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Infertility, Male

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Last Updated: July 23, 2002

Synonyms and related keywords: ejaculate volume, sperm concentration, oligospermia, too few sperm, low sperm count, azoospermia, no sperm in the ejaculate, sperm motility, sperm morphology, gonad, testis, testes, testicles, fertilization

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Background: Infertility is defined as the inability to achieve pregnancy after one year of unprotected intercourse. An estimated 15% of couples meet this criterion

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and are considered infertile. Historically, the workup for the infertile couple focused primarily on conditions of the female. Conditions of the male are estimated to account for nearly 30% of cases of infertility, and conditions of both the female and the male account for another 20%. Conditions of the male that affect fertility are still underdiagnosed and undertreated.

In general, causes of infertility in men can be explained by deficiencies in ejaculate volume, sperm concentration (eg, oligospermia [too few sperm], azoospermia [no sperm in the ejaculate]), sperm motility, or sperm morphology. This general division allows an appropriate workup of potential underlying causes of infertility and helps define a course of action for treatment. The initial evaluation of the male patient should be rapid, noninvasive, and cost-effective. Nearly 70% of conditions causing infertility in men can be diagnosed by history, physical examination, testicular volume estimation, and hormonal and semen analysis. A rational approach is necessary to perform the appropriate workup and to choose the best treatment options for the couple.

Various treatments exist for the infertile couple, ranging from optimizing the current semen parameters with medical therapy to minor surgical procedures and finally to complex sperm retrieval and assisted reproduction techniques. Technological advancements in assisted reproduction make conceiving a child possible with as little as one viable sperm and one egg. While the workup traditionally has been delayed until a couple has been unable to conceive for 12 months, beginning the workup at the first visit is now recommended because of a recent trend towards delaying family planning. This article summarizes current knowledge of causes of infertility in men and describes its workup and treatment.

Pathophysiology: The physiology of normal spermatogenesis, ejaculation, and fertility must be understood prior to performing a thorough workup of the infertile man. This includes knowledge of the hypothalamic-pituitary-testicular system (ie, the integration system controlling sperm and testosterone production), the embryology and physiology of the testis and accessory glands, and the process of fertilization.

Gonadal and sexual functions are mediated by the hypothalamic-pituitary-gonadal axis, a closed-loop system with feedback control from the testicles (see Image 1). The hypothalamus, the primary integration center, responds to a variety of signals from the CNS, pituitary, and testicles to secrete releasing factors, such as gonadotropin releasing hormone (GnRH), to modulate pituitary function. Hypothalamic input from the CNS includes signals from the amygdala, hippocampus, and mesencephalon, which respond to various internal and external stimuli.

GnRH is released from the medial basal hypothalamus in a pulsatile pattern approximately every 70-90 minutes. It then travels down the portal system to the anterior pituitary, where it stimulates the release of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The half-life of GnRH is 2-5 minutes. Its diurnal release may be due to melatonin from the pineal gland. GnRH release is inhibited by negative feedback signals from the testicle, specifically testosterone and inhibin. Additionally, corticotropin-releasing hormone (CRH), released during stress, and opiates, both internal and external, down-regulate GnRH secretion. The body responds to illness and stress by a decreased production of gonadotropins.

The pituitary gland, which lies on a stalk beneath the hypothalamus in the sella turcica, contains the gonadotropic cells that produce both FSH and LH. These are glycopeptides with a molecular weight of 10,000 daltons. They are made up of an alpha chain that is identical with that of human chorionic gonadotropin (HCG) and thyroid-stimulating hormone (TSH) and a beta chain that is unique for each. FSH has a lower plasma concentration and longer half-life than LH, and it has less obvious pulsatile changes. The pulsatile nature of GnRH is essential to normal gonadotropin release; a continuous stimulation inhibits their secretion. This is clinically significant and is used in the medical treatment of prostate cancer and endometriosis.

After release into the systemic circulation, FSH and LH exert their effect by binding to plasma membrane receptors of the target cells. LH mainly functions to stimulate testosterone secretion from the Leydig cells of the testicle, while FSH stimulates Sertoli cells to facilitate germ cell differentiation. Gonadotropin release is modulated by a variety of other signals, such as estradiol (a potent inhibitor of both LH and FSH release), and inhibin from the Sertoli cell, which causes a selective decrease in FSH release.

The pituitary also secretes prolactin, which normally functions to stimulate breast development and lactation. Prolactin release is held in check by the hypothalamic production of dopamine. The hypothalamus produces thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP). Both stimulate prolactin release. Men with elevated prolactin levels present with gynecomastia, diminished libido, erectile dysfunction, and, occasionally, galactorrhea. Prolactin inhibits the production of GnRH from the hypothalamus and LH and FSH from the pituitary.

The testicle (Image 2), the end organ of the axis, contains the Leydig cells and the Sertoli cells, which respond to LH and FSH, respectively, by the secretion of testosterone (Leydig cells) and maturation of the germ cells (Sertoli cells). The testicles are derived embryologically from the genital ridge near the kidneys, and they descend to the scrotum during gestation. The intermesenteric nerves of the renal plexus innervate the testicle, and the blood supply is from the internal spermatic artery, the artery to the vas deferens, and from the external spermatic (cremasteric) artery.

The thick tunica albuginea covers the testes and provides septae that divide it into approximately 200-350 pyramids. These pyramids are filled with the seminiferous tubules. A normal testicle contains 600-1200 seminiferous tubules with a total length of approximately 250 meters. The interstitium between the seminiferous tubules contains the Leydig cells, fibroblasts, lymphatics, blood vessels, and macrophages. Seminiferous tubules are made up of Sertoli cells and germ cells, and they are surrounded by peritubular and myoid cells.

Sertoli cells, which rest on the basement membrane of the seminiferous tubules, serve mainly to support, nourish, and protect the developing germ cells. Histologically, they are columnar, with irregular basal nuclei that have prominent nucleoli and fine chromatin. Sertoli cells additionally serve as the blood-testis barrier by their unique tight junctions that divide the seminiferous tubules into a basal and abluminal compartment. This provides a microenvironment that facilitates spermatogenesis and maintains the germ cells in an immunologically privileged location. Sertoli cells secrete inhibin, a feedback molecule, and androgen-binding protein, which helps modulate androgen activity in the seminiferous tubules. Normal Sertoli cell function is modulated by FSH, a high

level of intratesticular testosterone, and signals from elsewhere in the testicle such as the peritubular myoid cells bordering the seminiferous tubules.

