



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject Infertility Services

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- Follitropin Therapy
- Ganirelix (Antagon®)
- Genetic Testing for Cystic Fibrosis
- Human Chorionic Gonadotropin Therapy
- Hyperbaric Oxygen Therapy, Systemic & Topical
- Hysteroscopic Tubal Sterilization ESSURE®
- Infertility Injectables
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- Preimplantation Genetic Diagnosis
- Recurrent Pregnancy Loss: Diagnosis and Treatment

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

Coverage of diagnostic and treatment services associated with infertility is dependent upon medical and prescription drug benefit plan language. Infertility services benefit plan language differs significantly across plans. Coverage for any infertility-related service is subject to the terms, conditions, and limitations of the applicable benefit plan document and schedule of copayments. In addition, state mandates may apply. Please refer to the applicable benefit plan document to determine benefit availability and the terms, conditions, and limitations of coverage.

Once an individual meets the definition of infertility as outlined in the benefit plan or as listed below, CIGNA generally covers services associated with establishing the etiology of infertility under the core medical benefits of the plan. However, once the cause of infertility is established, no further infertility diagnostic testing is covered under the core medical benefits.

When not clearly specified in the benefit plan, infertility is defined as ONE of the following:

- The inability of opposite-sex partners to achieve conception after at least one year of unprotected intercourse.
- The inability of a woman to achieve conception after six trials of medically supervised artificial insemination over a one-year period.
- The inability of opposite-sex partners to achieve conception after six months of unprotected intercourse for a woman over the age of 35 years.

DIAGNOSTIC TESTING TO ESTABLISH THE ETIOLOGY OF INFERTILITY

The following services are covered as 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), human chorionic gonadotropin (HCG), estradiol, clomiphene challenge test, free and/or total testosterone, dehydroepiandrosterone sulfate (DHEA), progesterone, 17-hydroxyprogesterone, fasting glucose, glucose tolerance test, lipid panel (including total cholesterol, high density lipoproteins, triglycerides), progesterone challenge test, cervical culture, chlamydia culture, post-coital test and anti-sperm antibodies
- endometrial biopsy
- ultrasound (i.e., serial transvaginal, pelvic, ovarian)
- hysteroscopy
- hysterosalpingography
- sonohysterography
- diagnostic laparoscopy with or without chromotubation, in an asymptomatic individual
- salpingoscopy

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. Repeat semen analysis is covered every one to three months, up to a total of five tests.
- additional laboratory tests: endocrine evaluation (including FSH, total and free testosterone, prolactin, LH, TSH), antisperm antibodies, post-ejaculatory urinalysis, urine culture, and semen culture
- transrectal ultrasound (TRUS), scrotal ultrasound
- vasography and testicular biopsy in individuals with azoospermia
- scrotal exploration
- carrier genetic testing for cystic fibrosis in males with congenital bilateral absence of vas deferens*
- karyotyping for chromosomal abnormalities in males with nonobstructive azoospermia or severe oligospermia
- Y-chromosome microdeletion testing in males with nonobstructive azoospermia or severe oligospermia
- sperm penetration assay (hamster penetration test, zona free hamster oocyte test) for those with male factor infertility, who are considering IVF cycles and ICSI

*Note: For the specific medical necessity criteria for this testing, refer to the CIGNA Genetic Testing for Cystic Fibrosis Coverage Policy. All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or a licensed or certified genetic counselor.

TREATMENT OF INFERTILITY

If benefit coverage for infertility treatment is available, the following treatment services may be considered for coverage as medically necessary. Benefit availability for specific treatment modalities, medications and associated infertility services varies by plan and the specific plan options selected. The treatments, medications and associated services listed below may not be covered or may be

subject to limitations under specific plans, even if benefits are otherwise available for infertility treatment. Please refer to the applicable medical benefit and prescription drug benefit plan document and schedules to determine benefit availability and the terms, conditions and limitations of coverage:

