Infertility Services

Clinical Coverage Criteria

Overview

Infertility as defined in M.G.L. C 175 Section 47H shall mean the condition of an individual who is unable to conceive or produce conception during a period of 1 year if the female is age 35 or younger or during a period of 6 months if the female is over the age of 35. For purposes of meeting the criteria for infertility in this section, if a person conceives but is unable to carry that pregnancy to live birth, the period of time she attempted to conceive prior to achieving that pregnancy shall be included in the calculation of the 1 year or 6 month period, as applicable. Unable to conceive or produce conception during a period of one (1) year if the female is age 35 or younger or during a period of 6 months if the female is over the age of 35" presumes that the plan member would be expected to conceive naturally absent a medical problem (i.e., that the insured is of normal reproductive age).

There is no consensus on the definition of ART. In general, ART procedures involve removing eggs from a woman's ovaries, combining them with sperm in the laboratory, and returning them to the woman's body. ART does not include treatments in which only sperm are handled (i.e., intrauterine—or artificial—insemination) or procedures in which a woman takes drugs only to stimulate egg production without the intention of having eggs retrieved.

Definitions

ART cycle: Because ART consists of several steps over an interval of several weeks an ART procedure is more appropriately considered a cycle of treatment rather than a procedure at a single point in time. A typical ART cycle begins when a woman starts taking medication to stimulate the ovaries to develop eggs or, if no drugs are given, when the woman begins having her ovaries monitored (using ultrasound or blood tests) for natural egg production. If eggs are produced, the cycle then progresses to egg retrieval, a surgical procedure in which eggs are collected from a woman's ovaries. Once retrieved, eggs are combined with sperm in the laboratory. If fertilization is successful, one or more of the resulting embryos are selected for transfer, most often into a woman's uterus through the cervix (IVF), but sometimes into the fallopian tubes (e.g., GIFT or ZIFT). If one or more of the transferred embryos implant within the woman's uterus, the cycle then progresses to clinical pregnancy. A cycle may be discontinued at any step for specific medical reasons (e.g., no eggs are produced, the embryo transfer was not successful) or by patient choice.

Basal follicle stimulating hormone (FSH) level: An elevated basal FSH level predicts that the ovarian response to gonadotrophin will be reduced and conception will be less likely in IVF cycles.

Clomiphene citrate challenge test (CCCT): A provocative test in which a basal FSH level is determined, and if normal, 100 mg of clomiphene citrate is then administered on cycle days 5 to 9 followed by a second FSH level on day 10. The test is considered abnormal

if the FSH value on either day 3 or day 10 is elevated. Patients with diminished ovarian re-serve respond to clomiphene citrate with a smaller, less hormonally active cohort of follicles. This in turn leads to lower levels of estradiol (E2) and inhibin, resulting in an inadequate suppression of FSH. Presumably, higher detection rates would be achieved, as a number of women with a normal day 3, but abnormal day 10, FSH level would now be classified as having diminished ovarian reserve.

Hysterosalpinogram (HSG): A radiology procedure which involves injecting a dye through the cervix into the uterus and fallopian tubes. The dye provides a greater contrast than normal on x-ray which allows the radiologist to differentiate more easily between healthy tissue and abnormalities (e.g., uterine fibroids or polyps, blocked fallopian tubes, etc.). In the case of a hydrosalpinx (a damaged fallopian tube filled with excess fluid), the HSG can evaluate the extent of damage.

Intrauterine insemination (IUI): Also known as AI (artificial insemination), IUI is a medical procedure that involves placing sperm into a woman's uterus to facilitate fertilization.

In vitro fertilization: An ART procedure that involves removing eggs from a woman's ovaries and fertilizing them outside her body. The resulting embryos are then transferred (embryo transfer) into the woman's uterus through the cervix.

Menopause: The absence of menstrual periods for 12 consecutive months. Natural menopause is menopause that is not caused by any medical or surgical intervention. Natural menopause typically occurs between the ages of 48 and 55. On average, for women in the U.S, natural menopause occurs at age 51.

Primary infertility: A couple that has not been able to conceive after a minimum of one year of unprotected intercourse. Secondary infertility is the inability to conceive after already having conceived (and either carried the pregnancy to term, or had a miscarriage). Technically, secondary infertility is not present if there has been a change of partners.

Premature ovarian failure (POF): The loss of normal function of the ovaries before age 40. POI/POF may be caused by follicle depletion or follicle dysfunction. POF can be caused by an autoimmune disorder, genetics (10% to 20% of women with POF have a family history of this condition), radiation or chemotherapy for the treatment of cancer, thyroid dysfunction, etc. For the majority of women, the cause of POF is unknown. Some women with POF retain intermittent ovarian function for many years, and, unlike women who are menopausal, pregnancies may occur.

Spermatogenesis: The process by which male spermatogonia develop into mature spermatozoa, also known as a sperm cell. This process is continuous and requires about 72-74 days for maturation. It is most efficient at 34 degrees centigrade, so exposure to excessive heat or prolonged fever within 2-3 months of evaluation can adversely affect sperm count, motility, and morphology. Within the seminiferous tubules, Sertoli's cells sustain and regulate maturation, and Leydig's cells produce testosterone required for maintenance of spermatogenesis.

Superovulation: Controlled hyperstimulation of the ovary to produce more follicles with oocytes. Usually induced by gonadotrophins, superovulation is often performed with IUI

and IVF and other procedures of assisted conception in order to improve the pregnancy rates.

Policy

Fallon Health requires Prior Authorization for Infertility Services. Additionally Infertility Services are subject to the coverage at outlined in the Member's Evidence of Coverage/Member Handbook.

Members who have Pharmacy Benefits will not be approved for infertility drugs unless they meet criteria as defined in this policy.

No coverage will be provided for the diagnosis or treatment of infertility for individuals who are not plan members, with the exception of coverage for sperm, egg, and/or inseminated egg procurement and processing, and banking of sperm or inseminated eggs; to the extent such costs are not covered by the donor's insurer, if any.

No coverage will be provided for infertility services when the chance of achieving a live birth is futile or very poor. For the purposes of this policy, futile means that treatment, e.g., an IVF or IUI cycle, has a ≤ 1% chance of achieving a live birth; very poor means that treatment, e.g., an IVF or IUI cycle, has > 1% but ≤ 5% per cycle of achieving a live birth.

All of the following general eligibility criteria must be met (see specific criteria sets in the treating fertility section):

1. The plan member has been diagnosed with infertility. For the purposes of this policy, infertility shall mean "the condition of an individual who is unable to conceive or produce conception during a period of 1 year if the female is age 35 or younger or during a period of 6 months if the female is over the age of 35. For purposes of meeting the criteria for infertility in this section, if a person conceives but is unable to carry that pregnancy to live birth, the period of time she attempted to conceive prior to achieving that pregnancy shall be included in the calculation of the 1 year or 6 month period, as applicable." (M.G.L. C 175, Section 47H)
    - The female plan member has undergone elective sterilization:
        - In the case where a female plan member has undergone elective sterilization, it is presumed that the sterilization procedure is the cause of the inability to conceive or produce conception and no coverage shall be provided for infertility services.
        - Microsurgical tubal anastomosis for reversal of tubal sterilization has a significantly higher cumulative pregnancy rate than IVF, and is more cost-efficient, even in women 40 years of age or older. When there has been a procedure to reverse elective female sterilization (e.g., microsurgical tubal anastomosis), unilateral or bilateral tubal patency must be proven (e.g., by selective salpingography). After tubal patency has been proven, the female plan member must then demonstrate infertility (i.e., inability to conceive during the statutory time period).

- The male partner of a female plan member has undergone elective sterilization:
  - In the case where the male partner of a female plan member has elective sterilization, the female plan member must demonstrate infertility (i.e., inability to conceive during the statutory time period), through exposure to normal sperm. In such cases, infertility is defined as the inability to conceive after six (6) medically supervised IUI cycles. These six (6) IUI cycles must be fully documented in the plan member's medical record. All costs associated with these six (6) IUI cycles, including but not limited to the cost of donor sperm, (procurement, processing and storage), prescription medications, and professional, technical and facility charges are at the plan member's expense. Elective male partner sterilization ends coverage for donor sperm, even if the female plan member demonstrates her own infertility.
  - When the male partner has undergone a procedure to reverse male sterilization (e.g., microsurgical vasovasostomy or vasoepididymostomy), post-procedural semen analysis must establish fertility in the male partner (WHO 2010 reference values for evaluating semen: semen volume 1.5 ml; sperm concentration 15 (106/ml); total number 39 (106/ejaculate); total motility (PR + NP) 40%; progressive motility (PR) 32%; normal Forms 4%; vitality 58 %). After post-procedural semen analysis establishes male fertility, the female plan member must demonstrate infertility (i.e., inability to conceive during the statutory time period).
- The female plan member is without a male partner: the female plan member must demonstrate infertility (i.e., inability to conceive during the statutory time period), through exposure to normal sperm. In such cases, infertility is defined as the inability to conceive after six (6) medically supervised IUI cycles. These six (6) IUI cycles must be fully documented in the plan member's medical record. All costs associated with these six (6) IUI cycles, including but not limited to the cost of donor sperm, (procurement, processing and storage), prescription medications, and professional, technical and facility charges are at the plan member's expense.

