This test is used to determine if non-motile sperm are viable and may be done to determine if intracytoplasmic sperm injection (ICSI) is an option for treatment. The role of assessing sperm viability using the hypo-osmotic method in the diagnosis or treatment of infertility has not been established in the published, peer-reviewed scientific literature.

- Zona-free hamster oocyte test (sperm penetration assay): This test is generally reserved for patients in whom results will influence treatment strategy (American Urological Association [AUA] 2011[a]). It is used to assess the ability of spermatozoa to undergo capacitation (egg penetration) and achieve fertilization (Bradshaw, 1998). Evidence in the scientific literature has suggested a correlation between results of this test and in both vitro fertilization (IVF) cycles and intracytoplasmic sperm injection (ICSI).

- Hyaluronan binding assay (HBA): This test has been proposed as an additional evaluation tool to determine the maturity of sperm in a fresh semen sample. The assay is based on the ability of the mature sperm to bind to hyaluronan, a component of the external coating of the ova. It has been suggested that HBA may prove useful in determining a need for intracytoplasmic sperm injection; however, evidence in the published literature has not confirmed HBA can provide additional information over standard semen analysis for sperm-fertilizing ability.

- Hemizona test: This test assesses the ability of the sperm to bind to the zona pellucida. Like the sperm penetration assay, preliminary studies have suggested a correlation with in vitro fertilization outcomes. The role of this test in the diagnosis or treatment of infertility has not been established in the published, peer-reviewed scientific literature.

- Computer-assisted motion analysis: Time-lapsed photography, video micrography and computer-assisted motion analysis are techniques used to determine sperm velocity and linearity. Proponents of the computer-based method contend that it allows for the measurement of more sophisticated parameters such as lateral head displacement and flagellar beat frequency. There is insufficient evidence in the published, peer-reviewed scientific literature to support the use of this technology in the diagnosis or treatment of infertility.

- Sperm DNA integrity testing: It is theorized that sperm DNA damage may affect reproductive outcomes in select couples, and several tests for sperm DNA integrity are now available (e.g., Sperm Chromatin Structure Assay [SCSA], TUNEL assay, Comet assay). Another test to assess sperm DNA is the Sperm DNA Decondensation test (e.g., Human Sperm Activation Assay [HSAA], SDD™). Current methods for evaluating sperm DNA integrity do not reliably predict treatment outcomes, and no treatment for abnormal DNA integrity has proven clinical value. The AUA (2011a) reported that the assays demonstrate low sensitivity and high specificity. In 2015 the ASRM reported in their committee opinion regarding the diagnostic evaluation of the infertile male that DNA integrity testing is controversial because the prognostic clinical value may not affect treatment of couples (ASRM, 2015).

- Reactive oxygen species: Reactive oxygen species (ROS) may interfere with sperm function and are generated by both seminal leukocytes and sperm cells. ROS have a normal physiological role in the capacitation and acrosome reaction and as such have been

implicated as a cause of male factor infertility. Controversy exists regarding best methods of testing, the role of excess ROS in natural conception as well as reproductive technologies, and whether therapies are effective for improving clinical outcomes. Furthermore, there is insufficient published data to support ROS testing in the management of male factor infertility (AUA, 2011a). In 2024 the AUA/ASRM reported in their committee opinion regarding the diagnostic evaluation of the infertile male that ROS is not a test of fertility (AUA/ASRM, 2024).

- Sperm capacitation assay assessment: Capacitation is the process sperm must undergo that involves biochemical alterations which then allow the sperm to penetrate and fertilize the egg. The ability of sperm to undergo capacitation has been evaluated and reported on in the medical literature. One method to evaluate sperm capacitation is "Cap-Score" (Androvia LifeSciences, Mountainside, New Jersey])" which is a proprietary biomarker-based test to measure the sperm's ability to penetrate and fertilize an egg. More specifically, according to the manufacturer the test "measures the fundamental biological process that controls fertility and does so by proprietary technology that assesses the sperm's capacity to fertilize an egg. Cap-Score detects and analyzes localization patterns using fluorescent microscopy to distinguish fertile from infertile sperm cells, and those capable of going on to generate a pregnancy from those that cannot." Conducting a Cap-Score test involves the incubation of sperm in non-capacitating (Non-Cap) medium and medium containing capacitating stimuli (Cap). The sperm that respond to the capacitation stimuli are identified by specific GM1 localization patterns. The final readout—the "Cap-Score"—reports the proportion of sperm within a sample that displays the localization patterns that correspond with capacitation. Sperm capacitating assays are an emerging technology with evidence in the peer reviewed scientific literature evaluating sperm capacitation assays primarily in the form of observation or cohort studies; randomized controlled trials, systematic reviews and/or meta-analyses are lacking. In addition, the ASRM and AUA do not address sperm capacitation assays within their formal position statements and Practice Committee Opinions. Due to the paucity of evidence in the medical literature strong evidence based conclusions cannot be made regarding the clinical utility of this type of testing.

**Treatment of Female Infertility Factors**

Treatment of infertility typically begins with the confirmed diagnosis of infertility. Treatment is determined by the specific diagnosis and may involve oral or injectable medication, surgery, assisted reproductive technologies, or a combination of these. Infertility may be the result of endometriosis, tubal factors, uterine and endometrial factors, cervical factors, ovulatory factors, or unexplained factors. Pharmacologic and other medical treatment is typically attempted before more invasive interventions are sought.

**Endometriosis:** Endometriosis is the presence and growth of glands and stroma identical to the lining of the uterus in an unusual location. It is often associated with pelvic pain and infertility, although some individuals may be asymptomatic. The short-term goals of treatment include reduction of pelvic pain and promotion of fertility while long-term goals include halting the progression or recurrence of disease. Treatment usually consists of pharmacologic therapy, surgery or a combination of both. Pharmacologic therapy includes oral contraceptives, danazol, medroxyprogesterone acetate, and gonadotropin releasing hormone agonists. Surgical treatment involves the resection or destruction of endometrial implants, lysis of adhesions, and attempts to restore normal pelvic anatomy either through a laparoscopic approach or open laparotomy (Lobo, 2012a). Pelvic adhesions can lead to decreased mobility and function, affecting the biomechanics of the pelvic organs and may lead to infertility. Manual soft-tissue therapy (e.g., Wurn Technique®, Clear passage therapy) has been proposed as a method of breaking down the adhesions and improving elasticity, increasing pregnancy rates. The published data evaluating this

technique is limited (Wurn, et al, 2008; Wurn, et al., 2004) and the safety and efficacy of soft-tissue therapy as a method of treatment for infertility has not been established in the peer-reviewed medical literature.

**Tubal Factors:** There are numerous causes of tubal disorders, including: prior salpingitis (pelvic inflammatory disease and other causes), endometriosis, adhesions from prior surgery, complications of intrauterine devices, and prior ectopic pregnancy. Lysis of mild peritubal adhesions may be performed during laparoscopy; however, many patients will only achieve pregnancy after tuboplasty or in vitro fertilization and embryo transfer. Tubal infertility factors can also be related to previous voluntary sterilization procedures, such as tubal ligation.

Several methods are available to treat infertility related to tubal factors. Tubal recanalization is performed when adhesions or endometriosis occlude the fallopian tubes. Other treatments include salpingostomy, fimbrioplasty, tubal anastomosis, fluoroscopic/hysteroscopic selective tube cannulation, and salpingectomy. While this method is rather obsolete, low tubal ovum transfer (LTOT) is a method in which an ovum is retrieved from the ovary and inserted in the uterus near the uterotubal junction bypassing the blocked fallopian tube. These procedures are also performed to treat infertility that is the result of voluntary sterilization.

**Uterine and Endometrial Factors:** Uterine and endometrial factors which may contribute to infertility include tumors/myomas, congenital malformations such as septate uterus, endometriosis and adhesions.

Treatments of uterine and endometrial factors include the following:

- treatment of myomas: hysteroscopic removal of submucous myoma; myomectomy for intramural or other myomas
- repair of congenital malformations: repair of septate uterus may be performed via hysteroscopy or laparotomy
- treatment of uterine adhesions: lysis of adhesions performed via dilatation and curettage or hysteroscopy

Uterine transplantation is under investigation as a method of offering fertility options to women who have uterine factor infertility, whether congenital (e.g., Mullerian malformations) or acquired (e.g., Asherman's syndrome, intrauterine myomas). Live births have been reported following uterine transplantation, and donors in most cases have been live donors with few reports of deceased donors in the literature. Similar to other organ transplants, risk of rejection is a complication; higher doses of immunosuppressive agents, known to cross the placental barrier, are often required in pregnancy and pose additional risks. General recommendations currently indicate that as part of a pre-determined plan following completion of one or two successful pregnancies the uterus is then removed to limit the immunosuppression period. A position statement from the American Society of Reproductive Medicine was published in 2018. The ASRM position statement recognizes uterus transplantation as a successful medical treatment of absolute uterus factor infertility, while cautioning health professionals, patient advocacy groups and the public about its highly experimental nature. Uterus transplantation is considered an experimental treatment (ASRM 2018).

**Cervical Factors:** Cervical factors may also account for infertility, and primarily consist of abnormalities of the cervical mucus or a cervical stenosis. The quality of cervical mucus in many cases cannot be corrected through the use of pharmacologic agents (e.g., estrogen) and intrauterine insemination is recommended. In cases involving cervical infections, antibiotics are prescribed. Cervical stenosis may be corrected by hysteroscopy and cervical recanalization.