The Leydig cells are located in the interstitium between the seminiferous tubules and serve primarily to secrete testosterone in response to LH. Histologically, Leydig cells are polygonal with eosinophilic cytoplasm. Occasionally, crystalloids of Reinke may be observed in the cytoplasm after puberty. LH binds to a G protein–coupled receptor on the Leydig surface and up-regulates the enzymes involved in the conversion of cholesterol to testosterone.

Testosterone is secreted in a diurnal pattern, peaking early in the morning. In the body, testosterone circulates 2% in the free form, 44% bound to sex hormone–binding globulin (SHBG), and 54% bound to albumin. Testosterone is converted to dihydrotestosterone (DHT) by the action of 5-alpha reductase, both locally and in the periphery, and to estrogen in the periphery. A high level of intratesticular testosterone is necessary for normal spermatogenesis. Testosterone and estradiol also function as feedback inhibitors of gonadotropin release. These steroids exert their effect by crossing the plasma membrane and binding to specific receptors in the cytosol and nucleus.

Normal spermatogenesis requires complex interactions between the Sertoli cells, Leydig cells, and germ cells. Germ cells, precursors to spermatozoa, interdigitate with Sertoli cells. They are derived from the gonadal ridge and migrate as gonadocytes to the testicle before testicular descent. After puberty, because of stimulation by FSH, these cells become spermatogonia and undergo an ordered maturation to become spermatozoa. The entire process of development from spermatogonium to spermatid requires 74 days and is described in 14 steps; as they mature, the developing spermatids progress closer to the lumen of the seminiferous tubule.

Spermatogonia, which rest on the basement membrane, contain dense nuclei and prominent nucleoli. Three types are described. The stem cell, also known as A dark (Ad), divides to create more Ad cells (stem cell renewal) and differentiates into daughter A pale (Ap) cells every 16 days. These Ap cells mature into B spermatogonia, which are committed to becoming spermatids. The B cells undergo mitotic division to become primary spermatocytes, which are recognized by their large centrally located nuclei and beaded chromatin. The mitotic division does not result in complete separation; rather, daughter cells maintain intracellular bridges, which have functional significance in cell signaling and maturation.

Primary spermatocytes undergo meiosis as the cells successively pass through the preleptotene (R), leptotene (L), zygotene (Z), and pachytene (P) stages to become secondary spermatocytes (Sa). During this time, the cells cross from the basal to the abluminal compartments. Secondary spermatocytes contain smaller nuclei with fine chromatin. The secondary spermatocytes undergo a second meiosis and become spermatids. This reduction division, ie, meiosis, results in a haploid chromosome number. A total of 4 spermatids are made from each spermatocyte.

Next, the spermatids undergo the process of spermiogenesis through the successive Sb1, Sb2, Sc, Sd1, and Sd2 stages. This involves casting excess cytoplasm away as a residual body, the formation of the acrosome and flagella, and the migration of cytoplasmic organelles to their final cellular location. The acrosome, a derivative of the Golgi process, contains enzymes necessary to

penetrate the egg. It surrounds the nucleus anteriorly. The mature spermatid is adjacent to the lumen and contains dark chromatin with an oval-shaped nucleus, a mid piece with helically arranged mitochondria, a principal piece, and an end piece. The axoneme contains all the enzymes and structural proteins necessary for adenosine triphosphate (ATP) conversion to energy to propel the tail, which are cilia with a 9+2 microtubule core.

After their release from the Sertoli cells into the lumen of the seminiferous tubules, the spermatids enter the tubuli recti, rete testis, ductuli efferentes, and, finally, the epididymis (see Image 3). The epididymis is a 3- to 4-cm long structure with a tubular length of 4-5 m. As sperm move from the head to the tail, they mature and acquire fertilization capacity. Sperm from the head move with immature wide arcs and are generally unable to penetrate the egg, while those from the tail propel forward and have better penetration capacity. The transit time varies with age and sexual activity but is usually from 1-12 days. In addition, various substances are secreted for sperm nutrition and protection such as glycerophosphorylcholine, carnitine, and sialic acid.

During ejaculation, the sperm enter the vas deferens, a 30- to 35-cm long muscular conduit of wolffian duct origin. The vas is divided into the convoluted, scrotal, inguinal, retroperitoneal, and ampullary regions, and it receives its blood supply from the inferior vesicle artery. In addition to functioning as a conduit, the vas also has absorptive and secretory properties. During emission, sperm are propelled forward by peristalsis. After reaching its ampullary portion behind the bladder, the vas joins with the seminal vesicles, proceeding forward through the prostate parenchyma as the ejaculatory duct. The ejaculatory duct empties next to the verumontanum. Bladder neck closure during ejaculation is vital to ensure antegrade ejaculation. The semen is propelled forward by the rhythmic contractions of the smooth muscle surrounding the ducts and by the bulbourethral muscles and other pelvic muscles.

Semen is composed of secretions not only from the testis and epididymis but also from the bulbourethral (Cowper) glands, the glands of Litre (periurethral), the seminal vesicles, and the prostate. Usual ejaculate volume is 1.5-5.0 cc, and the pH is 7.05-7.80. The seminal vesicles produce 40-80% of the semen volume. Secretions include fructose for sperm nutrition, prostaglandins and other coagulating substances, and bicarbonate to buffer the acidic vaginal vault. Normal seminal fructose concentration is 120-450 mg/dL. A fructose level of less than 120 mg/dL is often due to an obstruction of the ejaculatory ducts or absence of the seminal vesicles, especially when associated with a low ejaculate volume and a thin, watery consistency. The prostate gland contributes approximately 10-30% (0.5 cc) of the ejaculate. Products include enzymes and proteases to liquefy the seminal coagulum. This usually occurs within 20-25 minutes. The prostate also secretes zinc, phospholipids, phosphatase, and spermine.

The ordered sequence of release is important for appropriate functioning. The prostate and vas provide most of the early ejaculate, which is rich in sperm. Cowper glands, which are found in the membranous urethra, and the glands of Litre each provide 2-5% (0.1-0.2 cc) of the total ejaculate volume, mainly to lubricate the urethra and to buffer the acidity of the residual urine. Finally, the testicular-epididymal component, including spermatozoa, comprises 5% of the ejaculate volume.

For conception, sperm must reach the cervix and penetrate the cervical mucus,

migrate up the uterus to the fallopian tube with the oocyte, and penetrate the zona pellucida and cell membrane. The cervical mucus changes consistency during the ovulatory cycle, being most hospitable and easily penetrated at mid cycle. The sperm must not only survive within the female genital tract but also be able to migrate to the site of fertilization, undergo capacitation and the acrosome reaction to digest the zona pellucida of the oocyte, attach to the inner membrane, and release its genetic contents within the egg. After fertilization, implantation may then take place in the uterus. Problems with any of these steps may lead to infertility.