2. The female plan member is of normal reproductive age. Female age and basal FSH level are independently associated with IVF outcome. They are both related to the same phenomenon, namely ovarian reserve, which can be defined as the quality and the quantity of the remaining follicles. The development of diminishing ovarian reserve generally reflects the process of follicular depletion and decline in oocyte quality.
   - A woman's chronological age is the most important factor affecting the chances of a live birth when her own eggs (autologous oocytes) are used. Centers for Disease Control (CDC) statistics show that live birth rates for ART cycles in women 44 years of age and older is 1%
   - Although oocyte number and quality decline with age, fertility may vary among women of a similar age. Basal FSH and clomiphene citrate challenge test (CCCT) are similar in predicting the ability to achieve a clinical pregnancy in women undergoing infertility treatment. With either

test, a normal result is not useful, but an abnormal result virtually confirms that pregnancy will not occur with treatment

- An elevated basal FSH level is a sign of diminished ovarian reserve. Increasing basal FSH levels are associated with decreasing response to ovarian stimulation, cancellations, and failure to conceive. Normal basal (cycle day 3) serum FSH is ≤ 10 mIU/ml (WHO Second International Standard IRP 78/549). A value > 10 and ≤ 11.4 mIU/mL signifies diminished ovarian reserve. A value > 11.4 mIU/mL signifies severely diminished ovarian reserve. The basal (cycle day 3) serum FSH in women age 40 and older must be ≤ 11.4 mIU/ml (IRP 78/549).
- An estradiol (E2) level must be performed in conjunction with a basal FSH, and the E2 level must be ≤ 80 pg/mL. E2 levels > 80 pg/ml on cycle day 3 can suppress the secretion of FSH so that the FSH level appears normal.
- The cycle day 3 FSH and E2 must be repeated every 6 months for any woman ≥ 40 years of age .

3. The plan member is optimizing their own natural fertility and their potential for successful infertility treatment outcome by maintaining a healthy lifestyle. Epidemiological studies indicate cigarette smoking and obesity are associated with a significant reduction in fertility. Alcohol use during pregnancy has well-documented detrimental effects on fetal development and no “safe” level of alcohol consumption during pregnancy has been established. Illicit drug use/abuse is associated with:
   - The best available scientific evidence indicates that cigarette smoking strongly contributes to female infertility and female response to infertility treatment (smoking women need up to twice the number of IVF cycles to conceive as non-smokers). Furthermore, smoking during pregnancy is regarded as an important preventable risk factor for an adverse pregnancy outcome (the relation between smoking and lower birth weight is a longstanding and consistent finding that is now regarded as causal). The substantial reproductive risks associated with smoking and the revelation that much of the reduced fecundity associated with smoking may be reversed within a year of cessation can be powerful incentives when included in physician counseling. When successful, smoking cessation represents an important part of effective treatment for infertility. To optimize the likelihood of a successful outcome, plan members should stop smoking 12 months prior to beginning infertility treatment.
   - Extremes of weight have an adverse effect on fertility. In some cases, infertility treatments can help an underweight or overweight woman become pregnant. However, these women are still at increased risk of adverse pregnancy outcomes that cannot be overcome. A BMI of less than 18.5 (underweight) may cause irregular menstrual cycles and anovulation. Women who are underweight should be counseled to achieve a BMI within the lower limits of normal. For most women, this will restore natural fertility and increase potential for a good pregnancy outcome. Obesity has a well-documented, significant detrimental effect on fertility, infertility treatment outcomes, and pregnancy complications and outcomes. Primary care physicians and gynecologists should provide education and counseling and

should encourage overweight and obese patients to undertake a weight-reduction program, including diet, exercise, and behavior modification, before attempting pregnancy. Fallon Health will review requests for infertility services for underweight, overweight and obese women on a case-by-case basis, balancing the detrimental effects of extremes of BMI on infertility treatment and perinatal outcomes. Fallon Health may require consultation with one or more specialists, including, but not limited to, anesthesiology, reproductive endocrinology, maternal-fetal medicine, and/or nutrition.

- Alcohol abuse and alcoholism are associated with disorders of reproductive function in both men and women. There is also a clearly established high risk of serious harm to a child associated with prenatal alcohol abuse. Maternal alcohol use is the leading known cause of mental retardation and is a preventable cause of birth defects. Children exposed to alcohol in utero are at risk for growth deficiencies, facial deformities, central nervous impairment, behavioral disorders, and impaired intellectual development. Consuming alcohol during pregnancy also increases the risk of miscarriage, low birth weight, and stillbirth. Women should avoid alcohol entirely while pregnant or trying to conceive because damage can occur in the earliest weeks of pregnancy, even before a woman knows that she is pregnant. Infertility services are not covered for a woman unwilling or unable to eliminate alcohol consumption.

4. The plan member has medically documented infertility. Infertility is the inability to conceive or produce conception after one year (12 months) of documented unprotected intercourse.
    - When the underlying cause of infertility is known, medically documented, and irreversible, and when the plan member meets eligibility criteria in all other respects (i.e., the plan member has not undergone elective sterilization and is of normal reproductive age), the one-year requirement may be waived by an Fallon Health Medical Director.
    - Women without male partners must demonstrate their inability to conceive with exposure to sperm. In such cases infertility is defined as the inability to conceive after six (6) intrauterine insemination (IUI) cycles that are supervised and medically documented by a physician. All costs associated with these six (6) IUI cycles, including but not limited to the cost of donor sperm (procurement, processing and storage), and professional, technical and facility charges are at the woman's expense.

Diagnosing male infertility

The initial evaluation of the infertile male should include (1) a medical and reproductive history, (2) physical examination, and (3) two properly performed semen analyses separated by a time period of approximately one month. If male infertility factor is present, it is almost always defined by the finding of an abnormal semen analysis.

Semen analysis is the foundation of the evaluation of male infertility and should generally precede any invasive procedures of the female partner. The patient should be given written instructions for semen collection. Values that fall outside the reference ranges suggest male infertility factor and indicate the need for additional evaluation. Careful attention should be paid to these ranges and the semen values should be interpreted in the right context. Although semen analysis is routinely used to evaluate the

male partner in infertile couples, reference values for semen parameters are not the same as the minimum values needed for conception, and men with semen values outside the reference ranges may be fertile. Conversely, men with values within the reference ranges may be infertile. Despite its limitations, semen analysis remains the most important tool in the investigation of male factor infertility.

A full evaluation by a urologist or other specialist in male reproduction should be done if the initial screening evaluation demonstrates an abnormal male reproductive history or an abnormal semen analysis. The full evaluation for male infertility should include a complete medical and reproductive history, a physical examination by a urologist or other specialist in male reproduction and at least two semen analyses. Based on the results of the full evaluation, the physician may recommend other procedures and tests to elucidate the etiology of a patient's infertility. These tests may include additional semen analyses, endocrine evaluation, post-ejaculatory urinalysis, ultrasonography, specialized tests on semen and sperm, and genetic screening.

1. Endocrine evaluation – normal sperm production and sexual function are dependent on a normal hormonal environment. Endocrine disorders are extremely uncommon in men with normal semen parameters. An endocrine evaluation should be conducted if there is any suspicion of endocrinopathy or evidence of oligospermia (low sperm count; sperm counts of less than 5 to 10 million per ejaculate):
    - The results of the semen analyses are abnormal; especially if sperm concentration is less than 10 million/ml,
    - There is impaired sexual function, or
    - Other clinical findings suggest a specific endocrinopathy.

The minimum endocrine evaluation should include measurement of serum FSH and total and free testosterone. If the testosterone level is low, a repeat measurement of total and free testosterone, as well as determination of serum LH and Prolactin levels should be obtained. The relationship of testosterone, LH, FSH and Prolactin may help to identify a clinical condition. Estradiol may be included for patients with high body mass index. Thyroid profile may be useful in selected individuals. While hormone problems account for only 10% of male fertility problems, most are easily treatable.

2. Urology evaluation – Further evaluation by a urologist should be performed when the initial evaluation demonstrates an abnormal male reproductive history or physical examination or if there is an abnormal semen analysis.
    - Semen leukocyte analysis – Leukocytes (white blood cells) are present in all ejaculates and may play an important role in immune surveillance and clearance of abnormal sperm. Leukocytospermia (an increase in leukocytes in the ejaculate) is defined as > 1 million leukocytes/ml semen. Studies have shown a relationship between poor sperm quality and leukocytospermia, however, no study has shown a relationship between leukocytospermia and subfertility. The cause of leukocyte infiltration is not clearly understood. Some proposed causes include bacterial and viral infection, cigarette smoking and environmental toxins. Patients with leukocytospermia should be evaluated for infection.
    - Post-ejaculatory urinalysis – A post-ejaculatory urinalysis should be performed in patients with ejaculate volume less than 1.0 ml, except in

patients with bilateral vasal agenesis or clinical signs of hypogonadism. It is also important to assure that improper or incomplete collection, or a very short abstinence period (less than one day) is not the cause of the low-volume ejaculate.

- Transrectal ultrasound (TRUS) – Transrectal ultrasound may be indicated in azoospermic patients with palpable vasa deferentia and low ejaculate volumes to determine if ejaculatory duct obstruction exists. Some experts recommend TRUS for oligospermic patients with low volume ejaculates, palpable vasa and normal testicular size, to determine if ejaculatory duct obstruction is present.
- Scrotal ultrasound – Scrotal ultrasonography may be indicated in those patients in whom physical examination of the scrotum is difficult or inadequate or in whom a testicular mass is suspected.
- Direct antisperm antibody (ASAB) testing – Direct ASAB testing in the absence of an abnormal semen analysis is not medically necessary. ASAB testing may be indicated when there is asthenospermia (poor motility; < 50% of sperm with progressive motility) with a history of testicular injury or sperm agglutination and AI or IVF is being considered. ASAB testing is not necessary if IVF with ICSI is already planned.
- Adjunctive sperm testing – Many specialized tests of sperm maturity, function and integrity have been developed. Specialized tests on semen are not required for diagnosing male infertility. Specialized testing should be reserved for patients in whom results will influence treatment strategy, e.g., to identify a couple who may benefit from ICSI as an adjunct to IVF.

4. Genetic evaluation – Genetic abnormalities may cause infertility by affecting sperm production or sperm transport. Men who have non-obstructive azoospermia or severe oligospermia (< 5 million sperm/ml) should be informed of the potential associated genetic abnormalities. Genetic counseling should be provided when a genetic abnormality is suspected. All genetic testing requires prior authorization by Fallon Health. (Refer to Fallon Health's Genetic Testing policy for additional information. The ordering physician must request prior authorization from Fallon Health) the most common genetic factors known to be related to male infertility are:
    - Cystic fibrosis gene mutations associated with congenital absence of the vas deferens
    - Karyotypic chromosomal abnormalities resulting in impaired testicular function
    - Y-chromosome microdeletions associated with isolated spermatogenic impairment.