**Ovulatory Factors:** Ovulatory dysfunction is a frequent cause of female infertility. Ovulation may be absent or occur irregularly due to ovary abnormalities or abnormal secretion of the hormones needed to support ovulation. Typically, fertility begins to decrease in women during the early- to mid- thirties. The standard test for determining decreased ovarian function is a day-3 follicle stimulating hormone (FSH) level. Normal day-3 FSH values vary among laboratories and specific assays; however, decreased ovarian function is seen with a level greater than 10–15 IU/L. Although some women with elevated day-3 FSH levels may become pregnant, the chance of establishing a pregnancy even with the use of in vitro fertilization (IVF) is markedly reduced.

Ovulatory dysfunction may also be related to diseases not directly linked to the reproductive system, such as medications, addictive drugs, weight loss, obesity, and psychological factors. Induction of ovulation through the use of pharmacotherapeutic agents is generally the first-line approach to treat conditions that prevent ovulation. Ovulation induction is also used as an adjunct to assisted reproductive techniques and intrauterine insemination. Originally, ovarian wedge resection was performed for patients with polycystic ovarian (PCO) syndrome who did not respond to drug treatment. Currently, surgical treatment of PCO with partial ovarian destruction utilizing electrocautery or laser, referred to as ovarian drilling, has been utilized in women when clomid has failed to induce ovulation. During this procedure, several punctures are made through the surface of the ovary with a needle and coagulated. Ovulatory cycles generally resume and androgen levels become normal. If ovulation does not occur spontaneously, most anovulatory women will ovulate with clomid.

The following drugs have been shown to induce ovulation:

- Clomiphene citrate, an oral synthetic nonsteroidal estrogen agonist-antagonist, enhances the release of pituitary gonadotropins resulting in follicular development and rupture.
- Gonadotropins, including but not limited to human menopausal gonadotropins (hMG) (e.g., Pergonal®, Repronex®, LH and FSH), human chorionic gonadotropin (HCG) (e.g., Pregnyl®, Novarel™), human FSH, and recombinant FSH/follitropins (e.g., Follistim®, Gonal-F®) may be administered to patients who have not responded to clomiphene
- Gonadotropin-releasing hormone (GnRH) (e.g., leuprolide, goserelin) is an alternative to gonadotropins in cases of low gonadotropin and estrogen levels. The drug is delivered intravenously or subcutaneously with the use of a computerized pump. One advantage of this pulsatile GnRH therapy over gonadotropin therapy is the reduced risk for multiple conception and ovarian hyperstimulation.
- Bromocriptine is an oral dopamine agonist used as the initial intervention for women with hyperprolactinemia and anovulation, oligo-ovulation, or luteal phase insufficiency.
- Metformin, an insulin sensitizing drug, may be considered in women with polycystic ovarian syndrome although its use should be restricted to those with glucose intolerance.

Emerging treatments for infertility that are currently under investigation include the use of acupuncture to improve live birth rates, intrauterine injection of platelet rich plasma to improve endometrial quality and implantation rates, and physiological, hyaluronan-based selection of sperm (PICSI) to improve live birth rates and decrease miscarriage rates. Nevertheless, well-designed clinical trials with rigorous methodological quality are needed to firmly establish the clinical utility of these emerging treatments.

**Treatment of Male Infertility Factors**

**Obstructive/Nonobstructive Azoospermia:** Azoospermia is defined as a complete absence of sperm in the ejaculate, including the absence of sperm after examination of centrifuged pellet (Schlegal, et al., (AUA/ASRM, 2024). It may be caused by obstruction of the extratesticular ductal system (obstructive azoospermia) or defects in spermatogenesis (nonobstructive azoospermia). Obstructive azoospermia may be congenital or acquired, and may be caused by epididymal, vas

deferens, or ejaculatory pathology. Acquired causes of azoospermia include previous vasectomy, genitourinary infection, scrotal or inguinal injury and congenital anomalies. Treatment of obstructive azoospermia, when performed in order to achieve pregnancy, includes: surgical correction of the obstruction, which provides the ability to produce pregnancy by intercourse; or retrieval of sperm from the male reproductive system for IVF and ICSI.

Surgical repair of obstruction can be achieved by (AUA/ASRM, 2024):

- surgical/microsurgical reconstruction of the vas and/or epididymis, including vasectomy reversal, epididymovasostomy, epididymectomy, vasovasostomy; or
- transurethral resection of the ejaculatory ducts (TURED) when there is ejaculatory duct obstruction

Sperm retrieval and cryopreservation may be performed at the time of microsurgical reconstruction in order to avoid a second procedure in the event that the microsurgical reconstruction does not reverse a patient's azoospermia (ASRM, 2019).

Males with nonobstructive azoospermia should have genetic testing before proceeding to assisted reproductive technologies, such as in vitro fertilization with intracytoplasmic sperm injection. Genetic disorders may be characterized as karyotype abnormalities. In some men, microdeletions of the Y chromosome contribute to azoospermia. Male offspring born to fathers of Y-chromosome microdeletion are expected to inherit these deletions. As such, genetic/clinical counseling regarding genetic issues should be considered a critical part of the male evaluation (Brugh, 2003; Society of Obstetricians and Gynaecologists of Canada (SOGC), Okun, Sierra, 2014).

**Abnormalities of Ejaculation:** Ejaculatory dysfunction may be associated with male factor infertility. Abnormalities of ejaculation may be caused by neurologic, anatomic or psychological abnormalities. Retrograde ejaculation is caused by incomplete closure of the bladder neck. For this condition, sperm may be obtained from the postejaculatory urine. Anejaculation is often due to spinal cord injury or other neurologic impairment (e.g., retroperitoneal surgery, trauma, diabetes). Treatment options may be medical or surgical. Options for sperm retrieval may include vibratory stimulation, electroejaculation or surgical retrieval. These techniques are often associated with poor sperm quality and, in most cases recovered sperm are used for intrauterine insemination (IUI), IVF or ICSI cycles (Schuster, Ohl, 2002).

**Seminal Tract Washout (STW):** STW is a technique involving the cannulation of the vas deferens and subsequent antegrade washing of the vas with collection of sperm from the bladder. STW may be used in situations where male infertility is due to incomplete voiding of the distal seminal tract, and spermatozoa can be retained downstream of the epididymis. Common conditions include diabetes, spinal cord injury, and extended retroperitoneal lymph node dissection.

**Other Procedures:** Other procedures used to treat male factor infertility include:

- repair of varicocele (dilatation of the pampiniform plexus of the scrotal veins), including spermatic vein ligation (retroperitoneal, inguinal, laparoscopic or scrotal), excision of spermatocele, orchiopexy
- treatment of endocrinopathies including:
  - hypogonadotropic hypogonadism: stimulation of secondary sexual characteristics and normal spermatogenesis through the use of HCG and hMG or pulsatile GnRH
  - disorders of LH or FSH function: treatment includes replacement of FSH and HCG
  - disorders of androgen function: treatment includes corticosteroids, mineralcorticosteroids, or androgens

  - medical and surgical treatment of adenomas of the pituitary gland
- excision of epididymal tumor

**Sperm Precursors:** There is insufficient evidence in the published, peer-reviewed scientific literature to support the use of sperm precursors (round or elongated spermatid nuclei, immature sperm) in the treatment of infertility with ICSI.

**Treatment of Unexplained Infertility**

Of couples experiencing infertility up to 30% are diagnosed with unexplained infertility (ASRM, 2020). For these couples, the infertility workup will not reveal any abnormalities. There is no specific treatment for unexplained infertility, but assisted reproductive technologies are sometimes pursued.

Treatment for unexplained infertility includes ovarian stimulation with timed intercourse, ovarian stimulation and intrauterine insemination (IUI), unstimulated intrauterine insemination (i.e., natural cycle IUI), and for some assisted reproductive technologies.

Within evidence-based guidelines published by the ASRM (2020) for couples with unexplained infertility the ASRM recommends the following:

- Clomiphene citrate with IUI
- Letrozole with IUI, as an alternative regimen to clomiphene citrate
- A single IUI be performed between 0-36 hours relative to hCG injection during ovarian stimulation/IUI cycles
- A course of 3-4 cycles of ovarian stimulation/IUI with oral agents , if unsuccessful followed by ovarian stimulation with IVF cycles rather than ovarian stimulation/IUI cycles with gonadotropins

The ASRM does not recommend the following as they are not more effective than expected management:

- natural cycle IUI , as it is less effective than ovarian stimulation with IUI
- Clomiphene citrate with timed intercourse
- Letrozole with timed intercourse
- use of gonadotropins with timed intercourse
- Letrozole or clomiphene citrate with conventional gonadotropins with IUI
- Low-dose or conventional-dose gonadotropins with IUI

**Artificial Insemination**

Artificial insemination (AI) is a procedure in which sperm are placed in the cervix or high in the uterine cavity through a transcervical catheter. The rationale is to deposit sperm as close to the oocyte as possible. A trial  intrauterine insemination (IUI) , also referred to as mock IUI, is a procedure performed solely to assess the cervix and uterus prior to the IUI, however trial/mock IUI is considered an integral part of the IUI procedure. AI, intrauterine insemination (IUI), or intracervical insemination (ICI) may be performed using either the partner's sperm or donor sperm. Artificial insemination may be preceded by ovarian stimulation with gonadotropins or clomiphene to encourage multiple oocyte development, especially in cases of unexplained infertility. AI techniques are typically attempted for up to six cycles before proceeding to more complex interventions such as in vitro fertilization.