Frequency:

- **In the US:** An estimated 10-15% of couples are considered infertile using the 12-month criterion. This correlates to approximately 1 in 25 American men. Low sperm counts, poor semen quality, or both account for 90% of cases; however, studies of infertile couples without treatment reveal that 23% conceive within 2 years and 10% more conceive within 4 years. Even patients with severe oligospermia (<2 million sperm per cc) have a 7.6% chance of conception within 2 years.

- **Internationally:** Patterns of male infertility vary greatly among regions and even within regions. The highest reported fertility rates are in Finland, while Great Britain has a low fertility rate. A combination of social habits, environmental conditions, and genetics is suspected to contribute to this variation.

  Recent debate has occurred in the literature regarding a poorer semen quality, decreased sperm numbers, and decreased fertility in men today compared to that of 50 years ago, citing a decrease in sperm counts from an average of 113 million per cc in 1940 to 66 million per cc in 1990. Investigators hypothesize that environmental conditions and toxins have led to this decline; however, others argue that this is solely because of differences in counting methods, laboratory techniques, and geographic variation.

Mortality/Morbidity: Many patients who present with infertility as their primary symptom have a serious underlying medical disease. Ruling out life-threatening or life-altering conditions in these patients during the workup is important. Examples include pituitary adenomas, hormonally active tumors, testicular cancer, liver and renal failure, and cystic fibrosis (CF).

Sex: Isolated conditions of the female are responsible for infertility in 35% of cases, isolated conditions of the male in 30%, conditions of both the male and female in 20%, and unexplained causes in 15%. Even if an obvious cause exists, evaluating both partners thoroughly is important. In addition, both partners may be aided by education and evaluation of their sexual practices.

Age:

- The effect of aging on fertility is unclear. As men age, their testosterone levels decrease, while estradiol and estrone levels increase. Studies have shown that as men age, their sperm density decreases. Young men have spermatids present in 90% of seminiferous tubules, which decreases to 50% by age 50-70 years and to 10% by age 80 years. Additionally, 50% of Sertoli cells are lost by age 50, and a loss of 50% of Leydig cells occurs by age 60

years. Despite this, aging men may achieve similar fertility rates as younger men, although conception often takes longer.

- A paradigm shift exists regarding the timing of the initial workup for infertility. Traditionally, couples are evaluated only after a 1-year trial. Because couples start family planning later in life, infertility is now commonly evaluated upon initial presentation. In part, this is because of advanced maternal ages, couples' anxiety, and the availability of more reliable and cost-effective treatment options.

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History: The initial step in the evaluation of an infertile male is to obtain a thorough medical and urologic history. This should focus on the duration of infertility, previous fertility in the patient or the partner, and prior workup evaluations and treatments. The couple should be asked specifically about their sexual habits. This includes their level of education regarding the optimal timing of intercourse and the use of potentially spermatocytic drugs and lubricants.

Patients should be asked about a history of childhood illnesses such as testicular torsion, postpubertal mumps, developmental delay, and precocious puberty, as well as urinary tract infections, sexually transmitted diseases, and bladder neck surgery. A history of neurological diseases, diabetes, and pulmonary infections should be elicited. Anosmia, galactorrhea, visual field defects, and sudden loss of libido can be due to pituitary tumors. The status of the partner's workup should also be known.

- Timing of puberty (early, normal, or delayed)
  - Precocious puberty, defined as the onset of puberty before the age 9 years in men, may be the sign of a serious underlying endocrinologic disorder. Hormonally active tumors from the testicle, adrenal gland, or pituitary, along with adrenal hyperplasia, may result in early puberty.
  - In contrast, a delay in puberty may be caused by problems with the secretion of testosterone due to hypothalamic, pituitary, or primary testicular insufficiency or end organ androgen insensitivity.

- Childhood urological disorders or surgery
  - Both unilateral and bilateral cryptorchidism are associated with a decrease in sperm production and semen quality, regardless of the timing of orchidopexy.
  - Patients with hypospadias may not place the semen at the cervical os.
  - Prenatal exposure to diethylstilbestrol (DES) may cause epididymal cysts and cryptorchidism.
  - A V-Y plasty of the bladder neck performed at the time of ureteral reimplantation may lead to retrograde ejaculation.
  - The vas deferens or the testicular blood supply may be injured or ligated at the time of inguinal surgery, hernia repair, hydrocelectomy, or varicocelectomy.
  - Testicular torsion and trauma may result in testicular atrophy and the production of antisperm antibodies.

- Medical history
  - Diabetes may cause autonomic neuropathy, neurogenic impotence, and retrograde ejaculation.
  - Obesity causes a change in hormonal metabolism with an increased peripheral conversion of testosterone to estrogen and decreased LH pulse amplitude.
  - Sickle cell disease may lead to sickling and, therefore, direct testicular ischemia and damage.
  - Infertility may be secondary to hemosiderosis due to multiple transfusions in patients with sickle cell disease or thalassemia.
  - Chronic renal failure leads to hypogonadism and feminization because of primary testicular failure.
  - Liver disease leads to decreased libido, impotence, decrease in male secondary sexual characteristics, testicular atrophy, and gynecomastia because of increased estrogen levels.
  - Hemochromatosis leads to hypogonadism and signs of androgen deficiency without gynecomastia, and it is associated with decreased estradiol levels.
  - Postpubertal mumps may lead to testicular atrophy and infertility.
  - Sexually transmitted diseases and tuberculosis can cause obstruction of the vas deferens or epididymis.
  - *Mycoplasma* fastens itself to sperm, causing decreased motility.

  - Smallpox, prostatitis, orchitis, seminal vesiculitis, and urethritis may lead to obstructive azoospermia.

- Acute and chronic medical illnesses
  - Patients should be asked about recent acute febrile illnesses, which may cause a temporary suppression of gonadotropins. The decrease in sperm production may not be realized until 1-3 months later in the semen analysis.
  - Anesthesia, surgery, starvation, myocardial infarction, hepatic coma, head injury, stroke, respiratory failure, congestive heart failure, sepsis, and burns are associated with a suppression of gonadotropins, possibly through an increase in dopamine and opiates.
  - Chronic medical illnesses may lead to end organ failure by directly suppressing sex hormone levels and sperm production.