Diagnosing female infertility:

The initial evaluation of the infertile female should include (1) a complete medical and reproductive history, (2) physical examination, (3) assessment of ovarian reserve, if indicated, and (4) hysterosalpingogram (HSG). A careful medical and reproductive history and physical examination can identify signs or symptoms suggesting a specific cause for infertility and thereby help to focus subsequent diagnostic evaluations on the factor(s) most likely responsible.

Subsequent evaluation should be directed toward identifying the cause(s) of infertility in a systematic, expeditious manner so as to identify all relevant factors with emphasis on the least invasive methods for detection.

1. Ovulatory factors – ovulatory factors commonly result in menstrual disturbances. The underlying cause should always be sought (e.g., thyroid disease, hyperandrogenism, pituitary tumor, obesity and eating disorders, or hyperprolactinemia) as correct diagnosis may suggest specific treatment. The exact cause of ovulatory dysfunction often remains obscure. Methods for evaluating ovulatory dysfunction may include any of the following:
    - Menstrual history may be all that is required. Patients with a well-documented history of irregular menstrual periods do not require a sophisticated diagnostic evaluation.
    - Basal body temperature recordings provide a simple and effective method for evaluating ovulatory function.
    - Serum progesterone during the luteal phase may be used to evaluate ovulatory function; values > 3.0 ng/ml provide presumptive evidence of ovulation.
    - Urinary luteinizing hormone (LH) determinations using over-the-counter ovulation predictor kits can identify the midcycle LH surge, and provide reliable evidence of ovulatory function.
    - Endometrial biopsy and histologic evaluation can demonstrate secretory endometrial development which results from the action of progesterone and thus implies ovulation. Dating the endometrium using established histologic criteria and demonstration of a consistent maturation delay is the traditional method for diagnosis of luteal phase defect.
    - Serial transvaginal ultrasounds can reveal the size and number of developing follicles and provide presumptive evidence of ovulation and luteinization. This method is generally reserved for patients in whom less complicated methods fail to provide the necessary information.
    - Other evaluations aimed at defining treatment are indicated in women found to absent or poor ovulatory function.
        - Serum thyroid-stimulating hormone (TSH) and prolactin level determinations will identify thyroid disorders and/or hyperprolactinemia, which require specific treatment.
        - Serum thyroid-stimulating hormone (TSH) and prolactin level determinations will identify thyroid disorders and/or hyperprolactinemia, which require specific treatment.
        - Serum progesterone is tested 6 to 8 days after the LH surge that precedes ovulation. Lower than normal progesterone levels indicate anovulation
        - Serum testosterone, 17a-hydroxyprogesterone and dehydroepiandrosterone sulfate (DHEAS) are used to evaluate hyperandrogenism. Hyperandrogenism may be a symptom of polycystic ovarian syndrome, congenital adrenal hyperplasia (CAH), or androgen-secreting tumors, all of which may cause infertility in women.
        - In amenorrheic women, a follicle-stimulating hormone (FSH) level will differentiate patients with ovarian failure (candidates for donor egg) from those with hypothalamic dysfunction

2. Ovarian reserve – assessment of ovarian reserve should be performed in selected women (i.e., women age 35 and older, women with suspected premature ovarian failure (POF), women with a single ovary or history of previous ovarian surgery, or women with documented poor response to exogenous gonadotropin stimulation, and women with exposure to chemotherapeutic agents or radiation) to obtain prognostic information that may have an influence on treatment recommendations. Basal serum follicle-stimulating hormone (FSH) measurement is used to assess ovarian reserve. (Basal FSH is evaluated on day 3 of the menstrual cycle.) A single day 3 serum FSH value >/= 10 mIU/ml connotes diminished ovarian reserve and a very poor prognosis even if the day 3 FSH level in a subsequent cycle is normal. To be valid, the FSH must be drawn in conjunction with an estradiol (E2) level, and the E2 level should be between 25 pg/mL and 75 pg/mL. E2 levels > 75 pg/ml on day 3 can suppress the secretion of FSH so that the FSH level appears normal.

3. Cervical factors – abnormalities of cervical mucus production or sperm/mucus interaction are rarely identified as the sole or principal cause of infertility. Examination of cervical mucus may reveal gross evidence of chronic cervicitis that deserves treatment. Cervical mucus abnormalities that are diagnosed as a contributing cause of infertility are generally treated with intrauterine insemination (IUI).

4. Uterine factors – examination of the uterine cavity is an integral part of any thorough evaluation of an infertile couple. Abnormalities of uterine anatomy or function are relatively uncommon causes of infertility in women. The method chosen may vary and should be tailored to the needs of the individual patient.
    - Hysterosalpingography (HSG) defines the size and shape of the uterine cavity and will reveal developmental anomalies or other acquired abnormalities with potential reproductive consequences.
    - Ultrasound may be used to diagnose uterine pathology.
    - Hysteroscopy is the definitive method for evaluation of the uterine cavity and diagnosis of associated abnormalities. It is generally reserved for evaluation and treatment of abnormalities defined by less invasive methods (HSG and ultrasound), however in patients with clear indications for laparoscopy, the addition of hysteroscopy is efficient and avoids redundancy.

5. Tubal factors – This category includes cases in which the woman has completely blocked fallopian tubes and also women who have either one blocked tube or no tubal blockage but tubal scarring or other tubal damage. Tubal factor infertility is usually caused by either pelvic infection, such as pelvic inflammatory disease (PID) or pelvic endometriosis. Sometimes it can be caused by scar tissue that forms after pelvic surgery. In cases of relatively minor tubal damage it is sometimes difficult to be certain that the infertility problem is solely due to the tubal damage and there are no other contributing causes to infertility. The methods for the evaluation of tubal patency are complementary and not mutually exclusive.
    - Hysterosalpingography (HSG) is the traditional method for evaluating tubal patency. Findings suggesting proximal tubal obstruction require

further evaluation to exclude transient occlusion resulting from tubal/myometrial contractions.

- Laparoscopy and chromotubation with a dilute solution of methylene blue or indigo carmine introduced via the cervix can demonstrate tubal patency or document proximal or distal tubal occlusive disease.
- Fluoroscopic or hysteroscopic selective salpingography and tubal catheterization will distinguish true from false proximal tubal occlusion suggested by HSG or laparoscopy. This will direct prompt entrance into IVF for patients with true occlusion, provide a chance to evaluate the distal tube radiographically for possible hydosalpinx, and impart a 30% to 40% chance of spontaneous pregnancy for women with successfully recanalized proximal tubes.

6. Peritoneal factors – such as endometriosis, infectious or non-infectious pelvic inflammatory diseases or pelvic/adnexal adhesions may cause or contribute to reproductive failure.
   - Ultrasound may reveal otherwise unrecognized pelvic pathology
   - Laparoscopy with direct visual examination of the pelvic anatomy is the only method available for specific diagnosis of otherwise unrecognized peritoneal factors that may have an adverse effect on fertility. Laparoscopy is generally indicated in women with signs or symptoms of endometriosis and in those whose history, physical examination and/or HSG demonstrates or suggests tubal disease that may be amenable to repair.

Treatment of infertility
Fallon Health covers treatments that have been demonstrated in peer-reviewed, evidence-based, scientific literature to have a reasonable likelihood of correcting potentially reversible causes of infertility, such as surgical laparoscopy, therapeutic hysteroscopy, lysis of adhesions, myomectomy, removal of tumors and cysts, septate uterus repair, ovarian wedge resection, and ovarian drilling for female plan members, and surgical/microsurgical reconstruction or repair of the vas and/or epididymis or other epididymis surgery, such as vasovasostomy, epididymovasostomy, and epididymectomy for male plan members.

Treatment of male infertility:
If a male infertility factor is present, it is almost always defined by the finding of an abnormal semen analysis, although other male factors may play a role even when the semen analysis is normal. When identification of the etiology of an abnormal semen analysis is not possible, as is the case in many patients, the condition is termed idiopathic. Most male factor infertility can be classified as either endocrine (hormonal), testicular, or ductal in origin. Some of these conditions are identifiable and reversible, such as hypogonadotropic hypogonadism and ductal obstruction. Other conditions may be identifiable, but not reversible. If specific corrective treatment is not available, it still may be possible to achieve pregnancy through techniques such as intracytoplasmic sperm injection (ICSI).