Other methods of insemination less frequently employed include direct intraperitoneal insemination (DIPI), intrafollicular insemination, (IFI), and fallopian tubal sperm perfusion (FSP). DIPI has not been shown to be more effective than IUI/ICI and is a more invasive method. IFI is a method of injecting motile sperm directly into the pre-ovulatory follicle. It is suggested that fertilization occurs prior to ovulation and the presence of follicular factors may provide stability to

the fertilized egg. FSP increases the number of motile sperm in the fallopian tube. These methods are not widely used, and there is insufficient evidence in the published literature regarding efficacy. Reported outcomes have been inconsistent, and they have not been proven in large, well-designed studies to increase pregnancy rates compared to AI.

Superovulation with intrauterine insemination involves the intentional development and ovulation of multiple follicles.

Indications for artificial insemination:

- pharmacologic treatment alone has not been successful
- unexplained infertility
- abnormal cervical mucus
- donor insemination
- presence of antisperm antibodies
- low sperm counts with normal motility

**Assisted Reproductive Technologies**

Assisted reproductive technologies (ART) describe a group of infertility treatment procedures that involve the extracorporeal manipulation of both oocytes and sperm, and/or embryos. Techniques include: in vitro fertilization with embryo transfer (IVF-ET), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), and intracytoplasmic sperm injection (ICSI). In addition, technologies such as co-culturing of embryos, assisted embryo hatching and Kruger's "strict criteria" for assessing sperm morphology may be recommended as part of an IVF cycle.

**In Vitro Fertilization with Embryo Transfer (IVF-ET):** IVF is a procedure that involves removing eggs from the ovaries and fertilizing them outside the body. The resulting embryos are then transferred into the uterus through the cervix. For the purpose of this Coverage Policy, an IVF cycle ending with embryo implantation is considered an attempt at IVF, whether there is one or more than one embryo implanted during that event. Additional embryo implantations would be considered a second IVF attempt or IVF cycle, whether those embryos were frozen or not. An embryo transfer that is unsuccessful in resulting in a pregnancy is considered a failed IVF attempt.

The success rate of IVF has been reported to be approximately 22.8% live births per egg retrieval. This is similar to the 20% chance that a healthy couple has of achieving a pregnancy that results in a live birth in a given month.

The steps involved in IVF are as follows:

1. Ovarian stimulation/hyperstimulation and monitoring.

2. Egg retrieval: After the follicle has ruptured, the physician removes multiple eggs transvaginally or by laparoscopy.

3. Fertilization: A semen sample from the male partner or donor is processed using sperm washing, in which active sperm are selected. Mature egg cells are combined with the selected sperm and cultured for approximately forty hours. Forty-six to fifty hours after egg retrieval, fertilization and cell division are evaluated. Two to six fertilized embryos are selected. Embryos may also be cryopreserved at this point for later use.

4. Embryo transfer: The selected fertilized embryos are placed in a catheter, combined with a transfer growth medium, and inserted through the patient's vagina and cervix into the

uterus. It is believed the transfer medium promotes implantation of the embryo and varies according to clinic; however, the most common protein used is synthetic albumin; other additives have been investigated (e.g., hyaluronan, EmbryoGlue®), but improvement in embryo development and implantation has not been clearly established in the published literature. Yung et al. (2021) performed a randomized, double blind, controlled trial, comparing the effects of hyaluronic acid (HA) –enriched transfer medium versus standard medium on live birth rate after frozen embryo transfer (FET). A total of 550 infertile women aged 43 years or less were randomly placed in two groups. The hyaluronic acid group (HA) used an enriched medium (EmbryoGlue), with an HA concentration of 0.5 mg/ml while the control group used the conventional G -2 (Vitrolife) medium with an HA concentration of 0.125 mg/ml. Results demonstrated that live birth rates in both groups were comparable (25% versus 25.8%, respectively). Logistic regression showed that type of transfer medium did not improve the live birth rates of frozen embryo transfer.

5. Embryo cryopreservation: If there are embryos that are not needed for transfer in the current cycle, cryopreservation may be used. This is a process in which the embryos are frozen in liquid nitrogen and may be thawed for future use. A significant percentage of embryos do not survive the process of freezing and thawing, however. Cryopreservation may result in hardening of the zona pellucida which may affect hatching and implantation of blastocyst (Liu, et al. 2007). Some embryos lose one or more blastomeres after thawing and are referred to as "partially damaged" embryos. While partially damaged embryos can give rise to term pregnancy, authors agree that the developmental potential of these embryos is inferior to those that are fully intact. Some authors have reported that laser-assisted removal of necrotic blastomeres from partially damaged cryopreserved embryos before embryo transfer increases embryo development potential (Liu, et al., 2007; Nagy, et al., 2005; Rienzi, et al; 2005, Rienzi 2002). However, while outcomes are encouraging regarding implantation and pregnancy rates, there is insufficient evidence in the peer-reviewed scientific literature regarding the safety and efficacy of the use of laser-assisted necrotic blastomere removal from cryopreserved embryos.

In many cases, assessment of the cervical canal and uterus is performed prior to an actual embryo transfer. A mock embryo transfer employs the use of a thin plastic catheter, without an embryo, that is passed through the cervix and into the uterus to evaluate the potential for embryo transfer. A second method, uterine sounding, employs the use of an instrument referred to as a uterine sound to determine depth and direction of the uterus prior to embryo transfer.

In natural cycle IVF or natural oocyte retrieval IVF, there is no hyperstimulation with ovulation induction drugs. Ovulation is allowed to occur naturally without intervention.

For standard IVF cycles, when fertilization occurs, the developing embryos are incubated for 2–3 days in culture and then placed into the uterus. In some cycles, embryos are cultured for 5–6 days (i.e., extended culture) and then transferred into the uterus at the blastocyst stage using a single medium, or in some cases two distinct media. During the natural process of embryo development, when the embryo reaches the blastocyst stage (i.e., 6–7 days after fertilization) it is ready for implantation. Although reliable criteria to identify embryos that may develop to blastocyst stage has not been established, according to the ASRM Practice Committee, some of the theoretical advantages of growing embryos to the blastocyst stage include higher implantation rates, a decrease in the number of embryos transferred, the opportunity to select more viable embryos, better synchronization of embryo and endometrial readiness, and the opportunity to perform preimplantation genetic diagnosis as a result of increased culture time (ASRM, 2008a). Evidence in the published literature indicates that transfer on day two or three and day five or six appear to be equally effective in terms of increased pregnancy and live birthrate rates per cycle started (Blake, et al., 2006; National Institute of Health and Clinical Excellence [NHS], 2004).

Evidence can also be found suggesting (more specifically) that when an equal number of embryos are transferred, the probability of live birth rate after fresh IVF is significantly higher after blastocyst-stage transfer compared to cleavage-stage transfer (Papanikolaou, et al., 2008). Conclusions from the ASRM Practice Committee (2018) indicate the following, in patients with good prognosis, the transfer of blastocysts has been observed to yield higher live birth rates than those achieved with transfer of equal numbers of cleavage-stage embryos. Due to high implantation rates with blastocysts elective single embryo transfer should routinely be used to minimize multiple gestation.

Tubal embryo transfer (TET) or pronuclear stage transfer (PROST), and tubal embryo stage transfer (TEST), are also considered variations of standard IVF-ET and involve transfer of embryos into the fallopian tubes at different stages. TET is similar to ZIFT, except the embryos are transferred 8–72 hours after fertilization.

Indications for IVF include the following:

- blocked or severely damaged fallopian tubes
- endometriosis
- male factor infertility
- failed six cycles of ovarian stimulation with intrauterine insemination
- unexplained infertility of long duration with failure of other treatments

Methods proposed for improving IVF success rates include the following:

- Co-culture of Embryos: Co-culturing of embryos is the culturing of embryos on a layer of cells that in theory, removes toxic substances produced by the embryo. It is a technique currently under investigation aimed at improving the quality of embryos and involves the use of various cell-lines. It may be recommended for individuals who have un-successful IVF cycles and poor quality embryos. Authors have identified various techniques of co-culturing of embryos (Kervancioglu, et al., 1997; Wiemer, et al., 1998; Rubio, et al., 2000). However, co-culturing of embryos using feeder cells (e.g., granulosa, endometrial, tubal) in order to improve implantation success has not been demonstrated in the published, peer-reviewed scientific literature to improve implantation or pregnancy rates. The role of this technique in the treatment of infertility has not been established.