- Sexual history
  - The frequency, timing, and methods of coitus and knowledge of the ovulatory cycle should be elicited.
  - Many lubricants, such as Surgilube, Keri lotion, KY Jelly, and even saliva are spermatotoxic and should be avoided. Lubricants such as egg whites, peanut oil, vegetable oil, and petroleum jelly are not known to be spermatotoxic but still should only be used in the smallest amounts possible.
  - Studies show that the optimal timing for intercourse is every 48 hours at mid cycle.

- Testicular cancers
  - Testicular cancer is associated with impaired spermatogenic function even before orchiectomy, but the degree of dysfunction is higher than explained by local tumor effect.
  - Oligospermia is observed in more than 60% of patients at the time of

diagnosis of testicular cancer.
- Germ cell tumors are believed to share common etiological factors with testicular dysfunction, such as testicular dysgenesis, androgen insensitivity, and cryptorchidism. This is known because of an increased incidence of contralateral abnormalities of spermatogenesis in patients with testicular cancer and the fact that sperm function remains impaired even after orchiectomy.

- Treatment for testicular cancer
  - Chemotherapy has a dose-dependent effect on germ cells. Alkylating agents, such as cyclophosphamide, mustine, and chlorambucil, severely alter the seminiferous tubules and destroy spermatogonia. Chemotherapy is also mutagenic, so sperm should be donated before treatment or attempts at conception should be postponed to more than 1 year after treatment.
  - Retroperitoneal lymph node dissection (RPLND) may result in impaired emission (of semen into the urethra) and/or retrograde ejaculation.
  - The effects of radiation depend on the total dose delivered and the developmental stage of germ cells. Radiation therapy (XRT) affects mainly type B spermatogonia and, possibly, spermatocytes. A dose of as little as 0.15 Gy may cause irreversible damage, although complete recovery may be observed if stem cell numbers are not depleted. After exposure of less than 1 Gy, sperm production may return in 9-18 months, while 4-6 years may be necessary to recover sperm production after a dose of up to 5 Gy. Despite XRT and chemotherapy, nearly two thirds of patients retain the ability to father a child if the ejaculatory function is retained.
  - To potentially decrease the morbidity of adjunct therapy, select patients with grade I germ cell tumors are now undergoing unilateral orchiectomy with surveillance. However, RPLND performed for salvage therapy is associated with a higher risk of retrograde ejaculation than that performed initially.
  - Patients with reference range FSH levels at baseline usually observe an improvement in semen parameters and sperm density after orchiectomy. This is thought to be unrelated to the orchiectomy, stress factors, and release of substances by the tumor because decreased sperm counts are observed even before surgery and they do not return to baseline after surgery. Therefore, the disturbance leading to testicular cancer is thought to be inherent and present in the primordial cell.
  - Patients with a testicular tumor in a solitary testicle may be offered a partial orchiectomy in an attempt to retain fertility. Additionally, healthy testicular tissue away from the tumor can be dissected free and cryopreserved at the time of orchiectomy for future use in in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI).

- Social history
  - Studies have linked smoking to a decreased libido, while both cigarettes and marijuana lead to a decrease in sperm density, motility, and morphology.
  - Alcohol has been shown to produce both an acute and a chronic decrease in testosterone secretion.
  - Emotional stress causes a blunted GnRH release, leading to hypogonadism.

- Excessive heat exposure from saunas, hot tubs, or the work environment may cause a temporary decrease in sperm production.
- Contrary to widely held beliefs, no evidence supports that wearing constrictive underwear, or "briefs," causes decreased fertility. Even with an elevation in temperature of 0.8-1.0 degrees caused by wearing constrictive underwear, no changes in sperm parameters, no decrease in spermatogenesis, and no changes in sperm function are observed.

- Medicines

  - Many therapeutic drugs are associated with decreased sperm production.
  - Spironolactone, cyproterone, ketoconazole, and cimetidine have antiandrogenic properties.
  - Tetracycline lowers testosterone levels 20%, while nitrofurantoin depresses spermatogenesis.
  - Sulfasalazine used for the treatment of ulcerative colitis leads to decreased sperm motility and density, which is reversible.
  - Infertility has also been associated with colchicine, methadone, methotrexate, phenytoin, thioridazine, and calcium channel blockers.

- Family history

  - Congenital midline defects, cryptorchidism, hypogonadotropism, and testicular atrophy in family members may be a sign of a congenital disease.
  - A history of CF or hypogonadism should be elicited.

- Respiratory disease

  - Infertility and recurrent respiratory infections may be due to immotile cilia syndrome. Immotile cilia may manifest as an isolated disease or as part of Kartagener syndrome with situs inversus.
  - CF is associated with congenital bilateral absence of the vas deferens (CBAVD), leading to obstructive azoospermia. While both copies of this recessive gene are necessary for clinical disease, the presence of only one copy may lead to CVABD.
  - Young syndrome results in recurrent pulmonary infections and azoospermia due to inspissated material in the epididymis causing obstruction.

- Environmental and/or occupational exposure

  - Many pesticides have estrogenlike effects.
  - Dibromochloropropane (DBCP) is a nematocide widely used in agriculture that causes azoospermia without recovery because of an unknown mechanism.
  - Lead affects the hypothalamic-pituitary axis, leading to suppression of testosterone.
  - Carbon disulfide exposure from the rayon industry leads to semen, pituitary, and hypothalamic changes.
  - Heat, such as in the steel and ceramic fields, affects spermatocyte maturation.

- Spinal cord injury

    ○ Severe spinal cord injury causes infertility by a variety of mechanisms. Many patients are unable to ejaculate. Fortunately, electroejaculation or sperm retrieval techniques may be used with some success.
    ○ For unknown reasons, patients with a spinal cord injury often have a gradual decline in their semen quality. Within a year after injury, semen analysis often reveals dead sperm with signs of neutrophil infiltration. This is thought to be due to accessory gland dysfunction rather than lack of ejaculation and atrophy.

    ○ Epididymal and testicular factors appear to play a role, although the most severe dysfunction seems to come from prostatic and seminal vesicle dysfunction.

    ○ In patients with spinal cord injury, sperm parameters from the vas deferens show 54% motility and 74% viability, while only 14% motility and 26% viability is observed in ejaculated sperm. These are both much lower than that of control subjects.

Physical: The physical examination should include a thorough inspection of the testicles, penis, secondary sexual characteristics, and body habitus. It should include a detailed examination of other body functions based on the history.