*Endocrine factor infertility***:**
Sperm production is dependent on the careful balance of pituitary and testicular hormones. The main pituitary hormones involved in reproduction are follicle stimulating

hormone (FSH) and leutinizing hormone (LH). Prolactin (PRL) is another pituitary hormone that, if elevated, drastically inhibits sperm production and function. While endocrinopathies account for only 10% of male fertility problems, most are easily treatable. The most common endocrinopathies associated with male infertility include:

- Hypothyroidism (as well as hyperthyroidism) can impact male fertility. Symptoms include poor semen quality, poor testicular function and decreased libido. Hypothyroidism may be caused by a diet high in iodine. Reducing iodine intake or beginning thyroid hormone replacement therapy can elevate sperm count. This condition is found in only 1% of infertile men.
- Hyperprolactinermia (elevated prolactin). Mild elevation of prolactin levels produces no symptoms, but greater elevations of the hormone reduce sperm production, reduces libido and may cause impotence. This condition responds well to the drugs.
- Adrenal disorders, such as Congenital Adrenal Hyperplasia, occur when the pituitary is suppressed by increased levels of adrenal androgens. Symptoms include low sperm count, an increased number of immature sperm cells, and low sperm cell motility. Congenital Adrenal Hyperplasia is treated with cortisone replacement therapy. This condition is found in only 1% of infertile men.
- Hypogonadotropic hypopituitarism (low pituitary output of LH and FSH). This condition arrests sperm development and causes the progressive loss of germ cells from the testes and causes the seminiferous tubules and Leydig (testosterone producing) cells to deteriorate. May be treated with the drugs, however, if all germ cells are destroyed before treatment commences, the male may be permanently infertile.
- Hypogonadism is defined as a testosterone deficiency with associated or signs, deficiency of spermatozoa production, or both. It may result from a disorder of the testes (primary hypogonadism) or of the hypothalamic-pituitary axis (secondary hypogonadism). Both may be congenital or acquired as the result of aging, disease, drugs, or other factors. Additionally, a number of congenital enzyme deficiencies cause varying degrees of target organ androgen resistance. Diagnosis is confirmed by hormone levels. Treatment varies with etiology but typically includes testosterone replacement.
    - Primary hypogonadism involves failure of the testes to respond to follicle-stimulating hormone (FSH) and luteinizing hormone (LH). When primary hypogonadism affects testosterone production, testosterone is insufficient to inhibit production of FSH and LH; hence, FSH and LH levels are elevated. The most common cause of primary hypogonadism is Klinefelter's syndrome. Infertility due to primary hypogonadism does not respond to hormonal therapy. Men with primary hypogonadism occasionally have a few intratesticular sperm that can be harvested with various microsurgical techniques and used to fertilize an egg by an assisted reproductive technique (e.g., intracytoplasmic injection).
    - Secondary hypogonadism is failure of the hypothalamus (or pituitary) to produce enough FSH and LH. With secondary hypogonadism, testosterone levels are low, but levels of FSH and LH are low or inappropriately normal. Any acute systemic illness

can cause temporary secondary hypogonadism. Because any systemic illness can temporarily decrease levels of testosterone, FSH, and LH, secondary hypogonadism should be confirmed by measuring these levels again after at least a 4-wk interval after resolution of the systemic illness. Secondary hypogonadism due to a hypothalamic defect (e.g., Kallmann's syndrome) is treated initially with LH and FSH because of their ready availability; if these are ineffective, GnRH replacement therapy (q2 h SC by a programmable pump) might be more effective. Most (80% to 90%) of men respond successfully to these regimens.

Testicular factor infertility:
Testicular problems often result in a decline in sperm production and/or function and require an evaluation by a urologist specializing in fertility. The most common identifiable cause of infertility in men is varicocele. This is a condition of enlarged veins in the scrotum that causes abnormalities in the temperature regulation of the testis. Varicoceles are present in 15 percent of the normal male population and in approximately 40 percent of men presenting with infertility.

- Varicocele – only palpable varicoceles have been documented to be associated with infertility. Therefore, ancillary diagnostic measures, such as scrotal ultrasonography, thermography, Doppler examination, radionuclide scanning and spermatic venography are not medically necessary. Scrotal ultrasonography, however, may be indicated for clarification of an inconclusive physical examination of the scrotum. Spermatic venography may be useful to demonstrate the anatomic position of refluxing spermatic veins that recur or persist after varicocele repair. When the male partner of a couple attempting to conceive has a varicocele, treatment of the varicocele should be considered when all of the following conditions are met: 1) the varicocele is palpable on physical examination of the scrotum; 2) the couple has known infertility; 3) the female partner has normal fertility or a potentially treatable cause of infertility; and 4) the male partner has abnormal semen parameters or abnormal results from sperm function tests. Varicocele treatment for infertility is not indicated in patients with either normal semen quality or a subclinical varicocele. There are two approaches to varicocele repair: surgery and percutaneous embolization. Surgical repair of a varicocele may be accomplished by various open surgical methods, including retroperitoneal, inguinal and subinguinal approaches, or by laparoscopy. Percutaneous embolization treatment of a varicocele is accomplished by percutaneous embolization of the refluxing internal spermatic vein(s). None of these methods has been proven to be superior to the others in its ability to improve fertility.

Ductal (epididymal, 13 assal, ejaculatory) factor infertility:

- Obstructive azoospermia – One of the most common causes of 13 assal obstruction is vasectomy. Reversal of vasectomy is not covered. Iatrogenic injuries to the vas deferens are found in 7.2% of men with obstructive azoospermia (most commonly after pediatric inguinal hernia repair). Often, the level of obstruction (vas deferens or epididymis) is not

known preoperatively. The presence of fructose (which is normally secreted in the seminal vesicles) in semen indicates that the ejaculatory ducts are unobstructed. It is not uncommon, that preoperatively thought 14 assal obstruction intraoperatively appears to be an epididymal obstruction. Approximately 1% of all infertile men are born with the congenital absence of the vas deferens (CABVD), basically the equivalent of a vasectomy. Unfortunately, there is no way to replace the vas deferens at this time, however, urologists are able to retrieve sperm from the epididymis and use them later for in vitro fertilization. Obstructive azoospermia can be caused by a urinary tract infection or by the sexually transmitted diseases chlamydia and gonorrhea when bacteria infect the epididymis. Infection of the epididymis can cause scarring and blockage which inhibits passage of sperm. With microsurgical techniques, blockage repair success rates are extremely high.

- Nonobstructive azoospermia – A male presenting with infertility is more likely than the general population to harbor a gene mutation or chromosomal abnormality. Indeed, up to 15% of men with azoospermia have an abnormality in their karyotype, Y chromosome microdeletion, or mutation in the cystic fibrosis transmembrane conductance regulating (CFTR) gene. Unfortunately helping men with Y chromosome microdeletion have children almost guarantees their male children will have the same infertility problem. However, these children will be healthy in every other way.
- Retrograde ejaculation – Recognized causes of retrograde ejaculation include previous genitourinary surgery involving the bladder neck, genitourinary trauma, neurologic conditions, and side effects from medications. Diagnosis of retrograde ejaculation is generally based on thorough history, limited physical evaluation, and focused laboratory testing. A number of therapeutic approaches are available for the treatment of retrograde ejaculation or retrograde ejaculation –related infertility. The management goal of retrograde ejaculation is either to induce spontaneous antegrade ejaculation or to provide sufficient quantities of motile sperm for use in assisted reproductive techniques.

Treatment of female infertility:

Ovulatory factor infertility:

Ovulatory factor infertility can be identified in 20% to 25% of couples presenting with infertility. Ovulatory factors are classified by the World Health Organization (WHO) as follows:

- WHO Class I (hypogonadotropic hypogonadal anovulation) – absent or decreased function of the ovaries caused by a lack of the gonadal stimulating pituitary hormones. It is considered a form of secondary hypogonadism, due to a malfunction of the pituitary or hypothalamus gland, excessive stress or exercise, malnutrition or low body weight, and is diagnosed by low FSH levels (< 5mIU/ml and a low estradiol level (< 40 g/ml). Infertility related to hypopituitarism is the result of LH and FSH deficiency in both men and women.

Most WHO Class I patients will respond to lifestyle modification. Gonadotropin therapy may be appropriate as first-line therapy for some WHO Class I patients (anovulatory women with hypopituitarism) or as a second-line therapy for WHO Class I patients who fail lifestyle modification.

- WHO Class II (normogonadotropic normoestrogenic anovulation) – accounts for the majority of ovulatory disorders in women of reproductive age; women with polycystic ovary syndrome (PCOS) fall into this class. The clinical manifestations of PCOS may include anovulation, signs of androgen excess, and obesity. Insulin resistance and elevated serum LH levels are also common features in PCOS. The level of circulating LH as well as its relation to FSH levels are significantly elevated in women with PCOS.

The vast majority of anovulatory women have PCOS and fall into WHO Class II. PCOS is characterized by chronic anovulation, hyperandrogenism, and polycystic ovaries. At least half of patients with PCOS are obese. For obese women with PCOS, the loss of just 5 to 10 percent of body weight is often sufficient to restore ovulation in 55% to 100% of these women within six months.

Weight loss is a low-intervention modality with no side effects and should be the first-line treatment for obese anovulatory women. Various ovulation-inducing agents (e.g., clomiphene citrate, aromatase inhibitors, gonadotropins), insulin-sensitizing drugs (e.g., metformin) have been used to treat WHO Class II patients either as first or second-line treatment. It is unclear which drug should be used as the first-line treatment. It appears that women with worse insulin resistance benefit the most from insulin-sensitizing drugs, whereas women with less severe forms of PCOS (less hyperandrogenism, normal weight, and normal insulin sensitivity) could have a better response to clomiphene.

Laparoscopic surgery (ovarian drilling) for ovulation induction completes the list of therapies for anovulatory women with PCOS and should only be considered for women who fail to conceive with other therapies or women who experience ovarian hyperstimulation syndrome. It is not clear why women with PCOS ovulate after ovarian drilling. After surgery, ovulation occurs spontaneously in 70-90% of women and the probability of pregnancy after one year is in the region of 40-60%. There is no increased risk of multiple pregnancy or OHSS.

- WHO Class III (hypergonadotropic/hypoestrogenic anovulation) – women with premature ovarian failure comprise the majority of these cases which is diagnosed by high FSH levels (typically > 20mIU/ml) and low estrogen levels indicating ovarian failure.

Premature ovarian failure (POF) is not menopause. Spontaneous pregnancies can and do occur, although not commonly. No intervention has been proven to increase the ovulation rate or restore fertility in patients with POF (WHO Class III). Gonadotropin therapy carries a theoretical risk of exacerbating autoimmune premature ovarian failure. Unproven treatments to restore fertility should be avoided because they have the potential of interfering with the development of a spontaneous pregnancy. Patients with POF can have successful pregnancy with a donor egg.