- Assisted Embryo Hatching: Assisted zona hatching is the artificial thinning or breachment of the zona pellucida such that an embryo that develops to the blastocyst stage can expand through the confines of the pellucida allowing the otherwise normal embryo to make contact with the endometrial lining and implant. It has been suggested by some studies that thick and hardened zona may prevent or reduce the efficiency of hatching of otherwise normal developing embryos. Thick or hardened zona may result from gonadotropin stimulation, the laboratory environment, culture techniques, age > 38, or with elevated day-3 FSH levels (Richlin, et al, 2003). The use of assisted hatching has been proposed as a method to facilitate implantation and pregnancy rates. It may be performed in conjunction with IVF, ZIFT, and ICSI to enhance the probability of achieving pregnancy. The procedure is typically performed on day three, five or six, and involves creating a gap in the zona by drilling with an acidified medium, partial zona dissection with a glass microneedle, laser photoablation, or use of a piezo-micromanipulator. Evidence in the published, peer-reviewed scientific literature has yielded few randomized clinical studies, inconsistent success rates, and no specific patient selection criteria. Although assisted hatching may facilitate implantation it is used selectively for cases of poor prognosis (repeated IVF failure, embryos of poor quality, thick zona, etc.). The Practice Committee of the ASRM (2022) reported, "Laser-AH should not be routinely recommended for all patients

undergoing IVF. There are insufficient data to make a recommendation for selected groups, such as patients with poor prognosis". According to published text (Richlin, et al., 2003), the indications for assisted hatching include: age greater than 38, elevated day-3 FSH, a prior failed IVF cycle with suspected implantation failure, increased zona thickness on microscopy, and excess oocyte fragmentation.

- Kruger's Strict Criteria for Sperm Morphology: Sperm morphology has become a useful indicator of successful fertilization with IVF. Kruger coined the term "strict criteria," which involves the identification and use of only those sperm which are determined to be morphologically normal. In studies using strict morphologic criteria, men with greater than 14% normal forms had normal fertilization rates in vitro. Patients with 4–14% normal forms had intermediate fertilization rates, while men with less than 4% normal forms had fertilization rates of 7–8%. The identification of sperm morphology using Kruger's strict criteria is considered an integral part of the sperm analysis prior to IVF. According to the AUA (2011a) strict criteria should not be used in isolation to make prognostic or therapeutic decisions.

- Time-lapse Monitoring: Time-lapse monitoring/imaging is a noninvasive method of embryo evaluation that allows 24-hour monitoring of embryo development. Although stable, controlled incubation systems are necessary for embryo development, conventional methods to assess embryos in IVF cycles are based on daily evaluation of morphology via a microscope, after removal from standard incubators at a defined point in time. Authors hypothesize time-lapsed monitoring, embryo assessment conducted without disturbance to the culture conditions and removal from the incubator, improves the quality and quantity of information regarding embryonic cleavages and morphologic assessment. Time-lapsed monitoring is purported to refine embryo selection, and thereby improve IVF clinical pregnancy rates (Rubio, et al., 2014). One device, the EmbryoScope ® Time-Lapse System (Vitrolife, Inc., Englewood, CO) provides a time-lapse video with thousands of snapshots of each embryo over three to five days of in vitro culture. A second test currently FDA approved and available is the Early Embryo Viability Assessment (Eeva™) test (Auxygyn, Inc.) While time-lapse monitoring may allow more detailed observations of embryonic development, there is insufficient evidence in the peer-reviewed published scientific literature supporting clinical utility, improved IVF outcomes, and improved pregnancy rates with the use of this technology.

**Intravaginal Culture/Incubation:** Although further study is required to support clinical efficacy, intravaginal culture of oocytes and sperm has been proposed as an alternative to conventional IVF. During this procedure, a small gas-permeable plastic device containing oocytes and sperm is placed into the vagina where fertilization and subsequent embryo development occurs during a three day incubation. The device is then removed; embryos are selected and then transferred into the uterus under ultrasound guidance. Use of the device simplifies the IVF procedure in that laboratory and embryologist-related services are reduced in addition to allowing fertilization to occur in the female reproductive tract which provides the $pCO_2$, $pO_2$, and temperature for culturing. Preliminary trials have supported clinical pregnancy rates that are comparable to conventional IVF cycles (Doody, et al., 2016; Mitri, et al., 2015; Lucena, et al 2012) however sample populations are small and concerns remain regarding the potential for abnormal fertilization and the reduced ability to monitor embryo development prior to transfer.

**Hyperbaric Oxygen Therapy (HBO):** It has been proposed that increasing oxygenation by HBO may aid in egg maturation and alignment of chromosomes during meiosis but there insufficient evidence to support this claim.

**Cryopreservation and In Vitro Maturation (IVM) of Immature Oocytes:** In vitro maturation of oocytes is a procedure where immature oocytes are retrieved from follicles which may or may not have been exposed to exogenous FSH, have not been exposed to exogenous LH or HCG, and are then allowed to mature in culture. Theoretically, the oocytes mature and can be fertilized. A committee opinion by the ASRM (2021) indicates that IVM is no longer considered experimental and that potential candidates for IVM include women with PCOS or PCO type ovaries or those with ovarian hyperstimulation syndrome. The efficacy of IVM for estrogen-sensitive cancers, or in women with limited time for initiating fertility preservation before undergoing potentially gonadotoxic cancer treatments, however, is still not clear according to the ASRM (2021). More specifically regarding cancer indications the ASRM cited literature indicating the reproductive potential of vitrified IVM oocytes is impaired owing to the vitrification-warming procedure in one study, and in another study the authors reported poor pregnancy and delivery outcomes from vitrified-thawed embryos derived from IVM oocytes for cancer patients. Furthermore, IVM of oocytes after recovery from thawed ovarian tissue frozen from postmenarchal versus premenarchal girls yielded decreased maturation rates in both groups (28.2% vs. 15.5%, respectively), which was further reduced in girls under 5 years of age (4.9%) (ASRM, 2021). It is the opinion of the ASRM that the procedure should only be offered by those with expertise gained by specific training, informed consent, and appropriate counseling about expected fertility preservation results (ASRM, 2021).

**Gamete Intrafallopian Transfer (GIFT):** The GIFT procedure is an alternative to IVF. In GIFT, the egg cells are retrieved laparoscopically and transferred to the fallopian tubes using a catheter containing 2–3 egg cells and approximately 100,000 sperm. Unfertilized oocytes are mixed with sperm and transferred back into the tubes. Fertilization occurs in the body as in unassisted reproduction, as compared to IVF in which fertilization occurs outside the body. Indications for GIFT are the same as for IVF, except that the woman must have one patent fallopian tube. GIFT has become exceedingly rare and is associated with increased risk to the patient due to the more invasive requirements for laparoscopy and increased risks of ectopic pregnancy. Current pregnancy rates for conventional in vitro fertilization are higher than GIFT.

**Zygote Intrafallopian Transfer (ZIFT):** ZIFT is another variation of IVF and GIFT without clear proven advantages. Following fertilization, which occurs in vitro, a one-cell zygote or pre-embryo is transferred into the fallopian tube. The pre-embryo then moves to the uterus by natural processes. ZIFT may be an option in rare situations when abnormality of the cervical canal prevents passage of an embryo transfer catheter into the uterus. Performance of ZIFT is also extremely rare, invasive, and is associated with increased risk to the patient. Furthermore, as noted above current pregnancy rates for conventional in vitro fertilization are higher than both GIFT and ZIFT.

**Intracytoplasmic Sperm Injection (ICSI):** ICSI is a laboratory procedure developed to assist couples who are undergoing IVF for severe male factor infertility. The ICSI procedure is used in conjunction with IVF, GIFT and ZIFT. This procedure has replaced two previously developed micromanipulation techniques, partial zona dissection (PZD) and subzonal insertion (SUZI) because it achieves higher fertilization rates. ICSI involves the injection of a single sperm directly into the cytoplasm of an oocyte. Several studies have demonstrated efficacy and short-term safety of ICSI (ASRM, 2008d).

It should be noted that in the United States, the reported risk of multiple gestations after ICSI is 30–35% for twin gestations and 5–10% for triplet or higher-order gestations. Some conditions may carry an increased risk for transmission of genetic abnormalities to offspring via ICSI (ASRM, 2008c). Whether the increased prevalence is related to the procedure or to the characteristics of couples who require ICSI is unclear. In general, due to the increased risk all couples who undergo ICSI should undergo genetic counseling.

The ICSI process is as follows:

1. Ovarian stimulation and monitoring: This step is similar to the process used in IVF.

2. Sperm extraction: The sperm sample is evaluated and processed to select healthy, viable sperm for fertilization. If there is an absence of sperm, surgical extraction procedures are performed. Microsurgical epididymal sperm aspiration (MESA) is used when sperm are unable to move through the genital tract. In this procedure, sperm are extracted directly from the epididymides. Sperm may also be extracted from the testes in a procedure called testicular sperm aspiration (TESA) or testicular fine needle aspiration (TEFNA). Although studies are few, some authors have proposed an FNA map prior to TESA to determine sperm location and availability of sperm in men with nonobstructive azoospermia considering TESA. (Turek, et al, 1999; Turek et al., 2000; Meng, et al., 2000). However, evidence is insufficient to support whether a map that shows no sperm is truly predictive of TESA failure. Consequently, the role of FNA mapping in the management of nonobstructive azoospermia is limited. Other techniques include: testicular sperm extraction (TESE), microscopic TESE, percutaneous epididymal sperm aspiration (PESA), vasal sperm aspiration, and seminal vesicle sperm aspiration aided by transrectal ultrasonography. Indications for MESA and PESA include: bilateral congenital absence of vas deferens (CAVD), cystic fibrosis, vasectomy of failed vasectomy reversal, inoperable ejaculatory ducts or distal vasal obstruction, post-inflammatory obstructions (e.g., gonorrhea), and radical cystoprostatectomy. Indications for TESA, TEFNA and TESE include: nonobstructive azoospermia (e.g., maturation arrest, hypospermatogenesis), obstructive azoospermia, anejaculation, complete terato/necrozoospermia, and complete sperm immobility. Microscopic TESE involves the use of a high magnification microscope for individuals with extremely low sperm production.