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
- artificial insemination, including intrauterine or intracervical insemination
- in vitro fertilization with embryo transfer (IVF-ET), 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, 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
- cryopreservation of embryos, only while the individual is currently under active infertility treatment
- gamete intrafallopian transfer (GIFT) and associated services
- zygote intrafallopian transfer (ZIFT) and associated services
- intracytoplasmic sperm injection (ICSI) and associated services, including sperm extraction and retrieval procedures

Male infertility treatment services:

- semen analysis
- Kruger strict criteria for sperm morphology
- 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 or 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

CIGNA does not cover ANY of the following infertility services or tests because they are considered experimental, investigational, or unproven:

- immunological testing (e.g., antiprothrombin antibodies, embryotoxicity assay, circulating natural killer cell measurement, antiphospholipid antibodies, reproductive immunophenotype [RIP])
- immune treatments (e.g., periimplantation glucocorticoids, anti-tumor necrosis factor agents, leukocyte immunization, IV immunoglobulins)
- computer-assisted sperm motion analysis

- cryopreservation, storage, and thawing of the following reproductive tissue: oocytes, ovaries, or testicular tissue
- culture of oocyte(s), embryo(s), less than 4 days with co-culture (i.e., co-culturing of embryos/oocytes)
- 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)
- ovarian reserve testing (e.g., serum inhibin B, anti-mullerian hormone)
- sperm DNA integrity testing (e.g., Sperm Chromatin Structure Assay [SCSA], TUNEL assay, Comet assay, Human Sperm Activation Assay [HSAA], Sperm DNA Decondensation™ [SDD™])
- 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
- 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)

Many benefit plans administered by CIGNA do not cover any of the following, even when benefits are available for infertility treatment because they are specifically excluded. In addition, all of these services are considered not medically necessary:

- 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 or pregnancy test kits
- cryopreservation and storage of embryos when not undergoing covered active infertility treatment

General Background

Infertility is defined as the failure to achieve pregnancy after 12 months of regular unprotected intercourse (Agency for Healthcare Research and Quality [AHRQ], 2008; American Society of Reproductive Medicine [ASRM], 2008). Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after six months for women over the age of 35 years (ASRM, 2008). 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 age 35 it is generally recommended that infertility testing begins after 6 months of unsuccessful attempts at conception (ASRM, 2008; 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, 2010a).

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 and laboratory studies, including: hormone levels, glucose levels, lipid panel, cervical culture and post-coital testing. Additional studies are performed when the initial workup fails to provide definitive information. Tests include:

- progesterone challenge test
- endometrial biopsy
- ultrasound
- hysteroscopy
- hysterosalpingography
- diagnostic laparoscopy with or without chromotubation in asymptomatic individuals
- sonohysterography
- salpingoscopy

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 two specimens at least one month apart, 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. Performing greater than five semen analyses provides little additional diagnostic value. 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 who 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 (refer to the Genetic Testing for Cystic Fibrosis Coverage Policy). 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 periimplantation glucocorticoids, anti-tumor necrosis factor agents (infliximab, etanercept), leukocyte immunization and IV immunoglobulin therapy. Nonetheless, evidence in the published, scientific literature is insufficient to support improved individual 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 (Ghazeeri and Kutteh, 2001; Baczkowski, et al., 2007; Ghazeeri and Kutteh, 2001).

Serum inhibin B is an enzyme immunoassay recommended by some authors 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 (RCOG, 2004; Creus, et al., 2000; Corson et al., 1999).

Anti-mullerian hormone, produced by granulosa cells from preantral and early antral follicles, has been evaluated as a predictor of ovarian reserve (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 the decline of ovarian reserve with aging is associated with a decrease in antimullerian hormone levels. Nonetheless there appears to be no consensus regarding a specific value of serum antimullerian hormone for defining those women who may respond poorly to assisted reproductive technologies such as in vitro fertilization. Antimullerian hormone level has not been shown to be a good predictor of pregnancy after assisted reproductive technology treatment Simone, et al., 2010; Tremellen, et al., 2010; Guerif, et al., 2009). Evidence supporting improved clinical outcomes as a result testing is not conclusive; some authors have reported strong predictive value, sensitivity and specificity, while others have not. Currently, early follicular phase FSH remains the most commonly used ovarian marker and authors acknowledge further studies are needed to more accurately define the clinical value of antimullerian hormone testing in infertile women.