Uterine factor infertility:
Abnormalities of the uterus can have a significant impact on the ability of a woman to conceive and to carry a pregnancy successfully. Some women have an abnormally developed uterus from birth (congenital) while others may develop a uterine problem due to infection or surgery (acquired). A variety of uterine factors can play a role in reproductive failure. These factors may contribute to infertility and also to recurrent miscarriage. Even when uterine factors are diagnosed, all other potential factors which might contribute to infertility should be aggressively evaluated and treated. Only when the entire picture is clearly understood and alternatives, risks, and benefits have been thoroughly discussed should a surgical approach be considered.
Fertility problems involving the uterus include:

- Uterine fibroids – It is uncommon for fibroids to be the sole cause of infertility. All other factors should be fully evaluated before deciding on removal of the fibroids (myomectomy). During myomectomy the surgeon will make an incision through the abdominal wall or vagina to gain access to the uterus and then remove the fibroids. After myectomy many physicians recommend a 3-6 month healing period before trying to conceive. If all other factors are normal, pregnancy rates are quite good following surgery.
- Congenital abnormalities – Between weeks 9 and 16 of pregnancy, the tubular systems forming in the fetus called the Müllerian ducts fuse together to form the uterus. If these ducts do not develop normally, congenital abnormalities of the uterus can occur. The most common congenital uterine anomaly is the septate uterus. While most women with a septate uterus have normal success in conceiving and delivering (though a somewhat higher rate of breech presentation and cesarean section), approximately 1 of 4 women with a septate uterus will have persistent reproductive failure. Generally, these women have problems with repetitive miscarriages more than with infertility. About 80% of these women carry their pregnancies successfully after surgical removal of the septum.
- Asherman's syndrome – Asherman's Syndrome is defined as the presence of scar tissue in the uterine cavity (intrauterine adhesions). It can be severe, in which case the whole uterine cavity is scarred and the woman does not menstruate, or mild, with only a few bands of scar tissue present. Removal of adhesions within the uterus is performed by hysteroscopy. For mild to moderate adhesions, there is a 60-80% chance of successful pregnancy after repair.
- Adenomyosis – Adenomyosis is the growth of glands from the endometrium into the muscle wall of the uterus. This condition can lead to excessive menstrual bleeding and pain. Treatment of adenomyosis is similar to that for endometriosis and may involve the use or drugs such as GnRH agonists.

Tubal factor infertility:
The treatment for tubal factor infertility is either tubal surgery to repair the damage or IVF. If surgery is successful, this approach has the advantage that additional treatment is not required for each attempt at conception. The most significant issues that impact this decision are the degree of tubal damage, the age of the female and whether other

infertility factors (male or female) are present. Male factor infertility plays a key role in decision making. If sperm quality is poor, IVF may be preferable.

The options for surgical treatment of tubal factor infertility are dependent on the morphology of tubal damage. Fallopian tube damage can take many forms:

- Proximal occlusion: obliterative fimbrosis, salpingitis isthmica nodosa, tubal polyps, corneal fibroids
- Midsegment occlusion: surgical sterilization (segmental salpingectomy) is the most common etiology of midtubal occlusion)
- Distal tubal occlusion:
  - Nonocclusive, preserved fimbria: fimbrial agglutination, mild prefimbrial phimosis, perifimbrial adhesions
  - Occlusive, absent fibria: hydrosalpinx, post-distal salpingectomy for ectopic pregnancy

Surgery for tubal factory infertility is most successful in women with distal tubal occlusion. Fimbrioplasty, the lysis of fimbrial adhesions or dilation of fimbrial structures may be performed via laparotomy or laparoscopy.

It has been shown that the presence of unilateral or bilateral hydrosalpinx adversely affects IVF and pregnancy rates therefore hydrosalpinx should be treated prior to IVF. Laparoscopic salpingectomy and proximal tubal occlusion (laparoscopic or transcervical) are equally effective in restoring IVF outcomes.

It is important to make a definitive diagnosis of proximal tubal occlusion as HSG may yield false results. Proximal tubal occlusion may be treated with hysteroscopic or fluoroscopic tubal catheterization. Recanalization of fallopian tubes has a high success rate, but some tubes do reocclude. The lowest pregnancy rates reported after successful recanalization occurred in women with coexistant distal tubal disease.

Macrosurgical tubal reimplantation or microsurgical tubocornual anastomosis necessitates a laparotomy and is not typically justified because a less invasive single IVF attempt can equal post-surgical pregnancy rates.

Peritoneal factor infertility:
Endometriosis is an estrogen-dependent disorder defined as the presence of tissue outside of the uterine cavity. The cause of endometriosis is unknown although there are a few theories that suggest possible causes. Endometriosis is a progressive disease that tends to worsen over time and can reoccur after treatment. A clinical staging system has been developed by the American Society for Reproductive Medicine. Determination of the stage of endometrial involvement is based on a weighted point system: Stage I is minimal, Stage II is mild, Stage III is moderate and Stage IV is severe

There is a reasonable body of evidence to demonstrate an association between endometriosis and infertility, however, a cause and effect relationship has not been established. Moreover, the available data are conflicting and prevent confident conclusions. Age, duration of infertility, family history, pelvic pain and stage of endometriosis should be taken into account when formulating a management plan.

The optimal treatment for endometriosis related infertility remains obscure. Surgical treatment is probably efficacious for all stages of the disease. Laparascopic ablation has been associated with small improvement in live birth rates in women with Stage I/II endometriosis.

On the basis of the available evidence, if early-stage endometriosis is diagnosed, surgical treatment can improve both spontaneous pregnancy rates and pregnancy rates following superovulation with IUI. Expectant management after laparoscopy is an option for younger women (<35 years of age). Alternatively, superovulation with IUI may be offered in surgically corrected endometriosis when pelvic anatomy is normal. Female age is an important factor in designing therapy. After age 35, there is a significant decrease in fecundity due to the two variables of endometriosis and age and age which may be additive. Consequently, in older women, a more aggressive therapy with superovulation and IUI or IVF may be may be reasonable rather than expectant management.

Combination medical and surgical therapy consists of either preoperative or postoperative medical therapy with a GnRH-agonist. Although theoretically advantageous, there is no evidence in the literature that combination medical-surgical treatment significantly enhances fertility and it may unnecessarily delay further fertility treatment.

For treatment of the infertility associated with Stage I/II endometriosis, controlled ovarian hyperstimulation (superovulation) with gonadotropins and IUI has been shown to be three times as likely to result in pregnancy as is ICI and twice as likely to result in pregnancy as is treatment with either superovulation and ICI or IUI alone. Infertility in women with severe endometriosis (Stage III/IV) is often resistant to treatment with ovarian stimulation plus IUI. These women will often require IVF in order to conceive.

Ovulation induction with timed intercourse, controlled ovarian hyperstimulation with intrauterine insemination (IUI) and in vitro fertilization (IVF). Despite improvements in both diagnostic assessment and treatment of infertile couples, many couples still have no explanation for their infertility. Unexplained infertility (the failure to conceive of a couple in whom no definitive cause for infertility can be found) has an incidence of 10-20% in all infertile couples. Unexplained infertility is not an absolute condition but rather a relative inability to conceive and many of these couples may eventually conceive without treatment. The treatment for unexplained infertility is therefore, by definition, empiric because it does not address a specific defect or functional impairment. The main treatments for unexplained infertility include ovulation induction with timed intercourse, controlled ovarian hyperstimulation with IUI, and IVF.

During the course of pregnancy, even women within the normal preconceptual BMI range are at a risk of developing many comorbid conditions, such as gestational diabetes, pregnancy-induced hypertension, thrombosis varicose veins, anemia, and lower-extremity edema. When obesity or morbid obesity is superimposed on pregnancy, the risk of developing a comorbid condition is significantly higher. Women who are severely obese (i.e., BMI 35.0-39.9) require an anesthesiology consultation prior to approval of ovulation induction or any assisted reproductive technology. Infertility services are not covered for women with morbid obesity (i.e., BMI > 40).

Interval between bariatric surgery and pregnancy: ACOG recommends that women should delay conception for 12-18 months after weight loss surgery to avoid conceiving during the period of rapid weight loss. As weight gain is the norm during pregnancy, the maternal benefits from the weight loss surgery may be limited.

Evaluation of ovarian reserve (cycle day 3 FSH) must be performed in selected women (i.e., women age 35 and older, women with suspected premature ovarian failure (POF), women with a single ovary or history of previous ovarian surgery, or women with documented poor response to exogenous gonadotropin stimulation, and women with exposure to chemotherapeutic agents or radiation) every 6 months to obtain prognostic information that may have an influence on treatment.

Infertility services are not covered when the chances of achieving a live birth are 5% or less.

Criteria sets:

Please note a Fallon Health Medical director may initiate a peer to peer conversation with the requesting provider should the member's FSH level exceed 12 mIU/ml. Other indicators considered AMH levels, quality effects, and number effects.

Ovulation induction - clomiphene citrate with timed intercourse
Clomiphene citrate is the medication most commonly prescribed for ovulation induction. It is the first-line treatment for women with normogonadotrophic normoestrogenic anovulation infertility (WHO Class II) and a normal BMI. Induction of ovulation in these women is aimed at inducing monofollicular development, subsequent ovulation and ultimately pregnancy and birth of a healthy newborn. Three ovulatory cycles are considered an adequate trial of clomiphene. An additional three cycles are allowed to allow for dose-titration or for additional adjunctive therapy (e.g., the addition of metformin in selected patients with clomiphene resistance). The majority of pregnancies occur by the third cycle.

Clomiphene citrate with timed intercourse is considered medically necessary for the following:

- First-line treatment for women with WHO Class II ovulatory factor infertility normogonadotropic normoestrogenic anovulation) and a normal BMI, such as, polycystic ovary syndrome (PCOS), amenorrhea-galactorrhea syndrome, psychogenic amenorrhea, post-oral-contraceptive amenorrhea, and certain cases of secondary amenorrhea of undetermined etiology.
- Second-line treatment for obese women with PCOS who have failed a 6-month trial of weight loss. Prior to initiation of ovulation induction, obese women with PCOS should be counseled to lose weight. Losing 10-15% body weight often restores ovulation in these women thereby avoiding the risks associated with clomiphene treatment.

