

## Infertility Testing and Treatment

**Policy MP-016**

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### Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. Services requiring prior-authorization may not be covered, if prior-authorization is not obtained.
4. **This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.**

### Description:

Infertility is a disease defined by the failure to achieve a successful pregnancy within 12 months of regular, unprotected intercourse or therapeutic donor insemination in women younger than 35 years or within 6 months in women older than 35 years, or due to an impairment in a person's capacity to reproduce with his or her partner, according to ACOG and the ASRM.

Infertility affects 15% of couples, with male factor being the cause of infertility in 40-50% of couples, and 30% of all infertility being unexplained.

ACOG and the ASRM recommend evaluation and treatment of any patient who by definition has infertility or is at high risk of infertility based on history. Women older than 40 years should be offered immediate evaluation and treatment. If either partner has a condition known to cause infertility, immediate evaluation should be offered.

Conception is a complicated process and depends on many factors: the production of healthy sperm by the man and healthy eggs by the woman; unblocked fallopian tubes that allow the sperm to reach the egg; the sperm's ability to fertilize the egg when they meet; the ability of the fertilized egg (embryo) to become implanted in the uterus; and sufficient embryo quality. For the pregnancy to continue to full-term, the embryo must be of viable genetic quality and the woman's hormonal and uterine structural environment adequate for its development.

## Policy Statement and Criteria

### 1. Commercial Plans

U of U Health Plans covers *certain* diagnostic testing to determine the etiology of infertility.

A. Laboratory tests covered as part of the infertility benefit in the evaluation of infertility:

Female:

- 17-hydroxyprogesterone
- Anti-Muellerian hormone (AMH)
- Dehydroepiandrosterone sulfate (DHEAS)
- Estradiol
- Fasting glucose
- Follicle stimulating hormone (FSH)
- Free and/or total testosterone
- Human chorionic gonadotropin (HCG)
- Luteinizing hormone (LH)
- Progesterone challenge test

Male:

- Follicle stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Post-ejaculatory urinalysis
- Semen analysis:
  - concentration
  - fructose
  - leukocyte count
  - microbiology
  - morphology
  - motility
  - pH
  - volume
- Semen culture
- Sperm antibodies

B. Procedural tests covered under the infertility benefit in the evaluation of infertility:

Female:

- Diagnostic laparoscopy with or without chromotubation
- Hysterosalpingography
- Hysteroscopy
- Salpingoscopy
- Sonohysterography
- Ultrasound (i.e., serial transvaginal, pelvic, ovarian)

Male:

- Scrotal exploration
- Scrotal ultrasound
- Sperm penetration assay (SPA)
- Testicular biopsy
- Transrectal ultrasound (TRUS)
- Vasography
- Y-chromosome microdeletion testing in males with non-obstructive azoospermia or severe oligospermia

**U of U Health Plans does NOT cover the following tests, treatments, or procedures for infertility, as they are considered investigational/experimental.**

A. Not covered tests, treatments, or procedures (list not all inclusive):

- Antiphospholipid antibodies
- Antiprothrombin antibodies
- Circulating natural killer cell measurement
- Clomiphene citrate challenge test (CCCT)
- Co-culturing of embryos/oocytes
- Computer-assisted sperm motion analysis
- Cryopreservation, storage, and thawing:
  - oocytes
  - ovaries
  - testicular tissue
- Cryopreservation and storage of embryos when not undergoing covered active
- Infertility treatment
- Direct intraperitoneal insemination
- Donor charges
- Embryoscope or Time-Lapse imaging of Embryos

- Embryotoxicity assay
- Endometrial receptivity testing
- Fallopian tube sperm transfusion
- Fine needle aspiration mapping
- Hemizona test
- Hyaluronan binding assay (HBA)
- Intrafollicular insemination
- IV immunoglobulins
- Karyotyping for chromosomal abnormalities
- Laser-assisted necrotic blastomere removal from cryopreserved embryos
- Leukocyte immunization
- Over-the-counter (OTC) prediction/pregnancy tests
- Post-coital test
- Reactive oxygen species testing (ROS)
- Receptiva (BCL6 assay) used for undiagnosed endometriosis
- Serum inhibin-B for detecting ovarian reserve
- Sperm DNA integrity testing
- Sperm precursors
- Sperm viability test (diagnostic)
- Surrogacy

***The following section is intended ONLY for employer groups who have elected infertility treatment coverage.***

**U of U Health Plans covers *certain* treatments for infertility as outlined below:**

A. Treatments covered under the fertility benefit include:

*Female:*

- 17-hydroxyprogesterone caproate
- Artificial insemination (intrauterine)
- Assisted embryo hatching
- Cryopreservation of embryos
- Fimbrioplasty
- Fluoroscopic/hysteroscopic selective tube cannulation
- Gamete intrafallopian transfer (GIFT) or pronuclear stage transfer (PROST), or natural cycle IVF

- In vitro fertilization with embryo transfer (IVF-ET)
- Intracytoplasmic sperm injection (ICSI)
- Low tubal ovum transfer (LTOT)
- Lysis of adhesions
- Myomectomy
- Operative hysterectomy
- Ovarian drilling and wedge resection
- Ovulation induction medications
- Ovulation monitoring studies
- Removal of tumors and cysts
- Salpingectomy
- Salpingostomy
- Septate uterus repair
- Surgical laparoscopy
- Zygote intrafallopian transfer (ZIFT)

Male:

- Electroejaculation
- Excision of tumors (e.g., epididymal)
- Microsurgical epididymal sperm aspiration (MESA)
- Orchiopexy
- Percutaneous epididymal sperm aspiration (PESA)
- Pharmacologic treatment of endocrinopathies:
  - androgens
  - corticosteroids
  - human chorionic gonadotropins
  - human menopausal gonadotropin
  - pulsatile gonadotropin-releasing hormone
- Repair of varicocele
- Seminal vesicle sperm aspiration
- Spermatic vein ligation
- Testicular fine needle aspiration (TEFNA)
- Testicular sperm aspiration (TESA)
- Testicular sperm extraction (TESE)
- Transurethral resection of the ejaculatory ducts (TURED)
- Vasal sperm aspiration

## 2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at: <https://medicaid.utah.gov/utah-medicaid-official-publications/> or the [Utah Medicaid code Look-Up tool](#)

**CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.**

### Clinical Rationale

An infertility evaluation is usually initiated after 1 year of regular unprotected intercourse in women under age 35 and after 6 months of unprotected intercourse in women age 35 and older. However, the evaluation may be initiated sooner in women with irregular menstrual cycles or known risk factors for infertility, such as endometriosis, a history of pelvic inflammatory disease, or reproductive tract malformations.

### Laboratory Tests for Females

For women over 35 years of age and younger women with risk factors for premature ovarian failure, testing for ovarian reserve with a day 3 FSH level is recommended. Other tests such as the clomiphene citrate challenge test (CCCT), antral follicle count, and anti-Müllerian hormone (AMH) level are utilized by specialists and in special circumstances.

#### Follicle Stimulating Hormone (FSH) and Clomiphene Citrate Challenge Test (CCCT)

Both the day 3 FSH level (where day 1 is the first day of full menstrual flow) and the CCCT, which is a provocative test for measurement of FSH, are widely used for screening ovarian reserve. The CCCT involves oral administration of 100 mg clomiphene citrate on cycle days 5-9 with measurement of day 3 and day 10 FSH levels and day 3 estradiol levels.

The basis of these tests is that women with good ovarian reserve have sufficient production of ovarian hormones from small follicles early in the menstrual cycle to maintain FSH at a low level. In contrast, women with a reduced pool of follicles and oocytes have insufficient production of ovarian hormones to provide normal inhibition of pituitary secretion of FSH, so FSH rises early in the cycle.

Meta-analyses of nonrandomized studies concluded that basal cycle day 3 FSH and the CCCT testing perform similarly for predicting ability to achieve a clinical pregnancy in women undergoing infertility treatment. With either test, a normal result is not useful in predicting fertility, but a highly abnormal result (FSH > 20 mIU/mL) suggests that pregnancy will not occur with treatment involving the woman's own oocytes.

Elevated basal estradiol levels are due to advanced premature follicle recruitment that occurs in women with poor ovarian reserve. High estradiol levels can inhibit pituitary FSH production and thus mask one of the signs of decreased ovarian reserve in perimenopausal women. Thus, measurement of both FSH and estradiol levels helps to avoid false-negative FSH testing.

According to the ASRM Clinical Practice Document, clomiphene challenge testing is not helpful to assess ovarian reserve and is not recommended.

#### Dehydroepiandrosterone Sulfate (DHEAS)

Women with signs of androgen excess or menstrual irregularity should be tested with levels of total and calculated free testosterone, as well as 17-hydroxyprogesterone and dehydroepiandrosterone sulfate levels to rule out CAH or androgen-secreting tumors.

#### Luteinizing Hormone (LH)

The luteinizing hormone (LH) is produced by the pituitary gland. In women, LH stimulates estrogen and progesterone production from the ovary. A surge of LH in the mid-menstrual cycle is responsible for ovulation, and continued LH secretion subsequently stimulates the corpus luteum to produce progesterone. Development of the ovarian follicle is largely under FSH control, and the secretion of estrogen from this follicle is dependent on FSH and LH. The granulosa cells of the ovary secrete inhibin, which plays a role in cellular differentiation.

#### Post-Coital Test

Sperm-cervical mucus interaction identifies whether the problem is in the sperm or in the cervical mucus and is assessed in vivo by the post-coital test and in vitro by the slide or capillary tube tests.

The post-coital test suffers from poor reproducibility and its positive predictive value for pregnancy is no better than 50%. Utilizing the post-coital test leads to more tests and treatments but yields no improvement in cumulative pregnancy rates.

#### Progesterone Challenge Test

This is given to see if a woman is still secreting estrogen. It consists of doses of progesterone given over a 10-day period. When the reproductive anatomy of a woman is normal, the absence or the loss of ovulation is usually caused by a hormonal condition. If estrogen is present, the progestin challenge test will then trigger a menstrual period in the woman. This situation is called ovulation, in which case estrogen levels are typically normal.