3. Egg retrieval: This step is similar to the IVF retrieval process.

4. Micromanipulation and fertilization with ICSI: Cumulus cells are removed from the oocyte, allowing the embryologist and/or physician to view the oocytes' maturity and suitability to undergo ICSI. A single sperm is injected directly into the cytoplasm of a mature egg using a microinjection pipette. This procedure may be repeated with several sperm and oocytes. ICSI can enhance fertilization of sperm which will not bind to or penetrate an egg. Attempts at ICSI may fail due to egg damage, eggs that are difficult to pierce, and fertilized eggs that fail to divide or stop developing.

5. Embryo transfer via IVF, GIFT, or ZIFT: Eggs may be transferred into the uterus or fallopian tube using IVF, GIFT, or ZIFT.

Indications for ICSI related to male factor infertility:

- very low numbers of motile sperm
- severe teratospermia (abnormal sperm)
- problems with sperm binding to and penetrating the egg
- antisperm antibodies of sufficient quality to prevent fertilization
- prior or repeated fertilization failure with standard IVF and fertilization methods
- frozen sperm collected prior to cancer treatment which may be limited in number and quality
- absence of sperm secondary to blockage or abnormality of the ejaculatory ducts (in this case, TESA or MESA is used)

While ICSI can improve fertilization in couples with male factor infertility ICSI is often used for couples with normal or borderline semen parameters. According to an ASRM practice committee report data does not support routine use of ICSI for non-male factor infertility, for unexplained infertility, for poor-quality oocytes, when there is low oocyte yield, or for advanced maternal age (ASRM, 2020). ICSI may be of benefit for individuals undergoing IVF with preimplantation genetic testing, for in vitro matured oocytes, and for cryopreserved oocytes (ASRM, 2020).

**Miscellaneous Issues Associated With ARTs**

**Ovarian Hyperstimulation Syndrome (OHS):** Ovarian hyperstimulation syndrome is a potential complication of controlled ovarian hyperstimulation with gonadotropin medications. It may be classified as mild, moderate or severe. Mild cases are not usually clinically relevant, although severe cases can be life-threatening. Severe cases may be characterized by extreme ovarian enlargement, ascites, elevated serum creatine, pleural effusions, oliguria, hemoconcentration and thromboembolic phenomena. Identification of high risk patients includes endocrine monitoring and follicular monitoring (ASRM, 2023). The syndrome is triggered by HCG and if there is potential to develop severe OHS, HCG injections are withheld and the cycle may be cancelled; in IVF cycles the embryos may be frozen (Lobo, 2012b). Other measures of preventing OHS such as coasting and administering HCG when endocrine levels decrease; the use of intravenous albumin at oocyte retrieval; and the use of GnRh antagonist protocols are debatable. Once the condition develops, treatment is supportive and includes correction of electrolyte imbalances and maintenance of urine output.

**Preimplantation Genetic Diagnosis (PGD):** Preimplantation genetic diagnosis is a technique that allows embryos to be tested for genetic disorders prior to implantation and pregnancy. It is a diagnostic procedure that provides an alternative to traditional prenatal genetic diagnosis. The procedure is recommended when embryos may be affected by certain genetic conditions. One or two cells are removed from the embryos by biopsy during IVF procedures and examined for genetic analysis. Embryos with normal biopsy results are available for transfer into the uterus while additional normal embryos may be frozen. Only normal, healthy embryos are transferred into the uterus, reducing the risk of adverse pregnancy outcomes such as birth defects and miscarriages and possible pregnancy termination after prenatal diagnosis. The value of PGD aneuploidy testing as a universal screening test for all IVF patients has not been demonstrated (ASRM, 2024).

**Elective Single Embryo Transfer (eSET):** Multiple gestations are associated with increased risk of complications in both the fetuses and the mother. Growing concern over this increased incidence of multiple pregnancies has led some countries to mandate limitations of the number of embryos used for transfer. Based on a report published by the Centers for Disease Control and Prevention (CDC), over the last decade, the percentage of SET among all patients increased dramatically from 20.6% in 2011 to 80.4% in 2020, and this trend was identified among all age groups. In addition, the percentage of embryo transfer cycles that resulted in singleton births increased from 22.7% in 2011 to 34.5% in 2020, while the percentage that resulted in multiple births decreased. Single embryo transfer likely contributed to this trend" (CDC, 2023). In the United States, there has never been a formal or regulated restriction on the number of embryos that a particular clinic may place in a woman's uterus. Clinical outcomes of women undergoing eSET with blastocyst or cleavage stage transfer have been investigated. Study results have demonstrated a decrease in multiple gestations and improved cryopreservation rates (Csokmay, et al, 2011), decreased risks of pre-term birth and low birth-weight (Grady, et al., 2012), and improved live-birth rates (Kresowik, et al., 2011). In 2012 the ASRM published a practice committee opinion regarding eSET. Within this publication they note eSET has been advocated as the only effective means of avoiding a multiple pregnancy in IVF cycles and defines eSET as " the transfer of a single embryo at either the cleavage stage or blastocyst stage of development, and that is selected from a large number of embryos." According to the committee opinion the ASRM

recommends consideration of eSET for women with a good prognosis which includes the following (ASRM, 2021a):

- age less than 35 years
- more than one top quality embryo available for transfer
- first or second treatment cycle
- previous successful IVF cycle
- recipient of embryos from donated eggs

Elective SET may be an option for women aged 35-40 years if they have top quality blastocyst-stage embryos available for transfer (ASRM, 2012).

**Number of Embryos to Use in Transfers:** The ASRM has issued updated practice guidelines (ASRM, 2021) on the appropriate number of embryos to transfer in ART practice. The guidelines were revised as an effort to promote singleton gestation and to reduce the number of multiple pregnancies. According to the ASRM guidelines, depending on the women's age and prognosis, the recommended number of embryos to transfer range varies.

The current guidelines are as follows (ASRM, 2021):

- For patients of any age with a favorable diagnosis, transfer of a euploid embryo has the most favorable prognosis and should be limited to one (Favorable prognosis factors include: young age, expectation of one or more high quality embryo for cryopreservation, euploid embryos, and previous live birth following an IVF cycle).
- For patients under the age of 35 who have a favorable prognosis, consideration should be given to transferring a single embryo, regardless of stage.
- For patients between the ages of 35–37 and having a more favorable prognosis, strong consideration should be given for a single-embryo transfer
- For patients between the ages of 38–40 who have a more favorable prognosis, no more than three untested cleavage-stage embryos should be transferred or no more than two blastocysts. When euploid embryos are available, a single blastocyst embryo should be the norm.
- For patients 41-42 years of age, no more than four untested cleavage stage embryos or three blastocysts should be transferred. When euploid embryos are available, a single blastocyst embryo should be the norm.
- In each of the above age groups, for patients with a less favorable prognosis, one additional embryo may be transferred according to individual circumstances. The patient must be counseled regarding the risk of multifetal pregnancy.
- If otherwise favorable patients fail to conceive after multiple cycles with high-quality embryos transferred, one additional embryo may be considered for transfer.
- In women > 43 years of age, there are insufficient data to recommend a limit on the number of embryos to transfer.
- In donor egg cycles, the age of the donor should be used in determining the number of embryos to transfer.
- Single embryo transfers should be considered in all gestational carrier cycles.
- Patients with a coexisting medical condition for which multiple pregnancy may increase risk of significant morbidity one embryo should be transferred.
- In frozen embryo transfer cycles, the number of good quality thawed embryos transferred should not exceed the recommended limit on the number of fresh embryos transferred for each age group.

**Low Birth-Weight and Multiple Births:** The use of assisted reproductive technology has been reported to be a contributor to the rate of low birth-weight in the United States, as it has been associated with a higher rate of multiple births. Multiple gestations are associated with increased risk for preterm delivery, low and very low birth weight and increased perinatal mortality (ASRM,

2021) Additionally, evidence suggests that there is a higher rate of low birth-weight among singleton infants conceived with assisted reproductive technology than among naturally conceived singleton infants or among all infants in the general population (CDC, 2009; McDonald, et al., 2009; Schieve, et al., 2002).

**Birth Defects:** Hansen et al. (2014) reported the results of a systematic review and meta-analysis (n=45 cohort studies) evaluating the risk of increased birth defects in ART and non-ART infants, and further assessed whether the risk differed between single or multiple births. The published results indicate that the risk of birth defects was higher in ART births compared to non-ART births and the risk further increased when limited to major birth defects or to single births; results regarding multiple births were not clear according to the authors. In general, several studies, systematic reviews, and meta analyses have been published evaluating the occurrence of birth defects in children after the use of ART. Currently, the literature is inconsistent in reported outcomes and in defining a clear relationship to the assisted reproductive technology. Criteria to define birth defects vary among countries making the analysis of ART safety data difficult to analyze (Alukal and Lamb, 2008). In addition, maternal factors may be the cause of birth defects rather than factors associated with the ART. While some authors suggest that there is an increased risk of birth defects with ART compared to spontaneous conceptions, it should be noted that other studies have not shown an increased risk of birth defects with either ICSI or standard IVF. As a result, large population-based studies are needed to address the exact etiology. Overall, the underlying biological mechanism by which ART affects adverse development remains unclear and couples considering ART should be informed of all potential risks and benefits.