The woman should be evaluated carefully to exclude pregnancy, ovarian enlargement, or ovarian cyst formation between each treatment cycle. The next course of clomiphene therapy should be delayed until these conditions have been excluded. The majority of patients who are going to ovulate will do so after the first course of therapy. If ovulation does not occur after three courses of therapy, further treatment with clomiphene is not

recommended and the plan member should be reevaluated. If three ovulatory responses occur, but pregnancy has not been achieved, further treatment is not recommended. Obesity, hyperandrogenism and insulin resistance are important factors in clomophene resistance.

Controlled Ovarian Hyperstimulation – injectable gonadotropins (FSH or LH w/ IUI)

Approximately 15% of women with ovulatory dysfunction will not ovulate following clomiphene citrate therapy. In addition, about 50% of women ovulating with clomiphene will not become pregnant. While there are a number of possible reasons, in many cases the FSH rise which is attainable with clomiphene citrate is either too low or does not last long enough to provide sufficient FSH stimulation to correct the underlying problem. In many of these cases, the women will respond better if higher levels of FSH can be attained over longer periods of time. These higher levels of FSH are achieved by directly injecting FSH in the form of injectable gonadotropins.

LH and FSH are the hormones which the pituitary would normally produce and release to stimulate the follicles developing within the ovary. In patients with anovulation or oligoovulation, the goal is to provide enough FSH to stimulate the development of a single follicle. Careful monitoring of treatment cycles using injectable gonadotropins is very important. The vast majority of women stimulated with injectable gonadotropins will ovulate, but not all of these will conceive. The majority of pregnancies occur within three treatment cycles. In general, patients should be offered IVF if they fail to conceive after 3 trials of controlled ovarian hyperstimulation with IUI.

A rare but serious side effect which is almost unique to ovulation induction cycles is ovarian hyperstimulation syndrome (OHSS). This syndrome is characterized by significant enlargement of the ovaries, possible fluid retention in the abdomen, and rarely generalized swelling throughout the body. Although the process is self-limited and usually resolves on its own, it may take a few days to a few weeks to go away. In severe cases women may have nausea, substantial weight gain from fluid retention, and may require close monitoring and/or treatment by their physician.

Injectable gonadotropin therapy with IUI is considered medically necessary for the following:

- First-line therapy for some women with hypogonadotropic hypogonadal anovulation (WHO Class I), such as anovulatory women with hypopituitarism, or as a second-line therapy for WHO Class I women who fail lifestyle modification.
- First-line treatment for unexplained infertility
- First-line treatment for mild to moderate male subfertility, i.e., the presence of at least one abnormal semen parameter according to WHO criteria, i.e., sperm concentration </= 20 x 106 /ml, motility < 50% and/or normal morphology < 30% (or < 15% according to strict criteria).
- First-line treatment for Stage I/II surgically corrected endometriosis.
- Second-line treatment for WHO Class II ovulatory factor infertility (normogonadotropic normoestrogenic anovulation), such as, PCOS, who have not ovulated or who have not conceived after a trial of three cycles of clomiphene.

Additionally the below is age specific requirement for coverage.

- For women 40 and 41 years of age: FSH level which is < 15mIU/mIU/ml on Cycle day 3 and the day 3 Estradiol level is < 80 pg/mL
- For women > age 42 years of age: FSH level which is < 12 mIU/ml on Cycle day 3 and the 3 day Estradiol level < 80 pg/mL

In vitro fertilization-embryo transfer (IVF-ET)

IVF-ET has high success rates in the treatment of infertility except when infertility is caused by an anatomic problem within the uterus, such as severe intrauterine adhesions. IVF-ET can also provide clues as to the cause of infertility, such as slow embryo development, excessive fragmentation of embryos, abnormal zona pellucida, etc.

IVF-ET is considered medically necessary for the following:

- First-line treatment for women with bilateral tubal occlusion (and normal semen parameters) that is not amenable to surgery.
- First-line treatment for women with Stage III/IV endometriosis and advanced reproductive age (> 35 years) or in the presence of another factor such as bilateral tubal occlusions.
- First-or second-line treatment for Stage III/IV endometriosis For women with Stage III/IV endometriosis-associated infertility and no other identifiable infertility factor, conservative surgical therapy is indicated as first-line therapy. Several studies suggest that surgical therapy increases fertility in women with advanced endometriosis. IVF-ET is a second-line treatment or women with Stage III/IV endometriosis who fail to conceive spontaneously after a minimum of 6 months following conservative surgery
- Second-line treatment for mild to moderate male factor subfertility following three (3) failed cycles of injectable gonadotropin therapy with IUI.
- Second-line treatment for persistent unexplained infertility following three (3) cycles of injectable gonadotropin therapy with IUI
- Third-line treatment for women with WHO Class II ovulatory factor infertility (normogonadotropic normoestrogenic anovulation), such as, PCOS, who have not ovulated or who have not conceived after a minimum of three (3) cycles of clomiphene followed by three (3) cycles of injectable gonadotropin therapy with IUI

Note: A plan member who does not have a successful pregnancy after an IUI cycle that is converted to IVF (to avoid cycle cancellation) must complete the required number of cycles of gonadotropin IUI (typically three cycles are required) before being considered for further IVF.

Gamete intrafallopian transfer (GIFT)/Zygote intrafallopian Transfer (ZIFT)

GIFT is similar to IVF, but the gametes (egg and sperm) are transferred to the fallopian tubes rather than the uterus, and fertilization takes place in the tubes rather than in the laboratory. GIFT involves a laparoscopic surgical procedure to transfer the sperm and egg into the tubes. GIFT accounts for approximately 2% of assisted reproductive technology (ART) procedures in the U.S.

ZIFT differs from GIFT in that the fertilization process still takes place in the laboratory versus the fallopian tubes. It is similar to GIFT in that the fertilized egg is transferred into fallopian tubes, and it involves a laparoscopic surgical procedure. Because ZIFT allows for fertilization to be confirmed before the eggs are inserted into the fallopian tubes, fewer eggs are usually used, lowering the risk of multiple pregnancy. ZIFT accounts for less than 1.5% of assisted reproductive technology (ART) procedures in the U.S.

For GIFT or ZIFT, a woman must have at least one functional fallopian tube. Most ART centers perform GIFT only rarely. GIFT may be indicated for patients who require diagnostic laparoscopy or laparoscopy for treatment of endometriosis, in which case combining the procedures is a cost saving measure. GIFT may also be considered when religious considerations permit fertilization in the body, as with GIFT, but prohibit extracorporal (in vitro) fertilization, as with IVF and ZIFT. If GIFT fails however, the clinician does not learn anything about the sperm's ability to fertilize the eggs. With IVF, the sperm fertilizes the egg in the laboratory, where a health care professional can tell whether fertilization has occurred, and can follow embryo development.

Because there is no demonstrable advantage for ZIFT over IVF, most ART centers no longer perform this procedure.

In vitro fertilization with intracytoplasmic sperm injection (ICSI)

Couples with severe male factor subfertility are at high risk for fertilization failure with IVF-ET. In severe male factor subfertility, live birth rates with ICSI are superior to those with other non-donor treatments. In non-male infertility, however, pregnancy rates are not better with ICSI that with IVF. ICSI offers no advantage in terms of clinical outcomes over IVF in cases of non-male factor subfertility and unexplained infertility. Whether ICSI is beneficial in cases of poor ovarian response or oocyte quality also remains to be investigated.

Chromosome abnormalities are much more frequent in males with subfertility than in the general population. Preimplantation genetic diagnosis (PGD) may be indicated when there is a high risk of aneuploidy because of genetic factors.

ICSI is considered medically necessary for the following. First-line therapy for severe male factor subfertility, defined as:

- Postwash total motile sperm count with insufficient sperm for conventional IVF-ET (<0.2 million/ml)
- Severe teratozoospermia (<5% normal morphology per strict criteria,
- Oligoasthenoteratozoospermia
- Sperm obtained from electroejaculation or retrograde ejaculation
- Obstructive azoospermia (e.g., congenital bilateral absence of the vas deferens) with sperm obtained by microsurgical epididymal sperm aspiration (MESA) or another sperm aspiration technique
- Non-obstructive azoospermia with testicular sperm obtained by fine needle aspiration or testicular biopsy

Additionally it is considered third-line treatment for mild-moderate male subfertility following unexplained failure or low fertilization rate (< 20%) in a previous standard IVF-ET cycle.

ICSI is covered on the day of scheduled in vitro fertilization if the post-processing semen analysis on that day meets the coverage criteria for severe male factor subfertility listed above. A retrospective authorization request must be submitted with a copy of the semen analysis.

Conversion from gonadotropin IUI to IVF-ET

The goal of gonadotropin IUI is to obtain two or three follicles of 16 to 18 mm at the time of human chorionic gonadotropin (hCG) administration. One of the risks associated with gonadotropin therapy is high-order multiple pregnancies. Many different strategies are used to decrease the rate of high-order multiple pregnancies, including withholding hCG, cycle cancellation or conversion to IVF-ET. Conversion of high response gonadotropin IUI patients to IVF-ET is an effective alternative to high-order multiple pregnancies and cycle cancellation for some women. Ovarian response is evaluated in terms of ultrasound measurement of follicles and estradiol (E2) levels. There is no absolute maximum agreed upon number of mature follicles or E2 level. Other factors, including the age of the woman and the presence of male factor subfertility are taken into consideration.

Where the goal of gonadotropin IUI is to obtain two or three follicles of 16 to 18 mm at the time of hCG administration, conversion from IUI to IVF-ET is considered medically necessary for women less than 35 years of age and:

- >/= 4 follicles >/= 15 mm on the day of hCG administration, or
- E2 level >/= 1,000 pg/ml on the day of hCG administration

Conversion from IUI to IVF-ET will be considered for other women on an individual case-by-case basis.