### **Laboratory Tests for Males**

#### Semen Analysis

The semen analysis is the cornerstone of the assessment of the male partner of an infertile couple. In addition to the standard analysis, specialized analyses can be performed in some laboratories. The semen sample should be collected after 2-7 days of abstinence and should be submitted to the laboratory within 1 hour of collection.

The semen analysis is the cornerstone of the assessment of the male partner of an infertile couple. In addition to the standard analysis, specialized analyses can be performed in some laboratories. The standard semen analysis consists of the following:

1. Measurement of semen volume and pH
2. Microscopy for debris and agglutination
3. Assessment of sperm concentration, motility, and morphology
4. Sperm leukocyte count
5. Search for immature germ cells

Because of the marked inherent variability of semen analyses, at least 2 samples should be collected 1-2 weeks apart. The semen analysis should be performed using standardized methods. In addition, the laboratory should employ internal quality control measures and participate in external quality control programs.

#### Sperm Autoantibodies

Sperm autoantibodies are present in about 4%-8% of subfertile men. The presence of agglutination in the initial semen analysis suggests sperm autoimmunity; this should be confirmed by the mixed antiglobulin reaction or the immunobead test, both of which detect sperm surface antibodies. Antibodies are considered clinically important when over 50% of the spermatozoa are coated with them and when the spermatozoa fail to penetrate preovulatory human cervical mucus or demonstrate impaired fertilizing capacity. Studies suggest use of new proteomic analyses to assess such antibodies may provide a greater understanding of this disorder.

#### Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

In men, LH stimulates testosterone production from the interstitial cells of the testes (Leydig cells). FSH stimulates testicular growth and enhances the production of an androgen-binding protein by the Sertoli cells, which are a component of the testicular tubule necessary for sustaining the maturing sperm cell. This androgen-binding protein causes high local concentrations of testosterone near the sperm, an essential factor in the development of normal spermatogenesis. Sertoli cells, under the influence of androgens, also secrete inhibin, a polypeptide, which may help to locally regulate spermatogenesis. Hence, maturation of spermatozoa requires FSH and LH.

#### Post-Ejaculatory Urinalysis (PEU)

This test is done to see whether or not some or all of the sperm is ejaculated backward into the bladder, a condition known as retrograde ejaculation. To perform this test, it is necessary for a man to provide a semen sample and, immediately afterwards, a urine sample. This post-ejaculatory urine is then examined for the presence of sperm.

#### Semen Culture

Semen culture is frequently performed in men whose semen samples contain inflammatory cells to diagnose bacterial contamination of the semen.

### **Procedural Tests for Females**

#### Diagnostic Laparoscopy with or without Chromotubation

The diagnosis and severity of endometriosis are established by laparoscopy and biopsy using the revised American Fertility Society system, which classifies the severity of endometriosis into 4 stages: stage I (minimal), stage II (mild), stage III (moderate); and stage IV (severe). This classification system is widely used and includes visual assessment, which is subject to inter- and intra-observer error. However, disease severity has not been shown to predict the chance of pregnancy.

Laparoscopy is indicated in women with a suspicion of endometriosis (dysmenorrhea, pelvic pain, deep dyspareunia) or pelvic adhesions/tubal disease (history of pelvic pain, complicated appendicitis, pelvic infection, pelvic surgery, or ectopic pregnancy) based on history, physical examination, or hysterosalpingogram (HSG). When laparoscopy is performed, chromotubation is also performed simultaneously to assess tubal patency and hysteroscopy to evaluate the uterine cavity. For this reason, if laparoscopy is planned, then HSG can be omitted.

The advantage of performing laparoscopy early in the evaluation of women suspected of having endometriosis or pelvic adhesions is that surgical therapy can be initiated, while avoiding potentially ineffective or unnecessary empiric medical treatment for ovulation induction. Endometriosis, if identified, can be excised or ablated at the time of the diagnostic procedure and pelvic adhesions can be lysed.

#### Endometrial Biopsy



This test is designed to evaluate the endometrial lining of the uterus and historically to obtain an objective assessment of ovulation or to rule out luteal phase defect (LPD). LPD is defined as either a short luteal phase (less than 12 days) which is the second part of the menstrual cycle after ovulation and until menstruation or inadequate progesterone production. Currently, LPD diagnosis is questionable and the practice of doing an endometrial biopsy solely to document ovulation is no longer acceptable. The most common reason for an endometrial biopsy is to rule out precancerous growth in the uterine cells called endometrial hyperplasia or endometrial cancer.

#### Hysterosalpingography

Hysterosalpingogram (HSG) is usually done in all patients to look for tubal occlusions, unless laparoscopy is planned. Either water or lipid soluble contrast media can be used. HSG also provides information about the uterine cavity. Women with abnormalities on HSG should be referred to a reproductive endocrinologist to discuss treatment options. HSG is not useful for detecting peritubal adhesions or endometriosis.

A meta-analysis of 20 studies involving 4,179 patients compared HSG and laparoscopy with chromotubation (the gold standard); the calculated sensitivity and specificity for diagnosis of tubal patency were only 65% and 83%, respectively. However, when subgroups of women undergoing HSG were analyzed, HSG appeared to have very high specificity and sensitivity for diagnosing distal tubal occlusion or major distal tubal adhesions, but much lower specificity for diagnosing proximal tubal occlusion.

Proximal tubal occlusion on HSG often represents testing artifact due to tubal spasm or poor catheter positioning leading to unilateral tubal perfusion. Given these deficiencies, findings of proximal tubal occlusion on HSG could be confirmed by a secondary test such as a repeat HSG, fluoroscopic or hysteroscopic selective tubal perfusion, or laparoscopic chromotubation if definitive diagnosis will influence further management.

Diagnostic HSG also appears to have therapeutic effects. A systematic review of 12 randomized trials found that pregnancy rates were significantly higher in subfertile women who underwent tubal flushing with oil soluble media than in those who did not undergo HSG (OR 3.30, 95% CI 2.00-5.43), and that pregnancy rates were similar whether oil or water soluble media were used (OR 1.21, 95%CI 0.95-1.54).

#### Hysteroscopy

Uterine abnormalities such as adhesions, polyps, submucous leiomyomas and septae have been found in 10%-15% of women seeking treatment for fertility problems. Compared with HSG, hysteroscopy is recognized as the 'gold standard' test for identifying uterine abnormalities as it allows direct visualization of the uterine cavity.

Opinions differ as to whether hysteroscopy should be considered as a routine investigation in addition to HSG and laparoscopy and dye in the infertile couple. A causal relationship between leiomyoma and infertility has not been established. In women undergoing assisted reproduction, the presence of uterine leiomyoma is associated with a reduced chance of clinical pregnancy or delivery. However, the effectiveness of surgical treatment of uterine abnormalities to enhance pregnancy rates is not established.

#### Salpingoscopy

Salpingoscopy is an endoscopic technique that allows direct evaluation of the ampullary tubal mucosa at the time of laparoscopy. It has been reported that the presence of ampullary mucosal adhesions can negatively affect reproductive outcome and increase the risk of ectopic tubal pregnancy. Various studies have suggested that the extent of intra-luminal adhesions may not correlate with the nature and extent

of periadnexal adhesions. Further studies on salpingoscopic and laparoscopic correlations with regard to fertility outcome have been reported in the literature. Recently microsalingoscopy has been introduced, with the number of nuclei stained by methylene blue dye employed as a prognostic factor of conception in women with infertility. As an alternative to salpingoscopy performed during laparoscopy, which requires hospitalization and general anesthesia, 2 groups have described salpingoscopy as an office procedure performed during transvaginal hydrolaparoscopy or in conjunction with fertiloscopy.

The prognostic value of salpingoscopy during operative laparoscopy for tubal factor infertility in terms of reproductive outcome has been confirmed. The prognostic significance of microsalingoscopy needs further validation in large-scale clinical trials. Transvaginal hydrolaparoscopy and fertiloscopy appear to be an alternative to hysterosalpingography as a first line procedure to investigate female infertility.

#### Sonohysterography

Saline infusion sonohysterography refers to a procedure in which fluid is instilled into the uterine cavity transcervically to provide enhanced endometrial visualization during transvaginal ultrasound examination. The technique improves sonographic detection of endometrial pathology, such as polyps, hyperplasia, cancer, leiomyomas, and adhesions. In addition, it can help avoid invasive diagnostic procedures in some patients as well as optimize the preoperative triage process for those women who require therapeutic intervention. It is easily and rapidly performed at minimal cost, well-tolerated by patients, and is virtually devoid of complications. Saline infusion sonohysterography is useful for detecting potential anatomic causes of reduced fertility, such as submucous myomas, endometrial polyps, anomalies, and intrauterine adhesions and appears comparable to or better than hysterosalpingography (HSG) or hysteroscopy. However, an outline of the fallopian tubes (as seen with HSG) is not observed with sonohysterography. Accretion of instilled fluid in the posterior cul-de-sac is a sign of patency of at least 1 tube.

#### Ultrasound (i.e., serial transvaginal, pelvic, ovarian)

Compared with bimanual pelvic examination, transvaginal ultrasound enables pelvic anatomy to be identified with more accuracy and reliability. Ultrasound can be used in the evaluation of pelvic pathology, such as endometriosis, endometrioma, cysts, polyps, leiomyoma, adnexal and ovarian abnormality, where such abnormalities are present. The diagnostic criteria for polycystic ovaries and polycystic ovary syndrome (PCOS), in which ultrasonic parameters have an important role, have been evolving over many years, and have recently been clarified in an international consensus statement.

### **Procedural Tests for Males**

#### Karyotyping for Chromosomal Abnormalities

Karyotyping as a screening test for male or female is not indicated as part of the initial evaluation because of the low incidence of abnormalities.