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).

The clinical utility of the tests noted below has not been demonstrated in the medical literature. These studies 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] 2010[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™). The Practice Committee of the ASRM (2008g) reported that up to 8% of infertile men will have abnormal DNA integrity despite a normal semen analysis—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 (2010a) reported that the assays demonstrate low sensitivity and high specificity; there is insufficient evidence to support the routine use of DNA integrity testing in the evaluation and management of male factor infertility.
- **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, 2010[a]).

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 from 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, 2007a). 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

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-30s. 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 human menopausal gonadotropins (hMG) (Pergonal[®], Repronex[®], LH and FSH), human chorionic gonadotropin (HCG) (Pregnyl[®], Novarel[™]), human FSH, and recombinant FSH/follitropins (Follistim[®], Gonal-F[®]) may be administered to patients who have not responded to clomiphene
- Gonadotropin-releasing hormone (GnRH) (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.

Treatment of Male Infertility Factors

Obstructive/Nonobstructive Azoospermia: Azoospermia is defined as a complete absence of sperm from at least two separate centrifuged semen samples (AUA, 2010[b]). It may be caused by obstruction of the extratesticular ductal system (obstructive azoospermia) or defects in spermatogenesis (nonobstructive azoospermia). Obstructive azoospermia may be caused by epididymal, vasal, or ejaculatory pathology. Previous vasectomy is a common cause of vasal obstruction. Other causes include 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:

- 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 (AUA, ASRM, 2001).

Males with nonobstructive azoospermia should have genetic testing before proceeding to assisted reproductive technologies. 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. Counseling regarding genetic issues should be a critical part of the male evaluation (Brugh, 2003).

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), spermatic vein embolization (balloon, coils, sclerosing agents, or transcatheter/transvenous occlusion), 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

In approximately 5–10% of 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: pharmacologic treatment, intrauterine insemination, superovulation with oral or injectable medications, combinations of intrauterine insemination with superovulation, and assisted reproductive technologies.

Assisted Reproductive Technologies

Assisted reproductive technologies (ART) describe a group of infertility treatment procedures that involve the extracorporeal manipulation of oocytes, embryos and sperm. Techniques include: artificial insemination, 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 the IVF cycle.

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. 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. In general, AI techniques are 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

In Vitro Fertilization with Embryo Transfer (IVF-ET): 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.
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, a mock embryo transfer is performed prior to the actual IVF procedure for the purpose of assessing the cervix and uterus. A thin plastic catheter, without an embryo, is passed through the cervix and into the uterus to evaluate the potential for 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 birth rate 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 (2008a) indicate the following:

- In trials of unselected patients, the transfer of blastocysts has not been shown to increase live birth rates compared to those achieved with transfer of cleavage-stage embryos.
- In trials of 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.
- In trials with populations of poor prognosis patients, blastocyst transfer does not increase and may decrease live birth rates.

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. Several 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; this allows the otherwise normal embryo to make contact with the endometrial lining and implant (Penzias & DeCherney, 1994). 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 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 (2008f) reported, "Assisted hatching may be clinically useful and individual ART programs should evaluate their own patient populations in order to determine which subgroups may benefit from the procedure. The routine use of assisted hatching in the treatment of all IVF patients appears at this point to be unwarranted. Assisted hatching may be clinically useful in patients with a poor prognosis, including those with ≥ 2 failed IVF cycles and poor embryo quality and older women (≥ 38 years of age)." 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 (2010a) strict criteria should not be use in isolation to make prognostic or therapeutic decisions.

Gamete Intrafallopian Transfer (GIFT): The GIFT procedure is similar 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. Reported pregnancy rates are comparable to those associated with IVF.

Zygote Intrafallopian Transfer (ZIFT): ZIFT is a 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. Although this procedure is performed less frequently than GIFT, the indications are similar to those for GIFT and IVF.

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. Genetic counseling may be appropriate in selected cases.