**Cryopreservation:** Cryopreservation may be employed as a method to preserve fertility or as part of assisted reproductive technologies. In general, preservation of fertility is considered not medically necessary. When employed as part of assisted reproductive technologies cryopreservation of some reproductive cells/tissue have been proven safe and effective, although some remain under investigation. Cryopreservation, storage and thawing of testicular tissue is considered unproven in the treatment of infertility (ASRM, 2019).

Cryopreservation of sperm and embryos are well-established services and have been proven safe and effective; cryopreservation of mature oocytes is no longer considered investigational. The ASRM reaffirmed a 2013 practice committee guideline (ASRM, 2021) for mature oocyte cryopreservation. This document was endorsed by the American College of Obstetricians and Gynecologists (ACOG) Committee on Gynecological Practice. Within the guidelines the ASRM notes limited data exists evaluating the effect of duration of storage on oocyte cryopreservation as well as clinical outcomes and that success rates may not be generalized. Although success rates generally decline with increased maternal age, there are no comparative trials evaluating success of cryopreserved versus fresh oocytes by age. Furthermore, whether or not the incidence of anomalies and developmental abnormalities of children born from cryopreserved oocytes is similar to those born from cryopreserved embryos has not been firmly established. Nevertheless, although the data is very limited, oocyte cryopreservation may be recommended, with appropriate counseling, for couples pursuing IVF with insufficient sperm on the day of retrieval (e.g., severe oligospermia, azoospermia) and for individuals undergoing chemotherapy or other gonadotoxic therapies.

**Fertility Preservation:** When undergoing potentially gonadotoxic therapies embryo, sperm, mature oocyte cryopreservation and ovarian transposition are considered viable options and standard practice for fertility preservation for select individuals (ASRM, 2019; NCCN, 2023; ASCO, 2018).

There is a paucity of evidence in the peer-reviewed literature evaluating the safety of ovarian tissue and testicular tissue cryopreservation procedures and live birth outcomes following such

procedures. In December 2019, the ASRM updated guidelines for fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy (ASRM, 2019). According to these guidelines ovarian tissue cryopreservation for prepubertal girls and for those who cannot delay cancer treatment to undergo ovarian stimulation and oocyte retrieval is no longer considered experimental. The ASRM supports that "data on the efficacy, safety, and reproductive outcomes after ovarian tissue cryopreservation are still limited. Given the current body of literature, ovarian tissue cryopreservation should be considered an established medical procedure with limited effectiveness that should be offered to carefully selected patients." Testicular tissue cryopreservation in prepubertal males is still considered experimental and should be conducted under research protocols when no other options are feasible. Ovarian transposition may be offered to women undergoing pelvic radiation.

In 2021 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for "Adolescent and Young Adult Oncology" (NCCN, 2024) provide the following guidance with regards to cryopreservation of ovarian tissue for females "Ovarian tissue cryopreservation is a promising strategy for female fertility preservation when there is insufficient time for oocyte or embryo cryopreservation and/or the patient is prepubertal. This technique does not require hormonal stimulation, so there is no long delay in initiation of treatment. It is not considered appropriate for certain women with cancer if there exists a potential for reintroduction of malignant cells with grafting. It is also not recommended for carriers of BRCA mutations due to the increased risk of ovarian cancer. It is recommended transplantation be performed with the purpose of regaining fertility and not gonadal endocrine function. While ovarian tissue cryopreservation is still considered investigational at some institutions, it may be discussed as an option for fertility preservation, if available. For males, cryopreservation and subsequent transplantation of spermatogonial stem cells may be an option for prepubertal males and pubertal males in whom semen cryopreservation is not possible. For individuals with hematologic or testicular malignancies, autologous transplantation of cryopreserved testicular tissue may not be appropriate for fear of reintroduction of tumor cells. However, immature testicular tissue cryopreservation is still considered experimental. Semen cryopreservation is the most reliable and well established means of preserving fertility for male adolescent and young adult cancers (NCCN; 2024).

The 2025 American Society of Clinical Oncology (ASCO) clinical practice guidelines for fertility preservation in patients with cancer recommends sperm cryopreservation for pubertal and adult males prior to receiving gonadotoxic cancer therapies. Other methods, such as testicular tissue cryopreservation and reimplantation or grafting of human testicular tissue, should be performed only as part of clinical trials or approved experimental protocols. For adult females, embryo cryopreservation and oocyte cryopreservation are recommended options. Ovarian tissue cryopreservation for the purpose of future transplantation does not require ovarian stimulation and can be performed immediately. In addition, it does not require sexual maturity and hence may be the only method available in children. Finally, this method may also restore global ovarian function (Su, et al.). However, it should be noted further investigation is needed to confirm whether it is safe in patients with leukemias (Oktay, et al., 2018).

Fertility preservation is not recommended for the following circumstances (ASRM, 2021; ACOG 2013):

- oocyte cryopreservation in donor populations/donor banking
- oocyte cryopreservation performed solely to defer childbearing
- oocyte cryopreservation routinely used in lieu of embryo cryopreservation.

## Medicare Coverage Determinations

| | Contractor | Determination Name/Number | Revision Effective Date |
|---|---|---|---|
| NCD | National | No determination found | |
| LCD | | No determination found | |

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

## Coding Information

**Notes:**

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Diagnostic Testing**

**Considered Medically Necessary under core medical benefits when criteria in the applicable policy statements listed above are met to establish the etiology of infertility:**

| CPT®* Codes | Description |
|---|---|
| 49320 | Laparoscopy, abdomen, peritoneum, and omentum, diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure) |
| 54500 | Biopsy of testis, needle (separate procedure) |
| 54505 | Biopsy of testis, incisional (separate procedure) |
| 55110 | Scrotal exploration |
| 55870 | Electroejaculation |
| 58100 | Endometrial sampling (biopsy) with or without endocervical sampling (biopsy), without cervical dilation, any method (separate procedure) |
| 58340† | Catheterization and introduction of saline or contrast material for saline infusion sonohysterography (SIS) or hysterosalpingography |
| 58345 | Transcervical introduction of fallopian tube catheter for diagnosis and/or re-establishing patency (any method), with or without hysterosalpingography |
| 58350 | Chromotubation of oviduct, including materials |
| 58555 | Hysteroscopy, diagnostic (separate procedure) |
| 74440 | Vasography, vesiculography, or epididymography, radiological supervision and interpretation |
| 74740† | Hysterosalpingography, radiological supervision and interpretation |
| 74742 | Transcervical catheterization of fallopian tube, radiological supervision and interpretation |
| 76830 | Ultrasound, transvaginal |
| 76831† | Saline infusion sonohysterosonography (SIS), including color flow Doppler, when performed |
| 76856 | Ultrasound, pelvic (nonobstetric), real time with image documentation; complete |
| 76870 | Ultrasound, scrotum and contents |
| 76872 | Ultrasound, transrectal |
| 81015 | Urinalysis; microscopic only |
| 82166 | Anti-mullerian hormone (AMH) |
| 82670 | Estradiol; total |

| CPT®* Codes | Description |
|---|---|
| 82671 | Estrogens; fractionated |
| 82672 | Estrogens; total |
| 82679 | Estrone |
| 82757 | Fructose, semen |
| 83001 | Gonadotropin; follicle stimulating hormone (FSH) |
| 83002 | Gonadotropin; luteinizing hormone (LH) |
| 84144 | Progesterone |
| 84146 | Prolactin |
| 84402 | Testosterone; free |
| 84403 | Testosterone; total |
| 84410 | Testosterone; bioavailable, direct measurement (eg, differential precipitation) |
| 84443 | Thyroid stimulating hormone (TSH) |
| 84830†† | Ovulation tests, by visual color comparison methods for human luteinizing hormone |
| 88280 | Chromosome analysis; additional karyotypes, each study |
| 89257 | Sperm identification from aspiration (other than seminal fluid) |
| 89260 | Sperm isolation; simple prep (eg, sperm wash and swim-up) for insemination or diagnosis with semen analysis |
| 89261 | Sperm isolation; complex prep (eg, Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis |
| 89264 | Sperm identification from testis tissue, fresh or cryopreserved |
| 89300 | Semen analysis; presence and/or motility of sperm including Huhner test (post coital) |
| 89310 | Semen analysis; motility and count (not including Huhner test) |
| 89320 | Semen analysis; volume, count, motility, and differential |
| 89321 | Semen analysis; sperm presence and motility of sperm, if performed |
| 89322 | Semen analysis; volume, count, motility, and differential using strict morphologic criteria (eg, Kruger) |
| 89325 | Sperm antibodies |
| 89330 | Sperm evaluation; cervical mucus penetration test, with or without spinnbarkeit test |
| 89331 | Sperm evaluation, for retrograde ejaculation, urine (sperm concentration, motility, and morphology, as indicated) |