- Testicles

    ○ The testicular examination should occur in a warm room with the patient relaxed. The testicles should be palpated individually between the thumb and first 2 fingers. The examiner should note the presence, size, and consistency of the testicles, and the testicles should be compared to each other.
    ○ A Prader orchidometer or ultrasound may be used to estimate the testicular volume, which is usually greater than 20 cc.
    ○ Calipers may be used to measure testicular length, which is usually greater than 4 cm, although the lower limits of normal length (mean minus 2 standard deviations) is 31 mm in white men and 34 mm in black men. The testes of Japanese men are typically smaller than the testes of white men.
    ○ Testicular atrophy may be observed in primary testicular failure, Klinefelter syndrome, endocrinopathies, postpubertal mumps, liver disease, and myotonic dystrophy.
    ○ Swelling with pain is indicative of orchitis, whereas nontender enlargement may be observed in testicular neoplasms, tuberculosis, and tertiary syphilis.

- Epididymis

    ○ The head, body, and tail of the epididymis should be palpated and assessed for their presence bilaterally.
    ○ Note induration and cystic changes. An enlarged, indurated epididymis with a cystic component should alert the examiner to the possibility of ductal obstruction.
    ○ Tenderness may be due to epididymitis.

- Vas deferens

  - Evaluate the vas for its presence bilaterally, and palpate along its entire length to check for defects, induration, nodularity, or swelling.
  - The complete absence bilaterally is observed almost exclusively in patients with either one or two copies of the CF gene, although even a small defect or gap indicates the possibility of a CF gene mutation.
  - A thickened nodular vas deferens may be observed in tuberculosis.
  - If a prior vasectomy has been performed, the presence of a nodular sperm granuloma at the proximal vasal end should be assessed.

- Spermatic cord

  - Check patients for the presence of a varicocele, which is the most common surgically correctable cause of infertility (see Image 4). To elicit this, the patient should perform a Valsalva maneuver in the sitting and standing positions in a warm room. Grade 1 varicocele is defined as palpable only with Valsalva, while grade 2 is palpable at standing, and grade 3 is visible at rest. The presence of asymmetry or an impulse with Valsalva may best help the examiner find a varicocele.

  - The sudden onset of a varicocele, a solitary right-sided varicocele, or a varicocele that does not change with Valsalva indicates the possibility of a retroperitoneal neoplastic process or vein thrombosis.

- Penis

  - The examination should focus on the location and patency of the urethral meatus and the presence of meatal strictures.
  - Patients with hypospadias or epispadias may not deposit semen appropriately at the cervix.
  - Penile curvature and the presence of penile plaques should be noted.

- Rectal examination

  - The prostate should be of normal size and without cysts, induration, or masses.

  - The seminal vesicles are usually not palpable.

  - A midline prostatic cyst or palpable seminal vesicles may be due to obstruction of the ejaculatory ducts.

- Body habitus

  - A eunuchoid body habitus, consisting of infantile hair distribution, poor muscle development, and a long lower body due to a delayed closure of the epiphyseal plates, may be observed in endocrinological disorders.

  - Truncal obesity, striae, and moon facies may be due to Cushing syndrome.

- Gynecomastia, galactorrhea, headaches, and a loss of visual fields may be observed in patients with pituitary adenomas.

- Focus the neck examination on thyromegaly and bruits.

- Palpate the liver for hepatomegaly and examine the lymph nodes to rule out lymphoma.

Causes: Causes generally can be divided into pretesticular, testicular, and posttesticular.

Pretesticular causes of infertility

Pretesticular causes of infertility include congenital or acquired diseases of the hypothalamus, pituitary, or peripheral organs that result in an alteration of the hypothalamic-pituitary axis.

Hypothalamus

Disorders of the hypothalamus lead to hypogonadotropic hypogonadism. GnRH is not secreted, and no release of LH and FSH from the pituitary occurs. Ideally, patients respond to replacement with exogenous GnRH or HCG, an LH analogue, although this does not always occur.

- Idiopathic hypogonadotropic hypogonadism

    - A failure of GnRH secretion without any discernible underlying cause may be observed alone (isolated) or as part of Kallmann syndrome, which is associated with midline defects such as anosmia, cleft lip and cleft palate, deafness, cryptorchidism, and color blindness. Kallmann syndrome has been described in both familial (X-linked and autosomal) and sporadic forms, and its incidence is estimated as 1 case per 10,000-60,000 births.
    - A failure of GnRH neurons to migrate to the proper location in the hypothalamus has been implicated. Patients generally have long arms and legs due to a delayed closure of the epiphyseal plates, delayed puberty, and atrophic testis. Testosterone therapy may allow patients to achieve a normal height, but it does not improve spermatogenesis because of insufficient intratesticular testosterone levels. Exogenous testosterone should never be administered in an attempt to boost sperm production because it actually leads to decreased intratesticular testosterone levels. Pulsatile GnRH and HCG have been used but result in only 20% achieving complete spermatogenesis.

- Prader-Willi syndrome: Patients have characteristic obesity, mental retardation, small hands and feet, and hypogonadotropic hypogonadism due to a GnRH deficiency. Prader-Willi syndrome is caused by a disorder of genomic imprinting with deletions of paternally derived chromosome arm 15q11-13.
- Laurence-Moon-Biedl syndrome: Patients with this syndrome have retinitis pigmentosa and polydactyly. Infertility is due to hypogonadotropic hypogonadism.
- Other conditions: A variety of other lesions and diseases, such as CNS

tumors, temporal lobe seizures, and many drugs (eg, dopamine antagonists) may interrupt the hypothalamic-pituitary axis at the hypothalamus.

Pituitary

Pituitary failure may be congenital or acquired, caused by tumor, infarction, radiation, infection, or granulomatous disease. Functional pituitary tumors may lead to unregulated gonadotropin release or prolactin excess. Even nonfunctional pituitary tumors can lead to pituitary failure by compressing the pituitary stalk or the gonadotropic cells, interrupting the proper chain of signals.

- Prolactinoma
  - A prolactin-secreting adenoma is the most common functional pituitary tumor. Because prolactin stimulates breast development and lactation, patients presenting with infertility often have gynecomastia and galactorrhea. Loss of peripheral visual fields bilaterally may be due to compression of the optic chiasm.
  - A prolactin level greater than 150 mcg/L is usually indicative of an adenoma, while levels greater than 300 mcg/L are nearly diagnostic. Patients should undergo an MRI or CT scan of the sella turcica for diagnostic purposes to determine whether a microprolactinoma or a macroprolactinoma is present.
  - Bromocriptine, a dopamine agonist, is used to suppress prolactin levels and is the therapy of choice for microprolactinomas. Cabergoline is also a treatment option. Some men respond not only with an increase in testosterone level but many also recover normal sperm counts. Transsphenoidal resection of a microprolactinoma is 80-90% successful, but as many as 17% recur. Surgical therapy of a macroprolactinoma is rarely curative, although this should be considered for patients with visual field defects or those who do not tolerate bromocriptine.