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 deferentia (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:

- 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)

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. 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, 2007b). 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: 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.

Number of Embryos to Use in Transfers: The ASRM has issued updated practice guidelines (ASRM, 2009) on the appropriate number of embryos to transfer in ART practice. According to the ASRM guidelines, depending on the women's age and prognosis, the recommended number of embryos to transfer ranges from two to five. The ASRM recommends that physicians and patients consider single embryo transfer in women younger than age 35 that have a favorable prognosis. More embryos may be transferred in select cases, depending on individual circumstances and after appropriate counseling.

The current guidelines are as follows (ASRM, 2009):

- For patients under the age of 35 who have a more favorable prognosis, consideration should be given to transferring only a single embryo. No more than two embryos (cleavage stage [two to three days after fertilization] or blastocyst stage [five to six days after fertilization]) should be transferred. (Favorable prognosis factors include: patients undergoing their first cycle of IVF; those who have had previous

success with IVF; those with embryos of sufficient quality and quantity for cryopreservation; and improved embryo quality as judged by morphologic features.)

- For patients between the ages of 35–37 and having a more favorable prognosis, no more than two cleavage-stage embryos should be transferred. All others in this age group should have no more than three cleavage-stage embryos transferred. If extended culture is performed, no more than two blastocysts should be transferred to women in this age group.
- For patients between the ages of 38–40 who have a more favorable prognosis, no more than three cleavage-stage embryos should be transferred or no more than two blastocysts. All other women in this group should have no more than four cleavage-stage embryos or three blastocysts transferred.
- For patients 41–42 years of age, no more than five cleavage stage embryos or three blastocysts should be transferred.
- In each of the above age groups, for patients with two or more previous failed fresh IVF cycles or less favorable prognosis, one additional embryo according to individual circumstances. The patient must be counseled regarding the risk of multifetal pregnancy; both counseling and justification for exceeding the limits must be documented in the patient's permanent record.
- 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.
- 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.

Based on a report published by the Centers for Disease Control and Prevention (CDC), approximately 43% of ART cycles that used fresh nondonor eggs or embryos and progressed to the embryo transfer stage in 2006 involved the transfer of three or more embryos, about 16% of cycles involved the transfer of four or more, and approximately 5% of cycles involved the transfer of five or more embryos (CDC, 2008). 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. 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.

In addition to the above ASRM recommendations, since all oocytes may not fertilize when GIFT is performed, one more oocyte than embryo may be transferred for each prognostic category.

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 birth weight and increased perinatal mortality (Alukal and Lamb, 2008). Additionally, studies have suggested 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 (McDonald, et al., 2009; Schieve, et al., 2002).

Birth Defects: Several studies 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. Additionally, the criteria to define birth defects vary among countries making the analysis of ART safety data difficult to analyze (Alukal and Lamb, 2008). In some cases maternal factors may be the cause and not the ART. Hansen et al. (2002) reported that infants conceived with ICSI or IVF have twice as high a risk of major birth defects as naturally conceived infants. In a systematic review conducted by Hansen et al. (2005), the authors reviewed 25 studies with data relating to the prevalence of birth defects in infants conceived following IVF and or ICSI compared to spontaneously-conceived infants. Independent expert reviewers determined whether studies were suitable for inclusion in a meta-analysis; seven selected studies were identified. Two-thirds of the 25 studies showed a 25% or greater increased risk of birth defects in ART infants. The results of the meta-analysis combined with the 25 studies suggest a statistically significant 30–40% increased risk of birth defects associated with ART. While these authors suggested 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. Larger population-based studies are needed to address the exact etiology. More recently Reefhuis et al. (2009) analyzed data from the National

Birth Defects Prevention Study to examine the association between ART and major structural birth defects. The authors noted the underlying biological mechanism by which ART affects adverse development remains unclear. ART was associated with some structural defects among singleton births however ART was not associated with birth defects among multiple births. The authors recommended couples considering ART be informed of all potential risks and benefits.