†**Note: Considered Experimental/Investigational/Unproven when used to report saline-air infused sono- hysterosalpingogram (e.g., femVue® [Femasys, Inc.]).**

††**Note: Considered Not Covered or Reimbursable when used to report home ovulation prediction test kits.**

| HCPCS Codes | Description |
|---|---|
| G0027 | Semen analysis; presence and/or motility of sperm excluding Huhner |
| S3655 | Antisperm antibodies test (immunobead) |

**Treatment of Infertility**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met if benefits are available for infertility treatment:**

| CPT® * Codes | Description |
|---|---|
| 10004††† | Fine needle aspiration biopsy, without imaging guidance; each additional lesion (List separately in addition to code for primary procedure) |
| 10005††† | Fine needle aspiration biopsy, including ultrasound guidance; first lesion |
| 10006††† | Fine needle aspiration biopsy, including ultrasound guidance; each additional lesion (List separately in addition to code for primary procedure) |
| 10021††† | Fine needle aspiration biopsy; without imaging guidance; first lesion |
| 49321 | Laparoscopy, surgical; with biopsy (single or multiple) |
| 52402 | Cystourethroscopy with transurethral resection or incision of ejaculatory ducts |
| 54500 | Biopsy of testis, needle (separate procedure) |
| 54505 | Biopsy of testis, incisional (separate procedure) |
| 54640 | Orchiopexy, inguinal or scrotal approach |
| 54650 | Orchiopexy, abdominal approach, for intra-abdominal testis (eg, Fowler Stephens) |
| 54800 | Biopsy of epididymis, needle |
| 54840 | Excision of spermatocele, with or without epididymectomy |
| 54860 | Epididymectomy; unilateral |
| 54861 | Epididymectomy; bilateral |
| 54900 | Epididymovasostomy, anastomosis of epididymis to vas deferens; unilateral |
| 54901 | Epididymovasostomy, anastomosis of epididymis to vas deferens; bilateral |
| 55400†††† | Vasovasostomy, vasovasorrhaphy |
| 55500 | Excision of hydrocele of spermatic cord, unilateral (separate procedure) |
| 55530 | Excision of varicocele or ligation of spermatic veins for varicocele; (separate procedure) |
| 55535 | Excision of varicocele or ligation of spermatic veins for varicocele; abdominal approach |
| 55540 | Excision of varicocele or ligation of spermatic veins for varicocele; with hernia repair |
| 55550 | Laparoscopy, surgical, with ligation of spermatic veins for varicocele |
| 55870 | Electroejaculation |
| 58140 | Myomectomy, excision of fibroid tumor(s) of uterus, 1 to 4 intramural myoma(s) with total weight of 250 g or less and/or removal of surface myomas; abdominal approach |
| 58145 | Myomectomy, excision of fibroid tumor(s) of uterus, 1 to 4 intramural myoma(s) with total weight of 250 g or less and/or removal of surface myomas; vaginal approach |
| 58146 | Myomectomy, excision of fibroid tumor(s) of uterus, 5 or more intramural myomas and/or intramural myomas with total weight greater than 250 g, abdominal approach |
| 58321 | Artificial insemination; intra-cervical |
| 58322 | Artificial insemination; intra-uterine |
| 58323 | Sperm washing for artificial insemination |
| 58345 | Transcervical introduction of fallopian tube catheter for diagnosis and/or re-establishing patency (any method), with or without hysterosalpingography |
| 58545 | Laparoscopy, surgical, myomectomy, excision; 1 to 4 intramural myomas with total weight of 250 g or less and/or removal of surface myomas |
| 58546 | Laparoscopy, surgical, myomectomy, excision; 5 or more intramural myomas and/or intramural myomas with total weight greater than 250 g |

| CPT® * Codes | Description |
|---|---|
| 58558 | Hysteroscopy, surgical; with sampling (biopsy) of endometrium and/or polypectomy, with or without D & C |
| 58559 | Hysteroscopy, surgical; with lysis of intrauterine adhesions (any method) |
| 58560 | Hysteroscopy, surgical; with division or resection of intrauterine septum (any method) |
| 58561 | Hysteroscopy, surgical; with removal of leiomyomata |
| 58660 | Laparoscopy, surgical; with lysis of adhesions (salpingolysis, ovariolysis) (separate procedure) |
| 58662 | Laparoscopy, surgical; with fulguration or excision of lesions of the ovary, pelvic viscera, or peritoneal surface by any method |
| 58670 | Laparoscopy, surgical; with fulguration of oviducts (with or without transection) |
| 58672 | Laparoscopy, surgical; with fimbrioplasty |
| 58673 | Laparoscopy, surgical; with salpingostomy (salpingoneostomy) |
| 58700 | Salpingectomy, complete or partial, unilateral or bilateral (separate procedure) |
| 58740 | Lysis of adhesions (salpingolysis, ovariolysis) |
| 58752 | Tubouterine implantation |
| 58760 | Fimbrioplasty |
| 58770 | Salpingostomy (salpingoneostomy) |
| 58800 | Drainage of ovarian cyst(s), unilateral or bilateral (separate procedure); vaginal approach |
| 58805 | Drainage of ovarian cyst(s), unilateral or bilateral (separate procedure); abdominal approach |
| 58920 | Wedge resection or bisection of ovary, unilateral or bilateral |
| 58925 | Ovarian cystectomy, unilateral or bilateral |
| 58970 | Follicle puncture for oocyte retrieval, any method |
| 58974 | Embryo transfer, intrauterine |
| 58976 | Gamete, zygote, or embryo intrafallopian transfer, any method |
| 74440 | Vasography, vesiculography, or epididymography, radiological supervision and interpretation |
| 74742 | Transcervical catheterization of fallopian tube, radiological supervision and interpretation |
| 76830 | Ultrasound, transvaginal |
| 76856 | Ultrasound, pelvic (nonobstetric), real time with image documentation; complete |
| 76857 | Ultrasound, pelvic (nonobstetric), real time with image documentation; limited or follow-up (eg, for follicles) |
| 76948 | Ultrasonic guidance for aspiration of ova, imaging supervision and interpretation |
| 82670 | Estradiol, total |
| 83001 | Gonadotropin; follicle stimulating hormone (FSH) |
| 83002 | Gonadotropin; luteinizing hormone (LH) |
| 84144 | Progesterone |
| 84830 | Ovulation tests, by visual color comparison methods for human luteinizing hormone |
| 89250 | Culture of oocyte(s)/embryo(s), less than 4 days |
| 89253 | Assisted embryo hatching, microtechniques (any method) |
| 89254 | Oocyte identification from follicular fluid |
| 89255 | Preparation of embryo for transfer (any method) |
| 89257 | Sperm identification from aspiration (other than seminal fluid) |
| 89260 | Sperm isolation; simple prep (eg, sperm wash and swim-up) for insemination or diagnosis with semen analysis |

| CPT® * Codes | Description |
|---|---|
| 89261 | Sperm isolation; complex prep (eg, 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 | Assisted oocyte fertilization, microtechnique; greater than 10 oocytes |
| 89290 | Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos |
| 89291 | Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos |

†††**Note: Considered Experimental/Investigational/Unproven when used to report fine needle aspiration mapping.**

††††**Note: Considered Not Medically Necessary when used to report the reversal of voluntary sterilization.**

| HCPCS Codes | Description |
|---|---|
| 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 |

**Considered Medically Necessary when used to report sperm extraction methods (e.g., testicular sperm extraction [TESE], micro-dissection testicular sperm extraction [micro-TESE], percutaneous testicular sperm extraction [PESA]) not otherwise coded:**

| CPT®* Codes | Description |
|---|---|
| 55899 | Unlisted procedure, male genital system |

**Considered Medically Necessary when used to report mock embryo transfer prior to a medically necessary IVF procedure:**

| CPT®* Codes | Description |
|---|---|
| 58999 | Unlisted procedure, female genital system (nonobstetrical) |

**Cryopreservation Services**

**State Mandate Coverage**

**If an applicable state mandate exists for fertility preservation, the following are generally considered medically necessary:**

- **Cryopreservation, storage and thawing of sperm, oocyte(s) and embryo(s) for individuals facing anticipated infertility resulting from chemotherapy, pelvic radiotherapy, or other procedures expected to render one permanently infertile (Please access the state specific mandate):**

| CPT®* Codes | Description |
|---|---|
| 89258 | Cryopreservation; embryo(s) |
| 89259 | Cryopreservation; sperm |
| 89337 | Cryopreservation, mature oocyte(s) |
| 89342 | Storage (per year); embryo(s) |
| 89343 | Storage, (per year); sperm/semen |
| 89346 | Storage, (per year); oocyte(s) |
| 89352 | Thawing of cryopreserved; embryo(s) |
| 89353 | Thawing of cryopreserved; sperm/semen, each aliquot |
| 89356 | Thawing of cryopreserved; oocytes, each aliquot |

| HCPCS Codes | Description |
|---|---|
| S4027 | Storage of previously frozen embryos |
| S4030 | Thawing of cryopreserved; sperm/semen, each aliquot |
| S4031 | Sperm procurement and cryopreservation services; subsequent visit |
| S4040 | Monitoring and storage of cryopreserved embryos, per 30 days |