- Isolated LH deficiency (fertile eunuch): LH is decreased while FSH levels are within the reference range. Patients have eunuchoidal body habitus, large testis, and a low ejaculatory volume. Treatment of choice is exogenous HCG.
- Isolated FSH deficiency: This is a very rare cause of infertility. Patients present with oligospermia but have LH levels within the reference range. Treatment is with human menopausal gonadotropin or exogenous FSH.
- Thalassemia: Patients with thalassemia have ineffective erythropoiesis and undergo multiple blood transfusions. Excess iron is deposited in the pituitary gland and the testis, causing parenchymal damage and both pituitary and testicular insufficiency. Treatment is with exogenous gonadotropins and iron-chelating therapy.
- Cushing disease: Increased cortisol levels cause a negative feedback on the hypothalamus, decreasing GnRH release.

Peripheral organs

The hypothalamus-pituitary axis may be interrupted by hormonally active peripheral tumors or other exogenous factors.

- Cortisol excess or deficiency: Excess cortisol may be produced by adrenal hyperplasia, adenomas, carcinoma, congenital adrenal hyperplasia (CAH), or lung tumors. A variety of enzyme defects leads to CAH. The most common

is 21-hydroxylase deficiency. Because cortisol is not secreted, a lack of feedback inhibition on the pituitary gland occurs, leading to adrenocorticotropic hormone (ACTH) hypersecretion. This leads to increased androgen secretion from the adrenal gland, causing feedback inhibition of GnRH release from the hypothalamus. Patients present with short stature, precocious puberty, small testis, and occasional bilateral testicular rests. Screening tests include increased plasma 17-hydroxylase and urine 17-ketosteroids. High cortisol levels, which cause negative feedback on the pituitary to decrease LH release, may be observed in Cushing syndrome.

- Estrogen: High estrogen levels may be secondary to Sertoli cell tumors, Leydig tumors, liver failure, or massive obesity. Estrogen causes negative feedback on the pituitary gland.
- Iatrogenic causes: High cortisol levels due to steroid therapy for ulcerative colitis, asthma, arthritis, or organ transplant may lead to inhibition of hypothalamic GnRH release.

Primary testicular causes of infertility

Primary testicular problems may be chromosomal or nonchromosomal in nature. While chromosomal failure is usually caused by abnormalities of the sex chromosomes, autosomal disorders are also observed.

Chromosomal abnormalities

An estimated 6% of infertile men have chromosomal abnormalities, compared to 0.6% of the general population. Patients with azoospermia or severe oligospermia are more likely to have a chromosomal abnormality (10-15%) than infertile men with sperm density within the reference range (1%). A karyotype test and a Y chromosome test for microdeletions are indicated in patients with azoospermia or severe oligospermia (<5 million sperm per cc).

- Klinefelter syndrome

  - Klinefelter syndrome is the most common chromosomal cause of male infertility, estimated to be present in 1 per 500-1000 male births. Classic Klinefelter syndrome has a 47,XXY karyotype and is caused by a nondisjunction during the first meiotic division, two thirds of which is of maternal origin; mosaic forms are due to nondisjunction following fertilization. The only known risk factor is advanced maternal age. Infertility is caused by primary testicular failure, and most patients are azoospermic. Hormonal analysis reveals increased gonadotropin levels, while 60% have decreased testosterone levels. Surprisingly, most patients have normal libido, erections, and orgasms, so testosterone therapy has only a limited role. Exogenous testosterone therapy may suppress any underlying sperm production so this is never a mode of treatment for azoospermia.
  - Physical examination in these patients reveals gynecomastia, small testis, and eunuchoid body proportions because of delayed puberty. In some patients, secondary sex characteristics develop normally, but they are usually completed late. These men are at a higher risk for breast cancer, leukemia, diabetes, empty sella syndrome, and pituitary tumors. Testicular histology reveals hyalinization of seminiferous tubules. Some men with Klinefelter syndrome may be able to conceive

with the help of assisted reproductive techniques. Of azoospermic patients with Klinefelter syndrome, 20% show the presence of residual foci of spermatogenesis. Although the XXY pattern is observed in the spermatogonia and primary spermatocytes, many of the secondary spermatocytes and spermatids have normal patterns. The chromosomal pattern of the resultant embryos can be assessed with preimplantation genetic diagnosis (PGD).

- XX male (sex reversal syndrome): An XX karyotype is due to a crossover of the sex-determining region (SRY) of the Y chromosome (with the testis determining factor) to either the X chromosome or an autosome. Patients are often short, with small firm testis and gynecomastia, but they have a normal-sized penis. Seminiferous tubules show sclerosis.
- XYY male: An XYY karyotype is observed in 0.1-0.4% of newborn males. These patients are often tall and severely oligospermic or azoospermic. This pattern is often associated with aggression and criminal behavior. Biopsy reveals maturation arrest or germ cell aplasia. Functional sperm that are present may have a normal karyotype.
- Noonan syndrome (46,XY): Patients with Noonan syndrome, also known as male Turner syndrome, have physical characteristics similar to that of women with Turner syndrome (45,X). Features include a webbed neck, short stature, low-set ears, ptosis, shieldlike chest, lymphedema of hands and feet, cardiovascular abnormalities, and cubitus valgus. Leydig cell function is impaired, and most patients are infertile because of primary testicular failure.
- Mixed gonadal dysgenesis (45,X/46,XY): Patients have ambiguous genitalia, a testis on one side, and a streaked gonad on the other.
- Y chromosome microdeletion syndrome: The long arm of the Y chromosome (Yq) is considered critical for fertility, especially Yq11.23 (interval 6). Macroscopic deletions of Yq11 are often observed in patients with azoospermia, although many new microdeletions have been implicated as a significant cause of infertility. These microdeletions are not observed on regular karyotype; rather, their identification requires polymerase chain reaction (PCR)–based sequence-tagged site mapping or Southern blot analysis. Three regions have been described, called azoospermic factors a, b, and c (AZFa, AZFb, AZFc). These deletions are observed in 3-19% of patients with idiopathic infertility and 6% of patients with oligospermia, although 7% of patients with other known causes of infertility also have a deletion. Patients with azoospermia or severe oligospermia seeking assisted reproductive techniques should be screened.
- Bilateral anorchia (vanishing testis syndrome): Patients have a normal male karyotype (46,XY) but are born without testis bilaterally. The male phenotype proves that androgen was present in utero. Potential causes are unknown, but it may be related to infection, vascular disease, or bilateral testicular torsion. Karyotype shows a normal SRY gene. Patients may achieve normal virilization and adult phenotype by the administration of exogenous testosterone, but they are infertile.
- Down syndrome: These patients have mild testicular dysfunction with varying degrees of reduction in germ cell number. LH and FSH are usually elevated.
- Myotonic dystrophy: This is an autosomal dominant defect in the dystrophin gene causing a delay in muscle relaxation after contraction. Seventy-five percent of patients have testicular atrophy and primary testicular failure due to degeneration of the seminiferous tubules. Leydig cells are normal. Histology reveals severe tubular sclerosis. No effective therapy exists.