Karyotype and Y-chromosome microdeletion analysis should be recommended for men with primary infertility AND azoospermia or severe oligozoospermia (<5 million sperm/mL) with elevated FSH or testicular atrophy or a presumed diagnosis of impaired sperm production as the cause of azoospermia.

Karyotype may be useful in male and female patients who have failed initial treatment approaches and plan to undergo in vitro fertilization (IVF), although the cost-effectiveness of universal karyotype screening prior to IVF has not been established.

#### Scrotal Exploration

Scrotal evaluations may reveal testicular defects, obstruction, or congenital defects of vas deferens to determine the location of the obstruction and attempt to correct it. This is major surgery, with all of its risks. It is an outpatient surgery procedure usually performed under general anesthesia. The variation in

cost will generally reflect the complexity of the repair and the time required to perform the operation, from 1 ½-5 hours. Before the scrotal exploration, the urologist may recommend a biopsy of the testicle as a separate procedure to determine if enough sperm are present before proceeding on to the more serious scrotal exploration. The biopsy is also an outpatient procedure that can be performed under either local or general anesthesia.

### Scrotal Ultrasound

Ultrasound (US) is a readily available and relatively inexpensive imaging modality that can be performed on patients at any age without the need for sedation or any other pretest preparation. US examinations are safe and there is no significant biologic risk from radiation exposure. Gray-scale US provides high-resolution depiction of scrotal anatomy and Doppler technique demonstrates perfusion.

Different pathologies of the scrotum may have similar clinical presentation, such as acute scrotal pain or scrotal mass. US of the scrotum can better guide treatment by improving the definition of the scrotal pathology. For these reasons, US became the imaging modality of choice for evaluation of scrotal pathology, and, in most cases, US is the first and only imaging needed for evaluation of scrotal pathology. This test uses high-frequency sound waves to produce images inside the body. A scrotal ultrasound can help find evidence of a varicocele or obstruction of the part of the testicle that stores sperm (epididymis). A small wand is moved over the surface of the scrotum to produce images on a video screen.

### Sperm Penetration Assay (SPA)

Originally, the SPA, also known Zona-free hamster oocyte penetration test was used primarily as a diagnostic technique for male infertility. More recently, the advent of sperm micromanipulation techniques, specifically ICSI, has changed the role of IVF and changed the role of SPA. IVF was originally developed as a treatment option for women with irreversible tubal damage, but the development of sperm micromanipulation techniques as an adjunct to IVF has now expanded the indications for IVF to those with severe male factor infertility. Thus, SPA can be used to identify those normospermic patients who would benefit from ICSI or other adjuncts to IVF. In 2001, Freeman et al. reported on the diagnostic accuracy of sperm penetration assay in predicting success of in vitro fertilization. Among 216 couples, the sperm penetration assay predicted IVF with high negative (84%) and positive (98%) predictive value, with correct prediction in 88% of cycles. While there is still concern regarding standardization of the procedure, these results suggest that the results of the SPA can be used to select patients for ICSI.

### Testicular Biopsy

Diagnostic testicular biopsy is 1 parameter for determining the testicular histopathology pattern and apparently it is the strongest indicator to foresee the possibility of finding sperms in the testis. Identification of the border line between normal and disturbed spermatogenesis substantiate the diagnosis of impaired male fertility. In the past, testicular biopsy was reserved for azoospermia patients with a normal-sized testis and normal findings on hormonal studies to evaluate for ductal obstruction. Azoospermic men with testicular failure (non-obstructive azoospermia) have either Sertoli cell only pattern, maturation arrest or hypospermatogenesis on testis biopsy. Until recently it was assumed that men with non-obstructive azoospermia were untreatable. The discovery that azoospermic men with germinal failure often have minute foci of spermatogenesis was observed in the early studies of quantitative analysis of spermatogenesis. However, testicular biopsy is now also an invaluable procedure for further workup of the infertile male and for therapeutic sperm retrieval in assisted reproductive techniques. One study confirms that testicular biopsy is an important tool in the investigation and the assessment of male infertility as it provides some light on the etiology as well as providing essential prognostic information of azoospermic men in Egypt. The most common finding in

this series was that of normal testis denoting obstruction (24%), while among cases of functional azoospermia, Sertoli cell only (34%) and spermatogenic arrest (28%) was the most frequent.

#### Transrectal Ultrasound (TRUS)

TRUS has replaced incisional vasography as diagnostic technique of choice in the evaluation of male pelvic reproductive anatomy. This is due in part to urologist's overall familiarity with TRUS for prostate anatomy and biopsies, along with the superb visual resolution of seminal vesicle and ejaculatory duct anatomy that TRUS provides.

TRUS is commonly performed with a high resolution 6.5-7.5 MHz probe with the patient's bladder partially filled to maximize bladder, perivesical and seminal vesicle anatomy. TRUS is most commonly obtained if the diagnosis of ejaculatory duct obstruction is being considered. As such, TRUS is indicated in infertile patients with low volume azoospermia and low volume oligoasthenospermia as well in men with painful ejaculation or recurrent hematospermia. As outlined in, several characteristic TRUS findings are highly suggestive of ejaculatory duct obstruction. These findings are derived from the normal anatomical findings described in fertile men, cadavers and prostatectomy patients. It is important to remember that these findings can be unilateral or bilateral.

#### Vasography

A vasogram involves the injection of dye or contrast media into the vas deferens to determine whether a physical obstruction exists in the vas deferens, seminal vesicles or ejaculatory ducts. Although bowing to TRUS as the first line diagnostic procedure in the setting of ejaculatory duct obstruction, it remains the "gold standard" procedure for diagnosis of pelvic, inguinal or scrotal vasal obstruction. Vasography can be performed in either an antegrade (testis to prostate) or retrograde (prostate to testis) fashion, by transrectal, transperineal, transurethral or transscrotal routes. The most reliable approach is transscrotal, but this procedure is also the most invasive as it involves a vasotomy, either microsurgical or by puncture. The risk of vasal scarring that attends this approach has led investigators to consider other, less invasive measures such as TRUS guided procedures to garner similar information.

#### Y-chromosome Microdeletion Testing in Males with Nonobstructive Azoospermia or Severe Oligospermia

Males with non-obstructive azoospermia should have genetic testing before proceeding to assisted reproductive technologies. Genetic disorders may be characterized as karyotype abnormalities. In some men, microdeletions of the Y chromosome contribute to azoospermia. Male offspring born to fathers of Y-chromosome microdeletion are expected to inherit these deletions. Counseling regarding genetic issues should be a critical part of the male evaluation.

### **Fertility Treatments for Females**

#### 17-alpha-hydroxyprogesterone caproate

Weekly injections of 17 alpha-hydroxyprogesterone caproate between 16 and 36 weeks of gestation may be considered medically necessary in pregnant women with a prior history of a preterm delivery before 37 weeks gestation.

Daily vaginal progesterone suppositories 24-34 weeks gestation may be considered medically necessary in pregnant women with a prior history of preterm delivery before 37 weeks gestation, a prior cervical cerclage or a uterine anomaly.

#### Artificial Insemination (intrauterine) [IUI]

Intrauterine insemination (IUI) is a procedure in which processed and concentrated motile sperm are placed directly into the uterine cavity. IUI is useful in couples with severe sexual dysfunction since coitus can be avoided. Its advantages in cervical factor and male factor infertility are that sperm bypass

potentially hostile cervical factors and the number of sperm that gain access to the uterine cavity is enhanced. In women undergoing ovulation induction, randomized trials have reported higher pregnancy rates with ovulation induction combined with IUI compared with ovulation induction alone, or with timed intercourse.

IUI is contraindicated in women with an active cervical, intrauterine, or pelvic infection. This would be in the setting of a recently documented or diagnosed infection, or if there were concern at time of IUI, such as purulent discharge from the cervix or recent exposure to a sexually transmitted disease.

The cumulative pregnancy rate after IUI generally ranges from 5%-20%; the reported range varies widely and depends upon multiple factors. Lower pregnancy rates may occur when there has been a longer duration of infertility, female age is over 40 years, or in the presence of severe male factor infertility. Higher pregnancy rates have been documented when ovulation induction was combined with IUI. This increase in pregnancy rates appears to be due to an increase in the number of mature oocytes available for fertilization, but multiple gestation rates were also increased to 10%-40%.

#### Assisted Embryo Hatching

Assisted hatching is a technique performed to enhance the likelihood that the transferred embryo will implant in the uterus and establish a viable pregnancy. The technique involves in vitro disruption of the zona pellucida surrounding the embryo so that the embryo can "escape" and implant into the uterine wall. Assisted hatching has also been referred to as zona drilling and partial zonal dissolution. Assisted hatching is commonly performed as part of an IVF procedure in women over 40, who have a decreased incidence of implantation after embryo transfer, and in women with prior failed IVF cycles due to failed implantation.

#### Cryopreservation of Embryos

If there are embryos that are not needed for transfer in the current cycle, cryopreservation may be used. This is a process in which the embryos are frozen in liquid nitrogen and may be thawed for future use. A significant percentage of embryos do not survive the process of freezing and thawing, however. Cryopreservation may result in hardening of the zona pellucida which may affect hatching and implantation of blastocyst. Some embryos lose 1 or more blastomeres after thawing and are referred to as "partially damaged" embryos. While partially damaged embryos can give rise to term pregnancy, authors agree that the developmental potential of these embryos is inferior to those that are fully intact. Some authors have reported that laser-assisted removal of necrotic blastomeres from partially damaged cryopreserved embryos before embryo transfer increases embryo development potential.

Available data on the effects of cryopreservation of embryos did not indicate any apparent negative impact on perinatal outcome, early infant development or congenital malformation rate. A retrospective study compared babies (n = 283) from births from cryopreserved embryos with babies (n = 961) after conventional IVF. There was no difference in the incidence of twins, triplets, their mean gestational age, birth weight and perinatal mortality rates between the 2 groups. The incidence of major congenital malformations was significantly lower in the cryopreserved group (1%) than in the IVF group (3%). One study matched 255 children from cryopreserved embryos for maternal age, parity, single or twin pregnancy and date of delivery with 255 children born after standard IVF with fresh embryos and 252 children from spontaneous pregnancies. The incidence of major malformations and the prevalence of chronic diseases at 18 months were similar in all 3 groups.