Cryopreservation of Reproductive Tissue: Women of childbearing age who undergo treatment for cancer (e.g., chemotherapy, radiation) are at high risk for decreased fertility and methods of preserving fertility have been studied. Cryopreservation of semen has been proven to be effective in preserving male fertility; however, there are currently no proven methods of preserving female fertility. The cryopreservation, storage and thawing of reproductive tissue including oocytes, ovaries and testicular tissue, are considered unproven techniques in the treatment of infertility. According to the ASRM (2008i) ovarian tissue cryopreservation or transplantation procedures should be performed only as experimental procedures under internal review board guidelines. The evidence in the published, peer-reviewed, scientific literature is insufficient to support the use of these techniques.

Summary

The diagnosis and treatment of infertility involves a systematic approach. Prognosis depends on the cause of infertility. In many cases, multiple factors contribute to the cause often involving both partners. In some cases, the cause remains unknown. Most hormonal imbalances can be effectively treated with medication. Anatomic abnormalities can be corrected through various surgical procedures, and several assisted reproductive techniques are available as treatment options.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Diagnostic tests generally covered under core medical benefits when medically necessary and performed solely 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)
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 hysterosonography (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
76870	Ultrasound, scrotum and contents
76872	Ultrasound, transrectal
80061	Lipid panel

80402	ACTH stimulation panel; for 21 hydroxylase deficiency
80406	ACTH stimulation panel; for 3 beta-hydroxydehydrogenase deficiency
80414	Chorionic gonadotropin stimulation panel; testosterone response
80415	Chorionic gonadotropin stimulation panel; estradiol response
80418	Combined rapid anterior pituitary evaluation panel
80426	Gonadotropin releasing hormone stimulation panel
80440	Thyrotropin releasing hormone (TRH) stimulation panel; for hyperprolactinemia
82626	Dehydroepiandrosterone (DHEA)
82627	Dehydroepiandrosterone-sulfate (DHEA-S)
82670	Estradiol
82671	Estrogens, fractionated
82672	Estrogens, total
82679	Estrone
82757	Fructose, semen
82947	Glucose; quantitative, blood
82951	Glucose; tolerance test (GTT), three specimens (includes glucose)
82952	Glucose; tolerance test, each additional beyond three specimens
83001	Gonadotropin; follicle stimulating hormone (FSH)
83002	Gonadotropin; luteinizing hormone (LH)
83498	Hydroxyprogesterone, 17-d
84144	Progesterone
84146	Prolactin
84402	Testosterone; free
84403	Testosterone; total
84443	Thyroid stimulating hormone (TSH)
84702	Gonadotropin, chorionic (hCG); quantitative
84703	Gonadotropin, chorionic (hCG); qualitative
84830	Ovulation test, by visual color comparison methods for human luteinizing hormone
85048	Blood count; leukocyte (WBC), automated
87070	Culture, bacterial; any other source except urine, blood or stool, with isolation and presumptive identification of isolates
87109	Culture, mycoplasma, any source
87110	Culture, chlamydia, any source
88280	Chromosome analysis; additional karyotypes, each study
89260	Sperm isolation; simple prep (e.g., sperm wash and swim-up) for insemination or diagnosis with semen analysis
89261	Sperm isolation; complex prep (e.g., Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis
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
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; complete (volume, count, motility, and differential)
89321	Semen analysis, presence and/or motility of sperm
89325	Sperm antibodies
89330	Sperm evaluation; cervical mucus penetration test, with or without spinnbarkeit test