- **When used to report re-transplantation of ovarian reproductive tissue and/or cryopreservation of ovarian reproductive tissue (Please access the state specific mandate):**

| CPT®* Codes | Description |
|---|---|
| 58999 | Unlisted procedure, female genital system (nonobstetrical) |
| 89398 | Unlisted reproductive medicine laboratory procedure |

**Considered Experimental/Investigational/Unproven when used to report testicular tissue cryopreservation, testicular tissue re-transplantation, immature oocytes and/or in vitro maturation (Please access the state specific mandate):**

| CPT®* Codes | Description |
|---|---|
| 55899 | Unlisted procedure, male genital system |
| 89335 | Cryopreservation, reproductive tissue, testicular |

| | |
|---|---|
| 89344 | Storage, (per year); reproductive tissue, testicular/ovarian |
| 89354 | Thawing of cryopreserved; reproductive tissue, testicular/ovarian |
| 89398 | Unlisted reproductive medicine laboratory procedure |

**Benefit Coverage**

**Considered Medically Necessary if specific benefit coverage for cryopreservation services are available:**

| CPT®* Codes | Description |
|---|---|
| 89258 | Cryopreservation; embryo(s) |
| 89337 | Cryopreservation, mature oocyte(s) |
| 89342 | Storage (per year); embryo(s) |
| 89346 | Storage, (per year); oocyte(s) |
| 89352 | Thawing of cryopreserved; embryo(s) |
| 89356 | Thawing of cryopreserved; oocytes, each aliquot |

| HCPCS Codes | Description |
|---|---|
| S4027 | Storage of previously frozen embryos |
| S4040 | Monitoring and storage of cryopreserved embryos, per 30 days |

**Considered Not Medically Necessary even if benefit specific coverage for cryopreservation services are available:**

| CPT®* Codes | Description |
|---|---|
| 89259 | Cryopreservation; sperm |
| 89343 | Storage, (per year); sperm/semen |
| 89353 | Thawing of cryopreserved; sperm/semen, each aliquot |

| HCPCS Codes | Description |
|---|---|
| S4030 | Sperm procurement and cryopreservation services; initial visit |
| S4031 | Sperm procurement and cryopreservation services; subsequent visit |

**Considered Experimental/Investigational/Unproven if specific benefit coverage for cryopreservation services are available:**

| CPT®* Codes | Description |
|---|---|
| 89335 | Cryopreservation, reproductive tissue, testicular |
| 89344 | Storage, (per year); reproductive tissue, testicular/ovarian |
| 89354 | Thawing of cryopreserved; reproductive tissue, testicular/ovarian |

**Considered Experimental/Investigational/Unproven if specific benefit coverage for cryopreservation services are available AND when used to report re-transplantation of ovarian or testicular reproductive tissue; cryopreservation of ovarian reproductive tissue; immature oocytes and/or in vitro maturation:**

| CPT®* Codes | Description |
|---|---|
| 55899 | Unlisted procedure, male genital system |
| 58999 | Unlisted procedure, female genital system (nonobstetrical) |
| 89398 | Unlisted reproductive medicine laboratory procedure |

**Experimental/Investigational/Unproven**

**Considered Experimental/Investigational/Unproven:**

| CPT®* Codes | Description |
|---|---|
| 86357 | Natural killer (NK) cells, total count |
| 89251 | Culture of oocyte(s)/embryo(s), less than 4 days; with co-culture of oocyte(s)/embryos |
| 97810 | Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient |
| 97811 | Acupuncture, 1 or more needles; without electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure) |
| 97813 | Acupuncture, 1 or more needles; with electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient |
| 97814 | Acupuncture, 1 or more needles; with electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure) |
| 99183 | Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session |
| 0664T | Donor hysterectomy (including cold preservation); open, from cadaver donor |
| 0665T | Donor hysterectomy (including cold preservation); open, from living donor |
| 0666T | Donor hysterectomy (including cold preservation); laparoscopic or robotic, from |
| 0667T | Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor |
| 0668T | Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and |
| 0669T | Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each |
| 0670T | Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each |

| HCPCS Codes | Description |
|---|---|
| G0277 | Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval |

**Considered Experimental/Investigational/Unproven when used to report INVOcell, direct intraperitoneal insemination, intrafollicular insemination, or fallopian tube sperm transfusion:**

| CPT®* Codes | Description |
|---|---|
| 58999 | Unlisted procedure, female genital system (nonobstetrical) |

**Considered Experimental/Investigational/Unproven when used to report immunological testing:**

| CPT®* Codes | Description |
|---|---|
| 83519 | Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA) |
| 86148 | Anti-phosphatidylserine (phospholipid) antibody |
| 86360 | T-cells; absolute CD4 and CD8 count, including ratio |

**Considered Experimental/Investigational/Unproven when used to report antiprothrombin (phospholipid cofactor) antibody or embryotoxicity assay:**

| CPT®* Codes | Description |
|---|---|
| 86849 | Unlisted immunology procedure |

**Considered Experimental/Investigational/Unproven when used to report reproductive immune-phenotype (RIP):**

| CPT®* Codes | Description |
|---|---|
| 88182 | Flow cytometry, cell cycle or DNA analysis |
| 88189 | Flow cytometry, interpretation, 16 or more markers |

**Considered Experimental/Investigational/Unproven when used to report computer-assisted sperm motion analysis, hemizona test, Hyaluronan Binding Assay (HBA), sperm viability test, sperm precursors, laser assisted necrotic blastomere removal from cryopreserved embryos, time-lapse monitoring/storage of embryos:**

| CPT®* Codes | Description |
|---|---|
| 89398 | Unlisted reproductive medicine laboratory procedure |

**Considered Experimental/Investigational/Unproven when used to report endometrial receptivity testing:**

| CPT®* Codes | Description |
|---|---|
| 88305 | Level IV - Surgical pathology, gross and microscopic examination |
| 88342 | Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure |

**Considered Experimental/Investigational/Unproven when used to report fine needle aspiration mapping:**

| CPT®* Codes | Description |
|---|---|
| 88173 | Cytopathology, evaluation of fine needle aspirate; interpretation and report |

| | |
|---|---|
| 88106 | Cytopathology, fluids, washings or brushings, except cervical or vaginal; simple filter method with interpretation |
| 88108 | Cytopathology, concentration technique, smears and interpretation (eg, Saccomanno technique) |
| 88305 | Level IV - Surgical pathology, gross and microscopic examination |

**Considered Experimental/Investigational/Unproven when used to report serum inhibin B:**

| **CPT®* Codes** | **Description** |
|---|---|
| 83520 | Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified |

**Considered Experimental/Investigational/Unproven when used to report manual soft tissue therapy for the treatment of pelvic adhesions (WURN Technique®, Clear Passage Therapy):**

| **CPT®* Codes** | **Description** |
|---|---|
| 97140 | Manual therapy techniques (eg, mobilization/manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes |

**Considered Experimental/Investigational/Unproven when used to report reactive oxygen species testing (ROS):**

| **CPT®* Codes** | **Description** |
|---|---|
| 82397 | Chemiluminescent assay |

**Considered Experimental/Investigational/Unproven when used to report vaginal microbiome testing:**

| **CPT®* Codes** | **Description** |
|---|---|
| 87999 | Unlisted microbiology procedure |
| 88199 | Unlisted cytopathology procedure |

**Considered Experimental/Investigational/Unproven when used to report saline-air infused sono- hysterosalpingogram (e.g., femVue® [Femasys, Inc.]):**

| **CPT®* Codes** | **Description** |
|---|---|
| 0568T | Introduction of mixture of saline and air for sonosalpingography to confirm occlusion of fallopian tubes, transcervical approach, including transvaginal ultrasound and pelvic ultrasound |

**Considered Experimental/Investigational/Unproven when used to report sperm capacitation assay function (e.g., Cap-Score™):**

| **CPT®* Codes** | **Description** |
|---|---|

| | |
|---|---|
| 0255U | Andrology (infertility), sperm-capacitation assessment of ganglioside GM1 distribution patterns, fluorescence microscopy, fresh or frozen specimen, reported as percentage of capacitated sperm and probability of generating a pregnancy score |

**Considered Not Covered or Reimbursable**

**Considered Not Covered or Reimbursable even if benefits are available for infertility treatment:**

| CPT®* Codes | Description |
|---|---|
| 58750 | Tubotubal anastomosis |
| 81025†††††† | Urine pregnancy test, by visual color comparison methods |
| 89259 | Cryopreservation; sperm |
| 89343 | Storage, (per year); sperm/semen |
| 89353 | Thawing of cryopreserved; sperm/semen, each aliquot |

†††††† **Note: Considered Not Covered or Reimbursable when used to report a home urine pregnancy test kit.**

| HCPCS Codes | Description |
|---|---|
| S4023 | Donor egg cycle, incomplete, case rate |
| S4025 | Donor services for in vitro fertilization (sperm or embryo), case rate |
| S4026 | Procurement of donor sperm from sperm bank |
| S4030 | Sperm procurement and cryopreservation services; initial visit |
| S4031 | Sperm procurement and cryopreservation services; subsequent visit |



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## Revision Details

| Type of Revision | Summary of Changes | Date |
|---|---|---|
| Annual Review | No clinical policy statement changes. | 6/15/2025 |
| Annual Review | Revised policy statement to reflect current ASRM definition of infertility. | 10/15/2024 |