#### Fimbrioplasty

Fimbrioplasty is performed for treatment of partial obstruction of the distal end of the fallopian tube. The tube is patent, but there are adhesive bands that surround the terminal end. The longitudinal folds of the tube are usually preserved. Fimbrioplasty involves dividing the peritoneal adhesive bands that

surround the fimbria. Gentle introduction of an alligator laparoscopic forceps into the tubal ostium followed by opening and withdrawal of the forceps helps to stretch the tube and release minor degrees of fimbrial agglutination.

In one series of 35 infertile women with severe fimbrial occlusions treated with laparoscopic fimbrioplasty, the intrauterine pregnancy rate was 51%, the live birth rate was 37%, and the ectopic pregnancy rate was 23% after 2 years follow-up. Another study found similar outcomes after fimbrioplasty or salpingostomy: the pregnancy and fecundity rates after laparoscopic fimbrioplasty were 40% and 4%, respectively, compared to 56% and 16% following salpingostomy. The overall ectopic pregnancy rate was about 5%. It appears that the results of salpingostomy are equivalent to that of fimbrioplasty. The latter procedure results in more normal tubal anatomy.

#### Fluoroscopic/Hysteroscopic Selective Tube Cannulation

Obstruction of the fallopian tube close to its insertion into the uterus, which is conventionally termed "proximal," is the most treatable because it often occurs because of the accumulation of mucus or debris, which forms an impacted plug in the interstitial or proximal isthmic portion of the tube. Fallopian tube catheterization has developed as an extension of hysterosalpingography. Tubal cannulation results in improved visualization of the fallopian tube anatomy. It is also a treatment for infertility caused by proximal tubal obstruction (10%-20% of patients with tubal disease).

Tubal cannulation has almost eliminated the real and false diagnosis of unilateral tubal occlusion, identified patients with proximal and distal occlusion ("bipolar tubal occlusion"), and eliminated or postponed the need for a costly hysteroscopy or laparoscopy. Distal obstruction in the tube is caused by fibrosis and peritubal disease, which are not amenable to catheter recanalization techniques.

The procedure should not be performed if catheterization is unlikely to be successful, such as patients with Müllerian anomaly, cornual fibroids, or severe salpingitis isthmica nodosa (SIN). Both wire recanalization and balloon tuboplasty yield 80%-90% tubal patency, and 40%-50% 6-month pregnancy rates in selected patients. In summary, the tubal cannulation and easy to perform coaxial system allows versatile diagnosis and treatment of cornual tubal occlusion, as well as isthmic tubal obstruction.

Occlusion that develops more distally in the isthmus, or in the ampullary or fimbriated portions of the tube is commonly due to previous pelvic infection or endometriosis. It is more difficult to recanalize and patients are less likely to have a successful intrauterine pregnancy. To estimate the potential impact of fallopian tube recanalization (FTR) depends on the percentage of cases in which the occlusion is proximal. Early figures ranged between 20%-25%, meaning that the number of potentially treatable patients in the U.S. may be as high as 230,000. However, since the overall incidence of tubal disease in the 2 populations is similar (219 patients or 44%), the implication is that the number of treatable patients in the U.S. may be only 140,000 or less.

There is no agreement between gynecologists and radiologists regarding the proper sequence for diagnosing and treating obstructed fallopian tubes, nor is there a consensus within either of those 2 disciplines. There are also no established reporting standards, so it is difficult to make accurate comparisons between techniques, success rates, and treatment strategies. Pregnancy rates vary widely among authors, not so much because of differences in technique, but because of how the results are reported.

#### Gamete Intrafallopian Transfer (GIFT), Pronuclear Stage Transfer (PROST), or Natural Cycle IVF

The GIFT procedure is also called pronuclear stage transfer (PROST), or natural cycle IVF. In GIFT, the egg cells are retrieved laparoscopically and transferred to the fallopian tubes using a catheter containing 2-3 egg cells and approximately 100,000 sperm. Unfertilized oocytes are mixed with sperm and transferred

back into the tubes. Fertilization occurs in the body as in unassisted reproduction, as compared to IVF in which fertilization occurs outside the body. Indications for GIFT are the same as for IVF, except that the woman must have 1 patent fallopian tube. Reported pregnancy rates are comparable to those associated with IVF.

In vitro fertilization (IVF) refers to a procedure designed to overcome infertility and produce a pregnancy as a direct result of the intervention. In general, the ovaries are stimulated by a combination of fertility medications and then 1 or more oocyte(s) are aspirated from ovarian follicles. These are fertilized in the laboratory ("in vitro"), after which, 1 or more embryo(s) are transferred into the uterine cavity. These steps occur over about a 2 week interval of time, which is called an IVF cycle.

The first pregnancy after the fertilization of a human egg in vitro and the first birth from an in vitro-fertilized embryo were reported more than 2 decades ago. Since then, a few million pregnancies have been achieved worldwide by IVF and its modifications known generically as assisted reproductive technologies (ARTs). As experience has accumulated, success rates have increased, and the indications for these procedures have expanded, ART now accounts for 1%-3% of live births in the United States and Europe.

A complete infertility evaluation should be performed on both partners prior to embarking on IVF.

The initial experience with IVF involved women with tubal disease that could not be surgically corrected. With its efficacy established, IVF has been made available to women with other causes of infertility.

Indications for IVF include:

- Tubal factor
- Ovulatory dysfunction (after failing treatment with less invasive therapies)
- Diminished ovarian reserve
- Endometriosis (after failing treatment with less invasive therapies)
- Severe male factor infertility
- Ovarian failure
- Unexplained infertility (after failing treatment with less invasive therapies)

The use of IVF in these subgroups of patients is discussed in detail in the individual topics reviews listed above.

Disadvantages of IVF include the high cost, the need for procedures and drugs associated with some risk to the woman, an increased rate of multiple gestations (which accounts for much of the direct cost of pregnancies conceived via IVF, and possibly a slight increase in fetal complications. Therefore, alternative treatment options, including observation, should be considered when counseling women with open fallopian tubes and without severe male factor infertility. Although such women may have some indications for IVF (e.g., pelvic disease, endometriosis, unexplained fertility, failed gonadotropin/intrauterine insemination therapy), they also have substantial treatment-independent pregnancy rates. In young women, treatable causes of subfertility should be treated prior to initiating IVF because treatment may enhance the likelihood of natural conception. In general, in the absence of absolute impediments for conception (blocked fallopian tubes, severe male factor), couples may be offered 3-6 cycles of superovulation and intrauterine insemination (IUI) before proceeding to IVF. A reasonable course when counseling young couples with no clear block to conception is to complete a total of 1 year of unprotected intercourse and 1 year of conventional treatment, since conception is quite likely during this time (about 85% conceive during the first year and a further 50% during the second year). A shorter period is generally used in older couples, as conventional treatment is less successful and time plays a

much greater role in the probability of conception. It is not unreasonable to offer IVF as a primary treatment option to couples with the female partner over 40 years of age.

#### In Vitro Fertilization with Embryo Transfer (IVF-ET)

The technique of IVF-ET is now being widely used to treat infertility. Although the method was originally restricted to women who had no functioning oviducts as a result of severe tubal disease, it is now being used for women with severe endometriosis and couples with male factor or unexplained infertility. Because the rate of pregnancy after IVF is directly related to the number of embryos placed in the uterine cavity, nearly all IVF clinics currently utilize some form of ovarian hyperstimulation to increase the number of oocytes obtained at the time of follicle aspiration. Stimulation protocols utilizing clomiphene citrate, HMG or FSH, or a combination of agents are being used. These agents are usually given after a period of suppression with a GnRH agonist. GnRH antagonists are increasingly being used only at mid-cycle, particularly in older women with poor responses. Monitoring of follicle growth is usually performed by both daily ultrasonography and estrogen measurement.

A few hours after egg retrieval, sperm that has been separated from semen are added to the culture medium. About 18 hours later the oocytes are observed to determine if fertilization has occurred. The oocytes that are fertilized are then cultured for an additional 48-96 hours, and from 1-4 normally cleaving embryos are then placed into the uterus of the patient in a sterile environment without the use of general anesthesia. Embryo placement is performed through a small catheter placed through the cervical canal. With the development of sequential culture media it has become possible to allow embryos to develop in vitro to the blastocyst stage, 5 days after fertilization, prior to transfer into the endometrial cavity. Several centers report per cycle pregnancy rates of 40%-60% with blastocyst culture and transfer. Most centers are freezing the embryos not utilized and transferring them in subsequent spontaneous ovulatory cycles, if pregnancy does not occur in the initial treatment cycle.

#### Intracytoplasmic Sperm Injection (ICSI)

ICSI is a laboratory procedure developed to assist couples who are undergoing IVF for severe male factor infertility. The ICSI procedure is used in conjunction with IVF, GIFT and zygote intrafallopian transfer (ZIFT). This procedure has replaced 2 previously developed micromanipulation techniques, partial zona dissection (PZD) and subzonal insertion (SUZI) because it achieves higher fertilization rates. ICSI involves the injection of a single sperm directly into the cytoplasm of an oocyte. Several studies have demonstrated efficacy and short-term safety of ICSI.

It should be noted that in the United States, the reported risk of multiple gestations after ICSI is 30%-35% for twin gestations and 5%-10% for triplet or higher-order gestations. Some conditions may carry an increased risk for transmission of genetic abnormalities to offspring via ICSI. Whether the increased prevalence is related to the procedure or to the characteristics of couples who require ICSI is unclear. Genetic counseling may be appropriate in selected cases.