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

ICD-9-CM Diagnosis Codes	Description
016.70-016.76	Tuberculosis of genitourinary system, other female genital organs
218.0-218.9	Uterine leiomyoma
227.3	Benign neoplasm pituitary gland and craniopharyngeal duct (pouch)
234.8	Carcinoma in situ, endocrine gland [any]
237.0	Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct
239.7	Neoplasm of unspecified nature, endocrine glands and other parts of nervous system
253.1	Other and unspecified anterior pituitary hyperfunction
253.2	Panhypopituitarism
253.3	Pituitary dwarfism
253.4	Other anterior pituitary disorders
253.8	Other disorders of the pituitary and other syndromes of diencephalohypophyseal origin
256.1	Other ovarian hyperfunction
256.31-256.39	Other ovarian failure
256.4	Polycystic ovaries
256.8	Other ovarian dysfunction
256.9	Unspecified ovarian dysfunction
456.4	Scrotal varices
606.0-606.9	Male infertility
608.89	Other specified disorders of male genital organs, other
614.1	Chronic salpingitis and oophoritis
614.2	Salpingitis and oophoritis not specified as acute, subacute or chronic
614.4	Chronic or unspecified parametritis and pelvic cellulitis
614.6	Pelvic peritoneal adhesions, female (postoperative) (postinfection)
616.8	Other specified inflammatory diseases of the cervix, vagina, and vulva
617.0-617.9	Endometriosis
620.0-620.9	Noninflammatory disorders of ovary, fallopian tube, and broad ligament
621.0-621.9	Disorders of the uterus, not elsewhere classified
625.0-625.9	Pain and other symptoms associated with female genital organs
626.0-626.9	Disorders of menstruation and other abnormal bleeding from genital tract
628.0 - 628.9	Female infertility
629.9	Unspecified disorder of female genital organs
648.10-648.14	Thyroid dysfunction
704.1	Hirsutism
752.0	Anomalies of ovaries
752.10-752.19	Anomalies of fallopian tubes and broad ligaments
752.2	Doubling of uterus
752.3	Other anomalies of uterus
792.2	Nonspecific abnormal findings, semen

If benefits are available for infertility treatment, the following may be considered for coverage. Coverage of all of the following is subject to the specific terms, conditions, and limitations of the applicable benefit plan. Services listed below will not be covered if they are not covered under the applicable plan or if they are associated with the treatment of infertility due to voluntary sterilization, even if benefits are available for infertility treatment:

CPT* Codes	Description
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37204	Transcatheter occlusion or embolization (eg, for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck
49321	Laparoscopy, surgical; with biopsy (single or multiple)
54500	Biopsy of testis, needle (separate procedure)
54505	Biopsy of testis, incisional (separate procedure)
54640	Orchiopexy, inguinal approach, with or without hernia repair
54650	Orchiopexy, abdominal approach, for intra-abdominal testis
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
55550	Laparoscopy, surgical, with ligation of spermatic veins for varicocele
58100	Endometrial sampling (biopsy) with or without endocervical sampling (biopsy), without cervical dilation, any method (separate procedure)
58145	Myomectomy, excision of fibroid tumor of uterus, single or multiple, vaginal 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
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 transaction)
58672	Laparoscopy, surgical; with fimbrioplasty
58673	Laparoscopy, surgical; with salpingostomy (salpingoneostomy)
58740	Lysis of adhesions (salpingolysis, ovariolysis)
58752	Tubouterine implantation
58760	Fimbrioplasty
58770	Salpingostomy (salpingoneostomy)
58970	Follicle puncture for oocyte retrieval, any method
58974	Embryo transfer, intrauterine
58976	Gamete, zygote, or embryo intrafallopian transfer, any method
74742	Transcervical catheterization of fallopian tube, radiological supervision and interpretation
76830	Ultrasound, transvaginal
76856	Ultrasound pelvic (nonobstetric), B-scan and/or real time with image documentation; complete
76857	Ultrasound pelvic (nonobstetric), B-scan and/or real time with image documentation; limited of follow-up (eg, for follicles)
76948	Ultrasonic guidance for aspiration of ova, imaging and supervision
80415	Chorionic gonadotropin stimulation panel; estradiol response
82626	Dehydroepiandrosterone-sulfate (DHEA)
82627	Dehydroepiandrosterone-sulfate (DHEA-S)
82670	Estradiol
83001	Gonadotropin; follicle stimulating hormone (FSH)
83002	Gonadotropin; luteinizing hormone (LH)
84144	Progesterone
84702	Gonadotropin, chorionic (hCG); quantitative
84703	Gonadotropin, chorionic (hCG); qualitative
84830	Ovulation test, by visual color comparison methods for human luteinizing