Frozen embryo transfer (FET), also known as a thaw cycle
Embryos that are not transferred during an IVF cycle can be subsequently cryopreserved. Cryopreservation of the embryos has been accomplished at all stages of embryo development. There is no universal agreement as to which stage of embryo development is the best for cryopreservation. If an embryo is frozen immediately after it has been fertilized (pronuclear stage), the survival of the embryo after thawing appears to be high. However, since the embryo was not cultured in the laboratory first, its potential viability is unknown. Therefore, after the embryo is thawed, it must then be cultured in the laboratory in the same way it would have been if it had not been frozen. It is impossible to predict how many of the thawed embryos will reach the stage of development desired by the physician for transfer. Therefore, a higher number of embryos must be thawed. If a large number of embryos do reach that stage of development, then there is a dilemma. Either a larger number of embryos must be transferred (which increases the risk of multiples) or the extra embryos must be discarded or refrozen.

An embryo can also be frozen after two to three days of embryo development. This is called the cleavage stage. Cleavage stage cryopreservation allows for some limited

assessment of the development of the embryos. Some embryos, for example, will not have developed or look abnormal and thus would not be frozen. On the downside, the survival of cleavage stage embryos is lower. As with the case of embryos frozen at the pronuclear stage, cleavage stage embryos can also be cultured after thawing to further help determine the best embryos for transfer. Embryos can also be frozen at the blastocyst stage. Since the embryos have been cultured for five to six days, this enables the best assessment for viability and thus fewer non-viable embryos will be frozen at this stage. In the past, survival of blastocyst embryos after thawing has not been very good. In recent years, however, techniques for freezing blastocysts have improved and in selected centers the survival rate is very good. Blastocyst cryopreservation allows for the thaw and transfer of embryos on the same day.

One of the advantages of FET is that ovarian hyperstimulation is not necessary and the embryo transfer can occur in a natural ovulatory cycle. The thaw survival rate is approximately 70%, therefore if there are less than three cryopreserved embryos, an FET cycle is not generally recommended. In terms of cost effectiveness, FET costs much less than an IVF cycle with ovarian hyperstimulation and egg retrieval. The success rate for FET varies from clinic to clinic. In some clinics, the live birth rates with frozen embryo transfer are as high as those achieved with fresh embryo transfer. Overall FET is somewhat less successful compared to fresh embryo transfer:

- Frozen embryo transfer:
  - Transfers resulting in live births, 28.9%
  - Transfers resulting in singleton live births, 21.9%
- Fresh embryo transfer:
  - Transfers resulting in live births, 35.4%
  - Transfers resulting in singleton live births, 24.5%

When three or more cryopreserved embryos are available for transfer, these embryos must be used prior to authorization for any additional IVF cycles with egg retrieval. FET is considered medically necessary when three or more cryopreserved embryos available for transfer and:

- The plan member meets criteria for and has authorization for an IVF-ET/GIFT/ZIFT cycle.

Single embryo transfer:

Single embryo transfer (mSET) is considered medically necessary for women with certain medical conditions, such as: diabetes, previous hysterectomy, uterine malformation, increased risk of ovarian hyperstimulation syndrome, or indication for preimplantation genetic diagnosis.

Elective single embryo transfer (eSET) will be considered on an individual case-by-case basis for:

- Women under age 35 with a favorable prognosis

Donor egg IVF:

A donor egg IVF cycle is where the eggs of another woman are used in an IVF cycle with the resultant embryos being transferred to the recipient mother. An egg donor agency will facilitate the egg donation process. Egg donor agencies abide by the American Society for Reproductive Medicine (ASRM) Ethics Committee guidelines. The

egg donor can be anonymous or arrangements can be made for a directed donation from a friend or family member. The egg donor must undergo a medical and social history, physical examination, psychological screening, and laboratory screening for sexually transmitted diseases prior to becoming a donor. Egg donor agencies typically charge a fee to cover the cost of donor services plus any additional expenses that may be incurred by the donor, such as travel and lodging, lost wages, attorney's fees, etc. and the associated costs are not covered by Fallon Health.

The egg donor should be between 21 and 34 years of age. The major advantage to using donor eggs is that the live birth rates usually coincide with the age of the donor. For example, if the eggs of a 22 year old woman are used in an IVF cycle with a 42 year old woman the live birth rates equal the 22 year old age group which is typically among the highest. This compares to dismal live birth rates using the eggs of a 42 year old.

Effective synchronization of the recipient's uterine lining (endometrium) with the growth of the donor's follicles and eggs and the resulting embryos is key to the success of donor egg IVF. Recipients with ovarian failure (e.g., premature menopause) will require uterine preparation with estrogen and progesterone as they lack ovarian function. Recipients with intact ovarian function (the majority of patients at most IVF centers) require treatment with estrogen and progesterone to align their cycle with those of the egg donors. Recipients with ovarian function are often pre-suppressed with a medication su, prior to the initiation of estrogen. Egg donors require ovarian stimulation with gonadotropins, ultrasound and/or endocrine monitoring (such as serum progesterone, LH and estradiol levels), and egg retrieval.

Donor egg IVF is considered medically necessary when the egg donor is between 21 and 34 years of age and the recipient is a female plan member:

- Age 39 or younger diagnosed with premature ovarian failure (POF) defined as the loss of normal functioning of the ovaries prior to age 40 and cycle day 3 FSH greater than or equal to 10 mIU/ml
- Age 43 or younger with a normal cycle day 3 FSH (i.e., </= 10 mIU/ml) and one or more previous failed IVF attempts (may be due to low response to gonadotropin stimulation, low antral follicle count, poor egg quality, etc.)
- With a genetic disorder that results in POF, genetic oocyte defects, recurrent loss due to chromosomal abnormalities, a high probability of passing sex-linked genetic disease, such as hemophilia, etc.

Women whose live birth rate is </= 5% are not eligible for coverage for infertility services. These women are experiencing a normal and age-related decline in fertility and therefore are not eligible for coverage for infertility services regardless of their FSH levels.

Donor embryo transfer:
In the current clinical practice of ART more embryos than can be transferred safely at one time commonly are generated. In the majority of infertility clinics these embryos are cryopreserved for later transfer. Couples who become pregnant and do not desire another pregnancy or have other reasons for choosing not to use their embryos have the option of discarding these embryos or donating them to other individuals or to research.

Donated embryos often come from couples who were coping with infertility problems themselves. Success rates with embryo donation depend on the quality of the embryos that were frozen, the age of the woman who provided the eggs, and the number of embryos transferred. There are no national statistics on the success of embryo donation due to the limited number of embryos donated nationwide.

In egg donation, the recipient is responsible for the egg donor's costs including screening testing, egg retrieval, travel and lodging, etc. No ovarian stimulation or egg retrieval is involved with embryo donation. In embryo donation, embryo donors are not compensated. However, all donated embryos undergo diagnostic screening before they are transferred. They also undergo genetic testing to reduce the chances of genetic or chromosomal defects. Fallon Health does not cover any costs related to donated embryo storage or screening/testing. Fallon Health covers costs associated with embryo transfer for a female plan member who meets eligibility criteria including fertility medications, endocrine monitoring, ultrasounds and placement of the embryo into the uterus (see frozen embryo transfer).

Donor embryo is considered medically necessary for a female plan member when both male and female partners are infertile and:

- The male partner has severe male subfertility (see coverage criteria for ICSI)
- The female partner meets criteria for donor egg, i.e., she is:
    - Age 39 or younger diagnosed with premature ovarian failure (POF) defined as the loss of normal functioning of the ovaries prior to age 40 and cycle day 3 FSH greater than or equal to 10 mIU/ml
    - Age 39 or younger with a normal cycle day 3 FSH (i.e., </= 10 mIU/ml) and one or more previous failed IVF attempts (may be due to low response to gonadotropin stimulation, low antral follicle count, etc.)
    - With a genetic disorder that results in POF, genetic oocyte defects, recurrent pregnancy loss due to chromosomal abnormalities, a high probability of passing sex-linked genetic disease, such as hemophilia, etc.

Women age 40 years of age and older are not eligible for donor embryo transfer regardless of their FSH levels. Women age 40 years of age or older who are unable to achieve a live birth outcome are experiencing a normal and age-related decline in fertility and therefore are not eligible for coverage for infertility services regardless of their FSH levels (the live birth rate is < 5%).

Other Related services:

1. Donor sperm: Fallon Health covers procurement of cryopreserved donor sperm from a sperm bank that is registered with the FDA and that complies with the guidelines established by the FDA for Human Cell and Tissue Products (HCT/Ps) for a male plan member who meets one of the eligibility criteria listed below and whose female partner has received prior authorization for an infertility/ART procedure, such as IUI, IVF-ET, etc.
    - Severe male factor subfertility (see ICSI for criteria for severe male factor subfertility)
    - Serious genetic disorders such as Sickle Cell Anemia and Huntington's disease

Fallon Health covers donor sperm for a female plan member whose male partner (who is not insured by Fallon Health) meets one of the criteria above to the extent that donor sperm is not covered by the male partner's insurer, if any. (Fallon Health will require documentation of the following prior to authorizing coverage of donor sperm: (1) documentation that the male partner has either severe male subfertility or a serious genetic disorder, and (2) documentation that the male partner's insurer, if any, does not provide benefits for donor sperm.)

Donor sperm is not covered for female plan members without male partners.

Donor sperm is not covered for male plan members (or male partners of female plan members) who have undergone elective sterilization regardless of whether the sterilization procedure has been reversed.

2. Cryopreservation of embryos or sperm
   Embryo and sperm cryopreservation are techniques designed to preserve embryos and sperm for future use. Embryo and sperm cryopreservation is a process where embryos or sperm are preserved by cooling to sub-zero temperatures, typically in liquid nitrogen (-196°C), for whatever period of time is designated. Patients who elect these procedures include women or men who are undergoing active infertility treatment, women or men who will undergo treatments that may destroy their future fertility (such as cancer treatments), or couples who want to preserve embryos for future use.