#### Low Tubal Ovum Transfer (LTOT)

A partial alternative to IVF, the ovum is aspirated from the dominant follicle during laparoscopy immediately preceding the expected time of ovulation, and injected back into the lumen of the fallopian tube above the utero-tubal junction (for upper tubal obstruction). After being mated, high number of pregnancies prevailed, thereby preserving the efficiency and safety inherent to in vivo fertilization.

#### Lysis of Adhesions

Pregnancy can occur in women with periadnexal adhesions, but the pregnancy rate appears to be higher in those who undergo adhesiolysis. In the only controlled study examining this issue, salpingo-ovariolysis was performed in 69 infertile women with pelvic adhesions, while 78 women with a similar degree of adhesions were not treated. The cumulative pregnancy rate at 24 months follow-up was significantly



higher in treated women, 45% vs.16% in the untreated group. Although adhesiolysis was done at laparotomy, equivalent results can be expected with laparoscopic adhesiolysis.

### Myomectomy

Myomectomy is the surgical removal of fibroids from the uterus. It allows the uterus to be left in place and, for some women, makes pregnancy more likely than before. Myomectomy is the preferred fibroid treatment for women who want to become pregnant. After myomectomy, chances of pregnancy may be improved but are not guaranteed.

Before myomectomy, shrinking fibroids with gonadotropin-releasing hormone analogue (GnRH-a) therapy may reduce blood loss from the surgery. GnRH-a therapy lowers the amount of estrogen the body makes. If patients have bleeding from a fibroid, GnRH-a therapy can also improve anemia before surgery by stopping uterine bleeding for several months.

### Ovarian Drilling and Wedge Resection

The traditional surgical treatment for PCOS was ovarian wedge resection. The procedure was performed by excising approximately one third of the ovary via laparotomy. In an initial series of 108 patients undergoing bilateral ovarian wedge resection, regular menstrual cyclicality was restored in 95% of patients, with a pregnancy rate of 85%. Subsequent reports confirmed the benefits of the procedure, with varying rates of success. However, it became clear that wedge resection was often associated with development of periadnexal adhesions, thus obviating the beneficial effects of surgery. Ovarian wedge resection can also be performed laparoscopically. One small series of 25 patients reported a pregnancy rate of 60%; however, 36% of patients developed postoperative adhesions, again negating some of the benefits of the surgery. In addition, ovarian resection, whether performed laparoscopically or by laparotomy, is associated with substantial tissue loss. Instances of premature ovarian failure have been described, rendering the procedure obsolete by any approach.

Laparoscopic ovarian drilling is a modification of the ovarian wedge resection. Multiple holes are made on the surface of the ovary using either laser or electrocautery. This results in a decrease in circulating androgen levels, with resumption of cyclic ovulation.

### Ovulation Induction Medications

Ovulatory disorders can be identified in the woman in 18%-25% of couples presenting with infertility. Most of these women have oligomenorrhea, arbitrarily defined as menstruation that occurs at intervals of 35 days to 6 months. While ovulation may occasionally occur, spontaneous conception is unlikely.

Induction of ovulation in these women is aimed at inducing monofollicular development, subsequent ovulation and ultimately pregnancy and birth of a healthy newborn. Induction of ovulation should be differentiated from stimulation of multiple follicle development in ovulatory women, as is done with assisted conception techniques.

The mechanism of action of antiestrogens is unclear. These agents are thought to occupy estrogen receptors in the hypothalamus and pituitary, thereby blocking the negative feedback action of estradiol. Thus, the main mechanism appears to be a rise in serum FSH concentrations by around 50%, resulting in stimulation of follicle growth and follicular estradiol production. However, other mechanisms, such as induced changes in the insulin-like growth factor system and SHBG levels, may also contribute.

### ANTIESTROGEN THERAPY

Clomiphene citrate (CC) is the most widely used antiestrogen for ovulation induction and is most effective in normogonadotropic anovulatory women.

Correction of hyperinsulinemia with metformin has been shown to have a beneficial effect in anovulatory women with PCOS by increasing menstrual cyclicity and improving spontaneous ovulation. However, it does not appear to improve live birth rates.

Aromatase inhibitors (Letrozole and anastrozole) are a class of drugs that block the conversion of testosterone and androstenedione to estradiol and estrone, respectively (unlike clomiphene which blocks estrogen action), thereby reducing negative estrogenic feedback at the pituitary. In contrast to CC, they appear to be free of the adverse effects on endometrial and cervical mucus attributed to clomiphene citrate.

#### GONADOTROPIN THERAPY

Since their introduction into clinical practice in 1961, gonadotropins extracted from the urine of postmenopausal women (human menopausal gonadotropins [hMG]), in which the ratio of LH to FSH bioactivity is 1:1, have assumed a central role in ovulation induction. Refinement of the initially crude preparation resulted in the availability of purified and highly purified urinary FSH. Since 1996, recombinant human FSH (rFSH, > 99% purity) has been available. Recombinant preparations are appealing due to their ease of administration (subcutaneous rather than intramuscular).

The aim of ovulation induction with gonadotropins, as with clomiphene, is the formation of a single dominant follicle. In spontaneous cycles, this is achieved at the beginning of the cycle by a transient increase in serum FSH concentrations above the threshold value. The concentrations then decrease, preventing more than 1 follicle from undergoing pre-ovulatory development. Because ovarian sensitivity to FSH stimulation varies among individual women, specific treatment and monitoring protocols are needed to achieve development of a single follicle when exogenous gonadotropin is administered.

In the conventional gonadotropin protocol, the starting dose of FSH is 150 int. units/day. However, this regimen is associated with a multiple pregnancy rate of up to 36% and ovarian hyperstimulation occurs in up to 14% of treatment cycles.

In patients with PCOS, who are at particular risk for complications, this approach has been largely abandoned in favor of a low-dose, step-up protocol designed to allow the FSH threshold to be reached gradually, minimizing excessive stimulation and therefore the risk of development of multiple follicles. In this protocol, the initial subcutaneous or intramuscular dose of FSH is 37.5-75 int. units/day; the dose is increased only if, after 14 days, no response is documented on ultrasonography and serum estradiol monitoring. Increments of 37.5 int. units then are given at weekly intervals up to a maximum of 225 int. units/day. Other clinicians choose to increase the FSH dose if there is no ovarian response after 5-7 days. The optimal interval for increasing the dose has not been well studied in PCOS patients.

The detection of an ovarian response is an indication to continue the current dose until human chorionic gonadotropin (HCG) can be given to trigger ovulation.

The low-dose step-down protocol of ovulation induction mimics more closely the physiology of normal cycles. Therapy with 150 int. units FSH /day is started shortly after spontaneous or progesterone-induced bleeding and continued until a dominant follicle (> 10 mm) is seen on transvaginal ultrasonography. The dose is then decreased to 112.5 int. units/day followed by a further decrease to 75 int. units/day 3 days later, which is continued until HCG is administered to induce ovulation. The appropriate starting dose can be determined by using the low-dose step-up regimen for the first treatment cycle.

The degree to which the type of FSH compound employed may influence outcome of ovulation induction remains the subject of controversy. Two meta-analyses comparing the effectiveness of daily

urinary FSH (uFSH) to daily human menopausal gonadotropin (HMG) for inducing ovulation in women with PCOS who had not responded to clomiphene citrate demonstrated no difference in pregnancy rate per treatment cycle. However, the women given FSH were less likely to have ovarian hyperstimulation syndrome.

In a meta-analysis of randomized controlled trials comparing recombinant human FSH (rhFSH) with uFSH for ovulation induction in women with clomiphene citrate-resistant PCOS, no significant differences were demonstrated for the ovulation rate (OR 1.19; 95% CI 0.78-1.80). Furthermore, the odds ratios for pregnancy rate (0.95; 95% CI 0.64-1.41), miscarriage rate (1.26; 95% CI 0.59-2.70), multiple pregnancy rate (0.44; 95% CI 0.16-1.21) and for ovarian hyperstimulation syndrome (1.55; 95% CI 0.50-4.84) showed no significant difference between rhFSH and uFSH.

Purified urinary FSH has some LH activity, but rFSH does not. The experience with rFSH in hypogonadotropic hypogonadal women indicates that those women who have very low serum LH concentrations (<0.5 int. units/L) need exogenous HCG (or 75 int. units/day sc recombinant LH) to maintain adequate estradiol biosynthesis and follicle development.

Long-acting recombinant FSH preparations are currently being studied, but are not yet commercially available.

Human chorionic gonadotropin (HCG) is used to trigger ovulation when the ovarian follicles are mature. Both urinary and recombinant HCG preparations are available. A dose of 250 mcg of recombinant HCG appears to be equivalent to the standard doses of urinary HCG (5,000-10,000 units).

Dopamine agonist drugs enhance the tonic suppression of prolactin synthesis and release from the pituitary, substituting for or supplementing endogenous dopamine. Bromocriptine, the first dopamine agonist drug to prove effective in the treatment of hyperprolactinemia, remains in widespread use. Drugs that bind more specifically to dopamine D2 receptors on the lactotroph cells, such as cabergoline are associated with fewer side effects. The safety of bromocriptine with regard to teratogenesis is much better established than that of cabergoline, so many physicians and patients prefer bromocriptine to attempt pregnancy, but patients who have severe side effects from bromocriptine prefer cabergoline.

However, cabergoline has been associated with a dose-dependent increase in valvular heart disease. Although most cases have occurred in patients taking high dose cabergoline for Parkinson's disease, long-term use of relatively low doses for hyperprolactinemia may also be associated with excess risk.

#### Ovulation Monitoring Studies

For couples pursuing pregnancy, the highest probability of conception appears to be with intercourse 1-2 days prior to ovulation. Therefore, attempting to identify the fertile period and timing intercourse during this interval maximizes the probability of conception. This can be inferred by comparing the results of the following studies: the first series consisted of 100 fertile couples who conceived without timed intercourse and reported pregnancy rates of 50% at 3 months, 75% at 6 months, and over 90% at 12 months. Whereas a second series of similar couples who used a method of fertility awareness with timed calendar and basal body temperature (BBT) methods, are not very reliable for identifying the fertile period because of normal variation in cycle length and because the temperature rise associated with ovulation occurs too late to be useful. Better alternatives are methods that have the woman examine her vaginal discharge for changes suggestive of a preovulatory estrogen effect, such as an increased volume of clear, stretchy, slippery mucus. Measurement of urinary luteinizing hormone is more expensive, but also effective.