	hormone
89250	Culture and fertilization of oocyte(s)
89253	Assisted embryo hatching, microtechniques (any method)
89254	Oocyte identification from follicular fluid
89255	Preparation of embryo transfer (any method)
89257	Sperm identification from aspiration (other than seminal fluid)
89258	Cryopreservation; embryo
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
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
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; complete (volume, count, motility, and differential)
89321	Semen analysis, presence and/or motility of sperm
89329	Sperm evaluation; hamster penetration test
89330	Sperm evaluation; cervical mucus penetration test, with or without spinnbarkeit test
89342	Storage, (per year); embryo(s)
89352	Thawing of cryopreserved; embryo(s)

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, case rate not otherwise specified
S4016	Frozen in vitro fertilization cycle, case rate
S4017	Incomplete cycle, treatment canceled prior to stimulation, case rate
S4018	Frozen embryo transfer procedure canceled before transfer, case rate
S4020	In vitro fertilization procedure canceled before aspiration, case rate
S4021	In vitro fertilization procedure canceled after aspiration, case rate
S4022	Assisted oocyte fertilization, case rate
S4027	Storage of previously frozen embryos
S4028	Microsurgical epididymal sperm aspiration (mesa)
S4035	Stimulated intrauterine insemination (IU), case rate
S4037	Cryopreserved embryo transfer, case rate
S4040	Monitoring and storage of cryopreserved embryos, per 30 days

ICD-9-CM Diagnosis Codes	Description
016.70-016.76	Tuberculosis of genitourinary system, other female genital organs
218.0-218.9	Uterine leiomyoma
227.3	Benign neoplasm pituitary gland and craniopharyngeal duct (pouch)
234.8	Carcinoma in situ, endocrine gland [any]
237.0	Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct
239.7	Neoplasm of unspecified nature, endocrine glands and other parts of nervous

	system
253.1	Other and unspecified anterior pituitary hyperfunction
253.2	Panhypopituitarism
253.3	Pituitary dwarfism
253.4	Other anterior pituitary disorders
253.8	Other disorders of the pituitary and other syndromes of diencephalohypophyseal origin
256.1	Other ovarian hyperfunction
256.31-256.39	Other ovarian failure
256.4	Polycystic ovaries
256.8	Other ovarian dysfunction
256.9	Unspecified ovarian dysfunction
456.4	Scrotal varices
606.0-606.9	Male infertility
608.89	Other specified disorders of male genital organs, other
614.1	Chronic salpingitis and oophoritis
614.2	Salpingitis and oophoritis not specified as acute, subacute or chronic
614.4	Chronic or unspecified parametritis and pelvic cellulitis
614.6	Pelvic peritoneal adhesions, female (postoperative) (postinfection)
616.81-616.89	Other specified inflammatory diseases of the cervix, vagina, and vulva
617.0-617.9	Endometriosis
620.0-620.9	Noninflammatory disorders of ovary, fallopian tube, and broad ligament
621.0-621.9	Disorders of the uterus, not elsewhere classified
625.0-626.9	Pain and other symptoms associated with female genital organs
628.0-628.9	Female infertility
629.9	Unspecified disorder of female genital organs
648.10-648.14	Thyroid dysfunction
704.1	Hirsutism
752.0	Anomalies of ovaries
752.10-752.19	Anomalies of fallopian tubes and broad ligaments
752.2	Doubling of uterus
752.3	Other anomalies of uterus
792.2	Nonspecific abnormal findings, semen
V26.1	Artificial insemination
V26.21	Procreative management, investigation and testing, fertility testing
V26.29	Procreative management, investigation and testing, other investigation and testing

Experimental, Investigational, Unproven and Not Covered:

The following ICD-9 table is applicable to all of the codes listed in the below CPT and HCPCS coding tables when performed for the diagnosis or treatment of infertility:

ICD-9-CM Diagnosis Codes	Description
016.70-016.76	Tuberculosis of genitourinary system, other female genital organs
218.0-218.9	Uterine leiomyoma
227.3	Benign neoplasm pituitary gland and craniopharyngeal duct (pouch)
234.8	Carcinoma in situ, endocrine gland [any]
237.0	Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct
239.7	Neoplasm of unspecified nature, endocrine glands and other parts of nervous system
253.1	Other and unspecified anterior pituitary hyperfunction
253.2	Panhypopituitarism
253.3	Pituitary dwarfism

253.4	Other anterior pituitary disorders
253.8	Other disorders of the pituitary and other syndromes of diencephalohypophyseal origin
256.1	Other ovarian hyperfunction
256.31-256.39	Other ovarian failure
256.4	Polycystic ovaries
256.8	Other ovarian dysfunction
256.9	Unspecified ovarian dysfunction
456.4	Scrotal varices
606.0-606.9	Male infertility
608.89	Other specified disorders of male genital organs, other
614.1	Chronic salpingitis and oophoritis
614.2	Salpingitis and oophoritis not specified as acute, subacute or chronic
614.4	Chronic or unspecified parametritis and pelvic cellulitis
614.6	Pelvic peritoneal adhesions, female (postoperative) (postinfection)
616.81-616.89	Other specified inflammatory diseases of the cervix, vagina, and vulva
617.0-617.9	Endometriosis
620.0-620.9	Noninflammatory disorders of ovary, fallopian tube, and broad ligament
621.0-621.9	Disorders of the uterus, not elsewhere classified
625.0-626.9	Pain and other symptoms associated with female genital organs
628.0-628.9	Female infertility
629.9	Unspecified disorder of female genital organs
648.10-648.14	Thyroid dysfunction
704.1	Hirsutism
752.0	Anomalies of ovaries
752.10-752.19	Anomalies of fallopian tubes and broad ligaments
752.2	Doubling of uterus
752.3	Other anomalies of uterus
792.2	Nonspecific abnormal findings, semen
V26.1	Artificial insemination
V26.21	Procreative management, investigation and testing, fertility testing
V26.29	Procreative management, investigation and testing, other investigation and testing

Reactive Oxygen Species Testing (ROS)

CPT* Codes	Description
82397	Chemiluminescent assay

Cryopreservation, storage, and thawing of reproductive tissue, including ovarian[†] and oocytes[†]

CPT* Codes	Description
89240 [†]	Unlisted miscellaneous pathology test
89335	Cryopreservation, reproductive tissue, testicular
89344	Storage, (per year); reproductive tissue (testicular/ovarian)
89346	Storage, (per year); oocyte
89354	Thawing of cryopreserved; reproductive tissue, testicular/ovarian
89356	Thawing of cryopreserved; oocytes, each aliquot

Manual soft tissue therapy for the treatment of pelvic adhesions (WURN Technique®, Clear Passage Therapy)

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

Immunological testing

CPT* Codes	Description
83519	Immunoassay, analyte, quantitative; by radiopharmaceutical technique (eg, RIA)
86357	Natural killer (NK) cells, total count
0030T	Antiprothrombin (phospholipid cofactor) antibody, each Ig class

Co-Culturing of embryos

CPT* Codes	Description
89251	Culture of oocyte(s)/embryo(s), less than 4 days; with co-culture of oocyte(s)/embryos

Reproductive immunophenotype (RIP)

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

Other miscellaneous procedures as defined in the coverage policy, including sperm hyaluronan binding assay or media preparation for storage of oocytes, sperm or embryos^{††}:

CPT* Codes	Description
89240 ^{††}	Unlisted miscellaneous pathology test
89398	Unlisted reproductive medicine laboratory procedure (replacement code for 0087T deleted 01/01/10)

Not covered, even if benefits are available for infertility treatment:

CPT* Codes	Description
55400	Vasovasostomy, vasovasorrhaphy
58750	Tubotubal anastomosis
89259	Cryopreservation; sperm
89343	Storage, (per year); sperm/semen
89353	Thawing of cryopreserved; sperm/semen, each aliquot

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

ICD-9-CM Diagnosis	Description
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Codes	
	All codes

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	6/15/2007	0089	Infertility Services

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