Fallon Health covers cryopreservation of embryos and sperm for plan members in active infertility treatment when there is an expectation that the embryos and/or sperm will be used for a future infertility/ART procedure for the plan member. A plan member is considered to be in active infertility treatment if he/she will undergo an infertility/ART procedure within 90 days.

Fallon Health does not cover cryopreservation of embryos or sperm for women or men who will undergo treatments that may destroy their future fertility (such as cancer treatments), or couples who want to preserve embryos for future use.

Fallon Health does not cover storage charges for embryos or sperm unless the member is in active treatment as stated above.

3. Assisted hatching: Artificially disrupting the zona pellucida is known as assisted hatching. A variety of techniques have since been employed to assist embryo hatching, including partial mechanical zona dissection, zona drilling and zona thinning making use of chemicals and lasers.

Assisted hatching is considered medically necessary in conjunction with IVF-ET (with or without ICSI) when:

- There is documentation of repeated unexplained implantation failure (2 or IVF cycles with good quality embryos)

Assisted hatching will not be authorized if preimplantation genetic diagnosis (PGD) is being performed as this process includes opening the zona pellucida.

4. Preimplantation genetic diagnosis (PGD): A technique used to identify genetic defects in embryos created through in vitro fertilization (IVF) prior to embryo transfer. PGD refers specifically to testing when one or both genetic parents have a known genetic abnormality and testing is performed on an embryo to see if it also carries a genetic abnormality.

Preimplantation genetic diagnosis (PGD) is sometimes recommended when couples are at risk of transmitting certain known genetic abnormalities to their children. In order to have PGD couples must undergo IVF. (Note: Fallon Health does not cover the cost of IVF for plan members who do not meet criteria for IVF contained in this policy.) After fertilization of the egg with sperm, embryos are allowed to develop into cleavage-stage embryos. On day 3 after egg retrieval (equivalent to 2 days after fertilization), a single blastomere is removed from the developing embryo for performance of FISH or PCR for genetic evaluation of the embryo. Usually, the genetic testing is completed within 24 hours of the embryo biopsy, allowing for a day 4 or day 5 embryo transfer.

PGD is considered medically necessary when laboratory documentation of one of the following:

- Both partners are known carriers of a single gene autosomal recessive disorder, such as cystic fibrosis, sickle cell anemia, or Tay Sachs disease.
- One partner is a known carrier of a single gene autosomal dominant disorder, such as Marfan syndrome or Huntington's disease.
- One partner is a known carrier of a single gene X-linked disorder (dominant or recessive). X-linked recessive disorders include hemophilia, fragile X syndrome and muscular dystrophy. X-linked dominant disorders include Rett syndrome, and vitamin-D resistant rickets.
- One partner is known to have a balanced chromosome translocation. (The concern regarding having a balanced chromosome translocation is that although the individual is healthy, the egg or sperm of that individual can have an unbalanced chromosome translocation that leads to the resultant embryo not implanting or pregnancy being lost or having a child with physical or mental defects that may be lethal.) Chromosomal rearrangement is detected through a technique known as fluorescent in situ hybridization (FISH).

PGD for human leukocyte antigen (HLA) tissue typing of embryos is not covered.

Preimplantation genetic screening (PGS) refers to techniques where embryos from presumed chromosomally normal genetic parents are screened for aneuploidy (such as trisomy 21). PGS is not covered.

5. Sperm retrieval techniques: Sperm retrieval refers to the group of procedures used to obtain sperm from the male reproductive tract. The collected sperm are intended specifically for use with intracytoplasmic sperm injection (ICSI). Sperm retrieval is reserved for men who have the most severe types of male factor infertility including no sperm in their ejaculate (azoospermia). The goals of sperm retrieval are (1) to obtain the best quality sperm; (2) to retrieve an adequate number of sperm for both immediate use and for cryopreservation, and (3) to minimize damage to the reproductive track so as not to jeopardize future attempts at sperm retrieval or surgical reconstruction.

Microsurgical epididymal sperm aspiration (MESA) is the optimal way of obtaining sperm in those men with an unreconstructable reproductive tract obstruction (i.e., congenital bilateral absence of the vas deferens or iatrogenic vasal injury from a previous scrotal/inguinal surgery). MESA allows for the recovery of the best and highest quantity of sperm compared with other sperm aspiration techniques. MESA is performed in an office/outpatient procedure room equipped with an operating microscope and microsurgical instruments. The epididymis is isolated through 1/2 inch incision made in the scrotal skin. An operating microscope is used to examine the very small tubules of the epididymis that contain the sperm. A dilated tubule is opened and the fluid is collected and examined for the presence and quality of sperm. All of the sperm containing fluid is collected and taken to the lab for processing. If the fluid is devoid of sperm or only dead sperm are found, then another area of the epididymis is sampled. This is done until enough sperm are obtained to use and to store for future use. Sperm retrieval from the epididymides of men with obstructive azoospermia is possible in over 99% of patients when performed by experienced microsurgeons.

Percutaneous epididymal sperm extraction (PESA) is a less invasive alternative to MESA that involves the aspiration of sperm from the epididymis using a fine gauge butterfly needle. It is an office-based procedure performed under local anesthesia. The success of PESA depends on palpation of the epididymis and correct positioning of the needle so that it enters the substance of the epididymis. While conceptually appealing, it is possible that insufficient sperm will be obtained and a second MESA may have to be performed to save the IVF cycle. Rarely are enough sperm obtained for freezing for future use and the procedure will have to be repeated with each IVF attempt. The most significant drawback is the blind nature of the procedure during which the delicate epididymal tubules can be easily damaged.

Testicular fine needle aspiration (TFNA), also known as testicular sperm aspiration (TESA) is a fine needle biopsy of the testicle. It is an office-based procedure performed under local anesthesia. From the results of retrospective studies, TESA is an effective alternative to MESA for azoospermic men with normal spermatogenesis but has the potential to cause damage to the epididymal tubules. TFNA offers largely lower chances of successful retrieval for nonobstructive azoospermia compared to TESE.

Nonobstructive azoospermia is a condition in which no sperm are present in the ejaculate. Nonobstructive azoospermia is the most challenging type of male-factor infertility to manage. Various conditions can lead to nonobstructive azoospermia including genetic (karyotypic abnormalities, Y-chromosome microdeletions); testicular (cryptorchidism, torsion, bilateral anorchia); endocrine (deficiencies in gonadotropin releasing hormone agonist, LH, and/or FSH, excess androgen, estrogen, Prolactin, glucorticoid, thyroid abnormalities, receptor abnormalities, varicocele, environmental hazards, iatrogenic causes, diseases (neoplastic diseases, infections or inflammatory, systemic illness), and drugs. While some of the underlying causes of nonobstructive azoospermia are reversible, advanced techniques that extract sperm from testicular tissue are needed for the majority of patients with this condition. Even with advanced techniques, 20% to 40% of men with this condition are not able to have sperm retrieved.

Microdissection testicular sperm extraction (TESE) is an open surgical procedure performed under direct visualization and is the technique of choice for men with

nonobstructive azoospermia. There is a threshold of quantitative sperm production below which no sperm will reach the ejaculate. This threshold phenomenon of spermatogenesis is the reason that in many cases of non-obstructive azoospermia, sperm can often be extracted from testicular tissue of azoospermic men with germinal failure, and used successfully for ICSI. A prior diagnostic testicle biopsy analyzed quantitatively can often predict the likelihood of finding sperm during a TESE attempt. A small piece of testicular tissue is removed through a 1/2 inch skin incision. The tissue is placed in culture media. Sperm are liberated from within the seminiferous tubules where they are produced and are then extracted from the surrounding testicular tissue. This can be an exhaustive process depending on the degree of sperm production.

The following sperm retrieval techniques are considered medically necessary for plan members with unreconstructable obstructive or nonobstructive azoospermia that is not amenable to treatment:

- MESA is covered for plan members with unreconstructable obstructive azoospermia (congenital bilateral absence of the vas deferens or iatrogenic vasal injury from a previous scrotal/inguinal surgery)
- Microdissection TESE is covered for plan members with nonobstructive azoospermia that is not amenable to treatment

Exclusions

- Infertility services for a plan member who has previously undergone a sterilization procedure, whether or not there has been a procedure to reverse the sterilization.
- Infertility services for women with morbid obesity (i.e., BMI > 40).
- Over-the-counter drugs or devices (e.g., ovulation predictor kits).
- Cryopreservation and/or storage of oocytes or ovarian tissue.
- Cryopreservation and/or storage of testicular tissue.
- Preimplantation HLA typing and selected embryo transfer of potential donor progeny.
- Postcoital test (PCT).
- Indirect (serum) antisperm antibody testing.
- Computer-aided or computer-assisted semen analysis.
- Human zona pellucida binding testing.
- Sperm acrosome reaction testing.
- Biochemical tests of sperm function including measurements of sperm creatine kinase and reactive oxygen species (ROS).
- Sperm DNA integrity testing and/or sperm DNA fragmentation testing (including commercially available testing such as the Sperm Chromatin Structure Assay and the Sperm DNA Fragmentation Assay).
- Clomiphene citrate challenge test, and other tests of ovarian reserve including but not limited to serum estradiol, serum inhibin B, anti-Müllerian hormone.
- The use of rescue ICSI in IVF. Rescue ICSI has failed to produce successful pregnancies in patients with unexplained fertilization failure. Further studies are needed.
- Thawing of cryopreserved testicular/ovarian reproductive tissue or oocytes.

The following services may be a component of an assisted reproductive technology procedure, such as IVF or IVF with ICSI. As such they are not separately reimbursable

and claims for these services will be denied provider liable leaving no member financial responsibility.

- Sperm evaluation; hamster penetration test (CPT code 89329), also known as sperm penetration assay or Zona free hamster oocyte test.
- Sperm viability testing (such as hypoosmotic swelling test).

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Policy History

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Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully-insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans. For Medicare and Medicaid members, this policy will apply unless Medicare and Medicaid policies extend coverage beyond this