The LH surge can be detected in either urine or serum samples. The LH surge appears in the urine within 12 hours after it appears in the serum; as a result, it can accurately predict ovulation and therefore the

optimal time for intercourse. The rise in serum LH typically occurs approximately 36 hours before the oocyte is released from the follicle into the fallopian tube. Women typically begin testing their urine 1 or 2 days before the expected surge, so that the increase over baseline levels can be clearly observed. Electronic monitors have been developed, which monitor both the estradiol and LH rise in urine to predict ovulation more precisely.

Any condition associated with elevated LH levels, such as polycystic ovary syndrome, premature ovarian failure, and menopause, can yield false positive results despite the absence of ovulation. Patients should be instructed in correct use of the kit as false positive interpretation of the LH surge occurs in 7% of cycles.

### Salpingectomy

There are several methods for total laparoscopic salpingectomy. One approach is to bring the fallopian tube through a pre-tied surgical loop using a grasping forceps and 2-3 laparoscopy ports. The knot is tightened and a second loop is similarly placed. The tube can then be resected and removed.

Alternatively, electrocautery can be used to fulgurate vessels in the mesosalpinx followed by resection of the specimen with scissors. The cornual portion of the tube is desiccated close to the uterus. It is important to elevate the tube when applying electrocautery to avoid inadvertently damaging the ovarian vessels. A partial or segmental salpingectomy can also be done.

Laparotomy is rarely performed due to the widespread acceptability of laparoscopy. Total salpingectomy is accomplished by placing a clamp across the mesosalpinx and then placing a second clamp across the proximal portion of the fallopian tube as close as possible to the cornua. The tips of the clamps should touch to completely occlude the vessels in the mesosalpinx. The tube is then excised and the pedicles ligated using a 2-0 or 3-0 synthetic absorbable suture.

If the tubal damage is confined to the tubal segment containing the ectopic gestation, a partial salpingectomy can be performed. The clamps are placed proximal and distal to the ectopic gestation.

The decision for partial vs. total salpingectomy depends on the patient's age and desire to conceive. In general, we perform partial salpingectomy to allow the option for tubal anastomosis at a future date. However, in women who will undergo IVF treatment, we prefer total salpingectomy to decrease the possibility of tubal stump pregnancy.

### Salpingostomy

Linear salpingostomy is the standard approach for management of ectopic pregnancy in women who wish to preserve their fertility. The ectopic pregnancy is identified and the tube is immobilized with laparoscopic forceps. A 22-gauge needle is inserted through a 5 mm portal and used to inject a solution of vasopressin (0.2 IU/mL of physiologic saline) into the wall of the tube at the area of maximal distention; this helps to minimize bleeding at the salpingostomy site. Using laser, unipolar needle electrocautery, ultrasonic cutting and coagulation device, or scissors, a 10-15 mm longitudinal incision is then made along the antimesenteric border overlying the ectopic. The products of conception are released from the tube using a combination of hydrodissection with irrigating solution under high pressure and gentle blunt dissection with a suction irrigator. The specimen can then be grasped with 10 mm claw forceps to remove it from the abdominal cavity; a laparoscopic pouch is useful for removal of large fragments of placental tissue.

The tube is carefully irrigated and inspected under water for hemostasis. Bleeding points can be controlled by pressure or coagulated with light application of bipolar coagulation. In order to avoid excessive coagulation to the tube, we use a microbipolar forceps. If bleeding persists, vessels in the mesosalpinx can be ligated with 6-0 polyglactin suture.

The placental bed inside the tube should not be coagulated because this will seriously damage the tube. The incision is left open to heal by secondary intention; the subsequent rates of fertility and adhesion formation are similar after secondary intention or primary closure.

#### Septate Uterus Repair

Hysteroscopic metroplasty has become the method of choice for repair of most uterine septa. Benefits to the transcervical approach include less morbidity, no abdominal or transmyometrial incisions, and faster return to normal activity. As there is no abdominal incision, possible infections and intra-abdominal adhesions that may cause future infertility problems or pain are avoided. Women may attempt pregnancy sooner after a vaginal/transcervical approach than after abdominal procedures. Vaginal delivery is not contraindicated.

#### Zygote Intrafallopian Transfer (ZIFT)

A technique in which a woman's egg is fertilized outside the body, then implanted in 1 of her fallopian tubes. First, the egg and the male sperm needed to fertilize it are harvested. Then the egg and the sperm are united in a petri dish, a multi-purpose glass or plastic container with a lid. If all goes well, the sperm fertilizes the egg, and the physicians then implant it in a fallopian tube. From there, nature takes its course, and the egg eventually is deposited by the fallopian tube into the uterus (womb) for development.

A zygote is the combined cell resulting from the union of sperm and egg. A zygote develops into an embryo. An embryo, a mass of cells with no recognizable human features, begins formation of a human body.

### **Fertility Treatments for Males**

#### Electroejaculation

This technique is used in patients with complete absence of antegrade ejaculation as well as a fructose-negative, sperm-negative, nonviscous postorgasmic urinalysis, usually in patients with spinal cord injury. This procedure involves use of a rectal probe to stimulate the perirectal, periprostatic sympathetic nerves electrically. Patients without a spinal cord injury or those with low or incomplete spinal cord lesions will require general anesthesia.

#### Excision of Tumors (e.g., epididymal, spermatocele, etc.)

Obstructions that inhibit the delivery of sperm may be caused by benign tumors and cysts. A spermatocele is a benign cystic accumulation of sperm that arises from the head of the epididymis. Although often disconcerting to the patient when noticed, these lesions are benign. Spermatoceles can develop in varying locations, ranging from the testicle itself to locations along the course of the vas deferens. Nevertheless, in common usage, spermatoceles are intrascrotal, paratesticular cystic collections of sperm that arise from the epididymis.

Most surgeries to excise tumors or cysts are aimed at testis-sparing surgeries through laparoscopic and microscopic techniques.

#### Microsurgical Epididymal Sperm Aspiration (MESA)

This technique is appropriate for men who have an epididymal or vasal obstruction. Microsurgical epididymal sperm aspiration enables the surgeon to collect large numbers of motile sperm for cryopreservation. The disadvantage of this method is that it involves a surgical procedure requiring an operating microscope and consequently increases the cost for a couple who also require IVF-ICSI.

### Orchiopexy

An undescended testis sometimes escapes detection until adulthood. If the contralateral testis is normal, these men are likely to be fertile. If both testes are truly undescended, infertility is very likely, with most of the patients being azoospermic. Bilateral orchiopexy in adults can result in induction of spermatogenesis and pregnancy, and preserves testicular hormonal function.

### Percutaneous Epididymal Sperm Aspiration (PESA)

Sperm are aspirated through a butterfly needle that is placed into the caudal portion of the epididymis. This method of obtaining sperm for cryopreservation or fresh IVF-ICSI is relatively quick and inexpensive compared with microsurgical open aspiration.

### Pharmacologic Treatment of Endocrinopathies:

- Androgens

Exogenous androgen treatment for male infertility is not indicated. Historically, androgens were among the first empiric treatments for idiopathic male infertility, based on the premise that raising serum testosterone levels would improve epididymal maturation and boost spermatogenesis. Another rationale for the use of androgens is the so-called “rebound phenomenon.” Exogenous testosterone inhibits the HPG axis and results in azoospermia; a transient increase in gonadotropins upon stopping testosterone administration has been observed.

A third hypothetical potential benefit of testosterone administration has been in the treatment of men who have androgen insensitivity. The resistance of these patients could be overcome with higher circulating testosterone levels. No data suggest this treatment approach is effective. More than 11 randomized, controlled trials have evaluated whether androgen therapy improves pregnancy rates. Testosterone enanthate, testosterone undecanoate or mesterolone (orally active dihydrotestosterone derivative) were used in these trials. Liu and Handelsman performed a meta-analysis pooling data from 10 of these studies involving more than 1,000 men and found no improvement in pregnancy rate with androgen therapy (OR, 1.09; 95% CI, 0.73–1.62). Two prior meta-analyses also did not demonstrate efficacy of androgens for idiopathic infertility. Available evidence strongly argues against any role of androgen monotherapy for idiopathic male infertility.

- Corticosteroids

Corticosteroids have been the most commonly employed medications used to attempt to suppress antisperm antibody formation. In some patients, corticosteroid treatment may result in improved fertility; however, this does not occur in the majority of patients.

- Human Chorionic Gonadotropins (HCG)

Sperm production cannot be stimulated in men who are infertile as a result of primary hypogonadism (due to damage to the seminiferous tubules). However, sperm production can usually be stimulated to a level sufficient to restore fertility in men who are infertile as a result of secondary hypogonadism, i.e., due to damage to the pituitary or hypothalamus. Men who have pituitary disease can be treated with gonadotropins, while those with hypothalamic disease can be treated with gonadotropins or gonadotropin-releasing hormone (GnRH). Secondary hypogonadism is associated with decreased secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in reductions in testosterone secretion and sperm production.

Gonadotropin treatment of men with hypogonadotropic hypogonadism results in the appearance of sperm in the ejaculate in up to 90% of these men, but often not to normal. Even if pregnancy does not occur spontaneously, the number of sperm is often sufficient that pregnancy can be achieved with the help of an assisted reproductive technique.