Nonchromosomal testicular failure

Testicular failure that is nonchromosomal in origin may be idiopathic or acquired by gonadotoxic drugs, radiation, orchitis, trauma, or torsion.

- Varicocele

    - A varicocele is the abnormal dilation of the veins of the pampiniform plexus of the scrotum. Varicoceles are present in 15% of the population but are observed in 30-35% of primary infertile men, making it the most common surgically correctable cause of male infertility. In addition, it has been implicated as the cause of 75-85% of cases of secondary infertility.
    - Varicoceles are usually asymptomatic, but they may cause pain or testicular atrophy. Varicoceles are observed more commonly on the left side than the right. Varicoceles lead to abnormalities of both testicular spermatogenesis and steroidogenesis, and they may be associated with nearly any abnormal pattern on semen analysis patterns. Etiology of these problems is unknown, although investigators have implicated an increased intratesticular temperature, reflux of toxic metabolites, and germ cell hypoxia as potential causes of infertility.
    - Indications for repair include a varicocele with infertility or a symptomatic varicocele. Much controversy exists over the issue of adolescent varicoceles and whether or not they should be repaired routinely. Many varicoceles are not associated with infertility, severe symptoms, or hypogonadism and do not need to be fixed. After repair, 40-70% of patients have improved semen parameters, while 40% are able to achieve a pregnancy without other intervention.

- Cryptorchidism: An estimated 3-4% of full-term males are born with an undescended testicle; however, less than 1% remain undescended by the age of 1 year. Risks for cryptorchidism include family history and prematurity. It may be observed as part of syndromes such as prune belly syndrome. Patients have an increased risk of infertility, despite orchidopexy. The higher and longer the testicle resides outside the scrotum, the greater the likelihood of damage to the seminiferous tubules. Testicular histology typically reveals a decreased number of Leydig cells and decreased spermatogenesis. Cryptorchidism may be due to inherent defects in both testes because even men with unilateral cryptorchidism have lower than expected sperm counts.
- Trauma: Testicular trauma is the second most common acquired cause of infertility. The testes are at risk for both thermal and physical trauma because of their exposed position
- Sertoli-cell-only syndrome (germinal cell aplasia): Patients with germinal cell aplasia have LH and testosterone levels within the reference range but have an increased FSH level. The etiology is unknown but is probably multifactorial. Patients present with small- to normal-sized testes and azoospermia. Secondary sex characteristics are normal. Histology reveals seminiferous tubules lined by Sertoli cells and a normal interstitium, although no germ cells are present.
- Chemotherapy: Chemotherapy is often most toxic to actively dividing cells, eg, the spermatogonia and spermatocytes. Germ cells up to the preleptotene stage are especially at risk. The most toxic drugs are the alkylating agents such as cyclophosphamide. Treatment for Hodgkin disease has been estimated to lead to infertility in as many as 80-100% of patients.

- Radiation therapy: While Leydig cells are relatively radioresistant because of their low rate of cell division, the Sertoli and germ cells are extremely radiosensitive. When stem cells remain viable, patients may regain fertility within several years. Patients are advised to avoid conception for 6 months to 2 years because of the possibility of chromosomal aberrations in their sperm caused by the mutagenic properties of XRT. Even with the testis shielded, XRT below the diaphragm potentially leads to infertility because of the release of reactive oxygen free radicals.
- Orchitis: The most common cause of acquired testicular failure in adults is viral orchitis, usually caused by the mumps virus, echovirus, or group B arbovirus. Of adults with mumps, 25% develop orchitis; two thirds of cases are unilateral orchitis, and one third of cases are bilateral. Orchitis develops within a few days after the onset of the parotid gland inflammation, but orchitis may precede parotid gland inflammation. The virus either directly affects the seminiferous tubules or indirectly causes ischemic damage because of the intense swelling of the testicle and subsequent compression against the tough tunica albuginea. After recovery, the testicle may return to normal or may atrophy. Atrophy is observed within 1-6 months, and the degree of atrophy does not correlate with the severity of orchitis or infertility. Normal fertility is observed in three fourths of patients with unilateral mumps orchitis and in one third of patients in bilateral orchitis.
- Granulomatous disease: Leprosy and sarcoidosis may infiltrate the testicle and lead to testicular failure.
- Sickle cell disease: Sickling of cells within the testis leads to microinfarcts and secondary testicular failure.
- Other causes: Use of alcohol, cigarettes, caffeine, and marijuana may lead to testicular failure.
- Idiopathic causes: Despite a thorough workup, nearly 25% of men have no discernible cause for their infertility.

Posttesticular causes of infertility

Posttesticular causes of infertility include problems with sperm transportation through the ductal system (congenital or acquired). Genital duct obstruction is a potentially curable cause of infertility, and it is observed in 7% of infertile patients. Additionally, the sperm may be unable to cross the cervical mucus or may have ultrastructural abnormalities.

- Cystic fibrosis: CF is the most common genetic disorder in white people. Patients with CF nearly uniformly have congenital bilateral absence of the vas deferens. The cystic fibrosis transmembrane regulator (CFTR) protein plays a role in mesonephric duct development during early fetal life, so these patients must be evaluated for urinary tract abnormalities using renal ultrasound or similar imaging tests. Patients are candidates for assisted reproduction techniques after appropriate genetic screening in the partner.

- DES exposure: An increased incidence of duct obstruction is observed in children of mothers who were exposed to DES during pregnancy.