- Human Menopausal Gonadotropin (HMG)  
Human menopausal gonadotropin (HMG) contains FSH and is the pharmaceutical preparation used to replace FSH in stimulating spermatogenesis in men who are infertile due to secondary hypogonadism. FSH appears to be necessary for the initiation of spermatogenesis, but not for its maintenance or re-initiation.
- Pulsatile Gonadotropin-releasing Hormone  
Gonadotropin-releasing hormone (GnRH) is administered in a pulsatile fashion by a pump and syringe that is programmed to deliver a bolus of GnRH every 2 hours and is connected to a subcutaneous needle. The apparatus is worn continuously until pregnancy occurs. The rationale for this treatment is that replacement of GnRH in a physiologic manner, in pulses every 2 hours, will stimulate the gonadotroph cells of the pituitary to secrete LH and FSH, which in turn will stimulate the testes to produce testosterone and sperm. Sperm may appear in the ejaculate as soon as 12 months after the initiation of treatment but more often 3 years or more are required.

#### Repair of Varicocele

A varicocele is a dilation of a vein (like a varicose vein) in the scrotum. Many men with varicocele have a low sperm count or abnormal sperm morphology (shape). The reason a varicocele affects the sperm may be related to a higher than normal temperature in the testicles, poor oxygen supply, and poor blood flow in the testes.

Varicocele can be treated surgically by cutting the veins connected to the varicocele. However, surgery does not always improve fertility and is not recommended for most men unless there is a large varicocele. A varicocele that has been present for a long time can cause irreversible damage that cannot be surgically treated.

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

#### Testicular Fine Needle Aspiration (TFNA)

The technique of testicular fine-needle aspiration (TFNA) of the testis was initially described as a diagnostic procedure in azoospermic men. Subsequently, testicular fine needle aspiration or biopsy for the recovery of spermatozoa has been described. Percutaneous puncture and aspiration of the testis can be performed using a 21-23-gauge needle connected to a 20cc syringe in a Menghini syringe holder. Percutaneous testicular needle biopsy can be performed with an automatic biopsy gun. The limited published experience to date with TFNA makes critical evaluation of this technique difficult, although it is evident from our experience that 1) sperm retrieval is routinely possible with TFNA for men with obstructive azoospermia, 2) occasional hematoceles and hematomas are possible with this technique. The advantages of percutaneous aspiration techniques are that they can be performed with local anesthesia, without open scrotal exploration and its attendant postoperative discomfort, and without microsurgical expertise.

#### Testicular Sperm Aspiration (TESA)

Testicular sperm aspiration (TESA) is a needle biopsy of the testicle. It is an office procedure performed under local anesthesia. A small incision is made in the scrotal skin and a spring loaded needle is fired through the testicle. While it is possible to retrieve sperm using this technique, the amount is often low because the needle cuts a thin sliver of tissue. Many embryologists find this small amount of tissue difficult to work with and do not get enough sperm to freeze for future use.

### Testicular Sperm Extraction (TESE)

Testicular sperm extraction (TESE) is an open procedure performed under direct vision and therefore minimizes potential complications. A small piece of testicular tissue is removed through a ½ inch skin incision. The tissue is placed in culture media and morselized into tiny pieces. Sperm are liberated from within the seminiferous tubules (picture to the right) 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.

### Transurethral Resection of the Ejaculatory Ducts (TURED)

Transurethral resection of the ejaculatory ducts (TURED) is the primary treatment of ejaculatory duct obstruction. A 24 French resectoscope is placed into the urethra, and resection is carried out at the level of the verumontanum. An O'Connor drape is used with a finger in the rectum to allow better depth perception and visualization of the posterior prostate. If an ejaculatory duct cyst is present, it is usually deep and just posterior to the verumontanum. Therefore, the verumontanum is deeply resected with care not to injure the rectum. Real-time ultrasonography can be used concurrently to visualize the resection of the ejaculatory cyst. Once efflux from the ejaculatory ducts of copious cloudy material or indigo carmine, if present, is identified, the resection is complete. If the cyst still is not unroofed, a Collings knife is used to make bilateral incisions just lateral to the base of the resected verumontanum. These incisions make it possible to open obstructed ejaculatory ducts that may have been missed during the initial midline incision. Electrocautery is used judiciously to avoid occlusion of the newly opened ejaculatory ducts.

### Vasal Sperm Aspiration

Vasal aspiration is an easy procedure requiring only local anesthetic. Those with an obstructed vas deferens or who have had a vasectomy within 5 years are candidates for this procedure. A syringe is inserted into the vas deferens and the liquid inside is removed. The vas deferens is massaged in order to produce more liquid. Recovery time is generally 1 day. This is the only surgical sperm retrieval procedure that retrieves mature sperm.

## **Applicable Coding**

### CPT Codes

- |              |  |
|--------------|--|
| <b>80414</b> | Chorionic gonadotropin stimulation panel; testosterone response. This panel must include the following: Testosterone (84403 x 2 on 3 pooled blood samples)                   |
| <b>80415</b> | Chorionic gonadotropin stimulation panel; estradiol response. This panel must include the following: Estradiol (82670 x 2 on 3 pooled blood samples)                         |
| <b>80426</b> | Gonadotropin releasing hormone stimulation panel. This panel must include the following: Follicle stimulating hormone (FSH) (83001 x 4) Luteinizing hormone (LH) (83002 x 4) |
| <b>82157</b> | Androstenedione  |
| <b>82160</b> | Androsterone   |
| <b>82397</b> | Chemiluminescent assay (AMH)   |
| <b>82627</b> | Dehydroepiandrosterone-sulfate (DHEA-S)*   |
| <b>82670</b> | Estradiol*   |



**82757** Fructose, semen

**83001** Gonadotropin; follicle stimulating hormone (FSH)/(CCCT?)\*

**83002** Gonadotropin; luteinizing hormone (LH)\*

**83491** Hydroxycorticosteroids, 17- (17-OHCS)\*

**83498** Hydroxyprogesterone, 17-d\*

**84144** Progesterone (Progesterone challenge?)\*

**84402** Testosterone; free\*

**84403** Testosterone; total\*

**88248** Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (eg, for ataxia telangiectasia, Fanconi anemia, fragile X)\*

**88261** Chromosome analysis; count 5 cells, 1 karyotype, with banding\*

**88262** Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding\*

**88263** Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding\*

**88280** Chromosome analysis; additional karyotypes, each study\*

**88283** Chromosome analysis; additional specialized banding technique (eg, NOR, C-banding)\*

**89260** Sperm isolation; simple prep (eg, sperm wash and swim-up) for insemination or diagnosis with semen analysis

**89261** Sperm isolation; complex prep (eg, Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis

**89300** Semen analysis; presence and/or motility of sperm including Huhner test (post coital)

**89310** Semen analysis; motility and count (not including Huhner test)

**89320** Semen analysis; volume, count, motility, and differential

**89321** Semen analysis; sperm presence and motility of sperm, if performed

**89322** Semen analysis; volume, count, motility, and differential using strict morphologic criteria (eg, Kruger)

**89325** Sperm antibodies

**89329** Sperm evaluation; hamster penetration test (culture) (sperm penetration assay [SPA])

**89330** Sperm evaluation; cervical mucus penetration test, with or without spinnbarkeit test

**89331** Sperm evaluation, for retrograde ejaculation, urine (sperm concentration, motility, and morphology, as indicated)

Female Procedures

- 49320** Laparoscopy, abdomen, peritoneum, and omentum, diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)\*
- 58140** Myomectomy, excision of fibroid tumor(s) of uterus, 1 to 4 intramural myoma(s) with total weight of 250 g or less and/or removal of surface myomas; abdominal approach\*
- 58145** Myomectomy, excision of fibroid tumor(s) of uterus, 1 to 4 intramural myoma(s) with total weight of 250 g or less and/or removal of surface myomas; vaginal approach\*
- 58146** Myomectomy, excision of fibroid tumor(s) of uterus, 5 or more intramural myomas and/or intramural myomas with total weight greater than 250 g, abdominal approach\*
- 58322** Artificial insemination; intra-uterine
- 58340** Catheterization and introduction of saline or contrast material for saline infusion sonohysterography (SIS) or hysterosalpingography\*
- 58345** Transcervical introduction of fallopian tube catheter for diagnosis and/or re-establishing patency (any method), with or without hysterosalpingography\*
- 58350** Chromotubation of oviduct, including materials
- 58540** Hysteroplasty, repair of uterine anomaly (Strassman type)
- 58545** Laparoscopy, surgical, myomectomy, excision; 1 to 4 intramural myomas with total weight of 250 g or less and/or removal of surface myomas\*
- 58546** Laparoscopy, surgical, myomectomy, excision; 5 or more intramural myomas and/or intramural myomas with total weight greater than 250 g\*
- 58555** Hysteroscopy, diagnostic (separate procedure)\*
- 58558** Hysteroscopy, surgical; with sampling (biopsy) of endometrium and/or polypectomy, with or without D & C\*
- 58559** Hysteroscopy, surgical; with lysis of intrauterine adhesions (any method)\*
- 58560** Hysteroscopy, surgical; with division or resection of intrauterine septum (any method)
- 58561** Hysteroscopy, surgical; with removal of leiomyomata\*
- 58562** Hysteroscopy, surgical; with removal of impacted foreign body\*
- 58563** Hysteroscopy, surgical; with endometrial ablation (eg, endometrial resection, electrosurgical ablation, thermoablation)\*

- 58578** Unlisted laparoscopy procedure, uterus\*
- 58660** Laparoscopy, surgical; with lysis of adhesions (salpingolysis, ovariolysis) (separate procedure)\*
- 58673** Laparoscopy, surgical; with salpingostomy (salpingoneostomy)
- 58700** Salpingectomy, complete or partial, unilateral or bilateral (separate procedure)\*
- 58740** Lysis of adhesions (salpingolysis, ovariolysis)\*
- 58760** Fimbrioplasty
- 58770** Salpingostomy (salpingoneostomy)
- 58920** Wedge resection or bisection of ovary, unilateral or bilateral\*
- 58974** Embryo transfer, intrauterine
- 58976** Gamete, zygote, or embryo intrafallopian transfer, any method
- 74740** Hysterosalpingography, radiological supervision and interpretation
- 76830** Ultrasound, transvaginal\*
- 76831** Saline infusion sonohysterography (SIS), including color flow Doppler, when performed\*
- 76856** Ultrasound, pelvic (nonobstetric), real time with image documentation; complete\*
- 76857** Ultrasound, pelvic (nonobstetric), real time with image documentation; limited or follow-up (eg, for follicles)
- 84830** Ovulation tests, by visual color comparison methods for human luteinizing hormone
- 88273** Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)\*
- 89253** Assisted embryo hatching, microtechniques (any method)
- 89255** Preparation of embryo for transfer (any method)
- 89258** Cryopreservation; embryo(s)
- 89264** Sperm identification from testis tissue, fresh or cryopreserved
- 89280** Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes
- 89281** ; greater than 10 oocytes

Male Procedures

- 52402** Cystourethroscopy with transurethral resection or incision of ejaculatory ducts\*
- 54500** Biopsy of testis, needle (separate procedure)\*

<b>54505</b>	Biopsy of testis, incisional (separate procedure)*
<b>54640</b>	Orchiopexy, inguinal approach, with or without hernia repair*
<b>54650</b>	Orchiopexy, abdominal approach, for intra-abdominal testis (eg, Fowler-Stephens)*
<b>54692</b>	Laparoscopy, surgical; orchiopexy for intra-abdominal testis*
<b>54699</b>	Unlisted laparoscopy procedure, testis*
<b>54800</b>	Biopsy of epididymis, needle*
<b>54830</b>	Excision of local lesion of epididymis*
<b>55110</b>	Scrotal exploration*
<b>55300</b>	Vasotomy for vasograms, seminal vesiculograms, or epididymograms, unilateral or bilateral
<b>55500</b>	Excision of hydrocele of spermatic cord, unilateral (separate procedure)*
<b>55530</b>	Excision of varicocele or ligation of spermatic veins for varicocele; (separate procedure)*
<b>55535</b>	Excision of varicocele or ligation of spermatic veins for varicocele; abdominal approach*
<b>55550</b>	Laparoscopy, surgical, with ligation of spermatic veins for varicocele*
<b>55870</b>	Electroejaculation
<b>55899</b>	Unlisted procedure, male genital system*
<b>74440</b>	Vasography, vesiculography, or epididymography, radiological supervision and interpretation
<b>76870</b>	Ultrasound, scrotum and contents*
<b>89257</b>	Sperm identification from aspiration (other than seminal fluid)
<b>76872</b>	Ultrasound, transrectal*;
<b>82964</b>	Sperm identification from testis tissue, fresh or cryopreserved
<b>89329</b>	Sperm evaluation; hamster penetration test

*\* Requires an infertility diagnosis code attached with the CPT code (ICD-10 infertility codes listed below) to be considered under infertility benefit, otherwise covered as medical benefit*

### **HCPCS Codes**

#### **Female Procedures**

<b>S4013</b>	Complete cycle, gamete intrafallopian transfer (GIFT), case rate
<b>S4014</b>	Complete cycle, zygote intrafallopian transfer (ZIFT), case rate

- S4035** Stimulated intrauterine insemination (IUI), case rate
- S4042** Management of ovulation induction (interpretation of diagnostic tests and studies, nonface-to-face medical management of the patient), per cycle

Male Procedures

- G0027** Semen analysis; presence and/or motility of sperm excluding Huhner
- Q0115** Post-coital direct, qualitative examinations of vaginal or cervical mucous
- S4013** Complete cycle, gamete intrafallopian transfer (GIFT), case rate
- S4014** Complete cycle, zygote intrafallopian transfer (ZIFT), case rate
- S4035** Stimulated intrauterine insemination (IUI), case rate
- S4042** Management of ovulation induction (interpretation of diagnostic tests and studies, nonface-to-face medical management of the patient), per cycle
- S4028** Microsurgical epididymal sperm aspiration (MESA)

ICD-10 Codes (Infertility Diagnoses)

- |                |   |                |   |
|----------------|---|----------------|---|
| <b>N46.01</b>  | Organic azoospermia                               | <b>N50.0</b>   | Atrophy of testis   |
| <b>N46.021</b> | Azoospermia due to drug therapy                   | <b>N50.89</b>  | Other specified disorders of the male genital organs              |
| <b>N46.022</b> | Azoospermia due to infection                      | <b>N50.9</b>   | Disorder of male genital organs, unspecified                      |
| <b>N46.023</b> | Azoospermia due to obstruction of efferent ducts  | <b>N51</b>     | Disorders of male genital organs in diseases classified elsewhere |
| <b>N46.024</b> | Azoospermia due to radiation                      | <b>N53.11</b>  | Retarded ejaculation  |
| <b>N46.025</b> | Azoospermia due to systemic disease               | <b>N53.14</b>  | Retrograde ejaculation  |
| <b>N46.029</b> | Azoospermia due to other extratesticular causes   | <b>N53.19</b>  | Other ejaculatory dysfunction                                     |
| <b>N46.11</b>  | Organic oligospermia                              | <b>N53.8</b>   | Other male sexual dysfunction                                     |
| <b>N46.121</b> | Oligospermia due to drug therapy                  | <b>N53.9</b>   | Unspecified male sexual dysfunction                               |
| <b>N46.122</b> | Oligospermia due to infection                     | <b>N83.311</b> | Acquired atrophy of right ovary                                   |
| <b>N46.123</b> | Oligospermia due to obstruction of efferent ducts | <b>N83.312</b> | Acquired atrophy of left ovary                                    |
| <b>N46.124</b> | Oligospermia due to radiation                     | <b>N83.319</b> | Acquired atrophy of ovary, unspecified side                       |
| <b>N46.125</b> | Oligospermia due to systemic disease              | <b>N83.331</b> | Acquired atrophy of right ovary and fallopian tube                |
| <b>N46.129</b> | Oligospermia due to other extratesticular causes  | <b>N83.332</b> | Acquired atrophy of left ovary and fallopian tube                 |
| <b>N46.8</b>   | Other male infertility                            |                |   |

<b>N83.339</b>	Acquired atrophy of ovary and fallopian tube, unspecified side	<b>Q52.120</b>	Longitudinal vaginal septum, non-obstructing
<b>N83.8</b>	Other noninflammatory disorders of ovary, fallopian tube and broad ligament	<b>Q52.121</b>	Longitudinal vaginal septum, obstructing, right side
<b>N83.9</b>	Noninflammatory disorder of ovary, fallopian tube and broad ligament, unspecified	<b>Q52.122</b>	Longitudinal vaginal septum, obstructing, left side
<b>N84.0</b>	Noninflammatory disorder of ovary, fallopian tube and broad ligament, unspecified	<b>Q52.123</b>	Longitudinal vaginal septum, microperforate, right side
<b>N85.6</b>	Intrauterine synechiae	<b>Q52.124</b>	Longitudinal vaginal septum, microperforate, left side
<b>N91.0</b>	Primary amenorrhea	<b>Q52.129</b>	Other and unspecified longitudinal vaginal septum
<b>N91.1</b>	Secondary amenorrhea	<b>Q52.4</b>	Other congenital malformations of vagina
<b>N91.2</b>	Amenorrhea, unspecified	<b>Q52.8</b>	Other specified congenital malformations of female genitalia
<b>N95.9</b>	Unspecified menopausal and perimenopausal disorder	<b>Q52.9</b>	Congenital malformation of female genitalia, unspecified
<b>N97.0</b>	Female infertility associated with anovulation	<b>Q55.29</b>	Other congenital malformations of testis and scrotum
<b>N97.1</b>	Female infertility of tubal origin	<b>Q55.4</b>	Other congenital malformations of vas deferens, epididymis, seminal vesicles and prostate
<b>N97.2</b>	Female infertility of uterine origin	<b>Q55.8</b>	Other specified congenital malformations of male genital organs
<b>N97.8</b>	Female infertility of other origin	<b>R86.0</b>	Abnormal level of enzymes in specimens from male genital organs
<b>N97.9</b>	Female infertility, unspecified	<b>R86.1</b>	Abnormal level of hormones in specimens from male genital organs
<b>N98.1</b>	Hyperstimulation of ovaries	<b>R86.2</b>	Abnormal level of other drugs, medicaments and biological substances in specimens from male genital organs
<b>Q50.01</b>	Congenital absence of ovary, unilateral	<b>R86.3</b>	Abnormal level of substances chiefly nonmedicinal as to source in specimens from male genital organs
<b>Q50.02</b>	Congenital absence of ovary, bilateral		
<b>Q50.32</b>	Ovarian streak		
<b>Q50.39</b>	Other congenital malformation of ovary		
<b>Q50.6</b>	Other congenital malformations of fallopian tube and broad ligament		
<b>Q51.0</b>	Agenesis and aplasia of uterus		
<b>Q51.5</b>	Agenesis and aplasia of cervix		
<b>Q52.11</b>	Transverse vaginal septum		

<b>R86.4</b>	Abnormal immunological findings in specimens from male genital organs	<b>Z31.41</b>	Encounter for fertility testing
		<b>Z31.448</b>	Encounter for other genetic testing of male for procreative management
<b>R86.5</b>	Abnormal microbiological findings in specimens from male genital organs	<b>Z31.89</b>	Encounter for other procreative management
<b>R86.6</b>	Abnormal cytological findings in specimens from male genital organs	<b>Z52.810</b>	Egg (Oocyte) donor under age 35, anonymous recipient
<b>R86.7</b>	Abnormal histological findings in specimens from male genital organs	<b>Z52.811</b>	Egg (Oocyte) donor under age 35, designated recipient
		<b>Z52.812</b>	Egg (Oocyte) donor age 35 and over, anonymous recipient
<b>R86.8</b>	Other abnormal findings in specimens from male genital organs	<b>Z52.813</b>	Egg (Oocyte) donor age 35 and over, designated recipient
<b>R86.9</b>	Unspecified abnormal finding in specimens from male genital organs	<b>Z52.819</b>	Egg (Oocyte) donor, unspecified

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