- Blockage (acquired): Genital ducts may become obstructed secondary to infections such as chlamydia, gonorrhea, tuberculosis, and smallpox. Young syndrome leads to inspissation of material in the vas deferens. Trauma, previous attempts at sperm aspiration, and inguinal surgery may result in blockage. Small calculi may block the ejaculatory ducts, or prostatic cysts

may extrinsically block the ducts.

- Antisperm antibodies: Antisperm antibodies bind to sperm and impair motility. They may lead to clumping as well. This can impair movement through the female reproductive tract and interaction with the oocyte.

- Immotile cilia syndrome: This is isolated or part of Kartagener syndrome with situs inversus. Because of a defect in the dynein arms, spokes, or microtubule doublet, cilia in the respiratory tract and in sperm do not function properly. Patients experience sinusitis, bronchiectasis, and infertility.

- Schmidt syndrome: Schmidt syndrome is a generalized autoimmune disorder characterized by multiple primary endocrine deficiencies and circulating antibodies against the basement membrane of the testis.

- Retrograde ejaculation: This is caused by an open bladder neck during ejaculation. Retrograde ejaculation may be due to causes such as diabetes, bladder neck surgery, RPLND, alpha-antagonists, transurethral prostatectomy (TURP), colon or rectal surgery, multiple sclerosis, or spinal cord injury. Diagnosis is made by observing 10-15 sperm per high-power field (HPF) in the postejaculatory urine.

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Adrenal Adenoma
Adrenal Carcinoma
C-11 Hydroxylase Deficiency
C-17 Hydroxylase Deficiency
Cannabis Compound Abuse
Chlamydial Genitourinary Infections
Cryptorchidism
Follicle-Stimulating Hormone Abnormalities
Growth Hormone Deficiency
Growth Hormone Replacement in Older Men
Gynecomastia
Hematospermia
Hemochromatosis
Infertility, Male
Intestinal Radiation Injury
Kallmann Syndrome and Idiopathic Hypogonadotropic Hypogonadism
Luteinizing Hormone Deficiency
Luteinizing Hormone-Releasing Hormone Deficiency
Lymph Node Dissection, Retroperitoneal
Open Prostatectomy
Prostatitis, Bacterial
Scrotal Trauma
Sertoli-Cell-Only Syndrome
Spinal Malformation
Teratology and Drug Use During Pregnancy
Testicular Choriocarcinoma
Testicular Seminoma

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Lab Studies:

- Semen analysis: The semen analysis is the cornerstone of the male infertility workup. A specimen is collected by masturbation into a clean, dry, sterile container or during coitus using special condoms (containing no spermicidal lubricants). The patient should be abstinent for 2-3 days prior to maximize sperm number and quality. Each day of abstinence is typically associated with an increase in semen volume of 0.4 cc and an increase in sperm density by 10-15 million sperm per cc for up to 7 days. The sample should be processed within 0.5-1 hour, and 2-3 samples (at a minimum of 2-3 d apart) must be evaluated to assess for variations in sperm number and quality. A variety of parameters is measured, such as ejaculate volume and sperm density, quality, motility, and morphology. Individual tests evaluate only one aspect of a quality necessary for fertility and do not imply the ability or inability to achieve conception (see Table 1).

  - Volume: Normal ejaculate volume is 1.5-5.0 cc. A small ejaculate volume may be observed in patients with retrograde ejaculation, absence of the vas deferens or seminal vesicles, ductal obstruction, hypogonadotropism, or poor sympathetic response. An increased volume rarely is observed and is often caused by a contaminant, such as urine.

  - Semen quality: Semen is initially a coagulum that liquifies in 5-25 minutes because of prostatic enzymes. At this point, pouring the semen drop by drop should be possible. Semen that is not initially a coagulum is often caused by an ejaculatory duct obstruction or the absence of seminal vesicles. Nonliquification of the semen can be differentiated from benign hyperviscosity by a normal postcoital test finding. No excessive sperm agglutination should exist.

  - Sperm density: Normal sperm density is greater than 20 million sperm per cc or at least 50-60 million total sperm. Oligospermia is defined as less than 20 million sperm per cc, severe oligospermia is less than 5 million sperm per cc, and azoospermia is defined as no sperm present. To verify azoospermia, centrifuge the semen and evaluate the pellet under the microscope. Also, a postejaculatory urine sample should be analyzed for sperm. Truly azoospermic patients should be evaluated for ejaculatory duct obstruction by transrectal ultrasound (TRUS) and should undergo a hormonal evaluation; oligospermia may be due to partial ejaculatory duct obstruction or antisperm antibodies. A decreased FSH level implies possible hypothalamic or pituitary insufficiency. Patients with testicular failure may have FSH levels that are either high or within the reference range.

  - Sperm motility: Motility is described as the percent of sperm present with flagellar motion

viewed on a bright-field or phase contrast microscope. Normal motility is defined as more than 60% of sperm having normal movement. Grading is as follows: grade 0 is no movement, grade 1 is sluggish movement, grade 2 is slow movement but not straight, grade 3 is movement in a straight line, and grade 4 is terrific speed. Evaluate patients with abnormal motility for pyospermia, antisperm antibodies, varicocele, sperm ultrastructural abnormalities, or partial ductal obstruction.

- Sperm morphology
  - The head, acrosome, mid piece, and tail of individual spermatozoa are analyzed by phase-contrast microscopy after fixation with Papanicolaou stain. At least 200 sperm are analyzed. Normal sperm have a smooth oval head approximately 3-5 μm long and 2-3 μm wide. More than 60% of sperm should be normal, and less than 2-3% should be immature.

  - Teratospermia is defined as less than 30% normal morphology. Abnormal head shapes are described as tapered, duplicated, small, large, amorphous, and pyriform. The acrosome should be 40-70% of the size of the head, and no mid piece or tail abnormalities should be present.
  - Evaluate patients with a high number of immature sperm for exposure to heat, radiation, or infectious processes. These sperm show a high level of retained cytoplasmic droplets around the mid piece.
  - Kruger introduced the definition of strict criteria in 1986. He objectified this test by specifically defining the normal morphological parameters, thus enhancing consistency and reproducibility among laboratory technicians. He reported a clinically significant threshold of 14% normal forms as an excellent predictor of IVF success. Patients with less than of 14% normal forms had a substantially reduced success rate.

- Computer-aided semen analysis (CASA): Introduced in the late 1980s, CASA uses a video camera and computer to visualize and analyze sperm concentration and movement. This semiautomated technique is thought to potentially standardize the evaluation of semen. Parameters measured include the curvilinear velocity, defined as the average distance per unit time between successive sperm positions; the straight-line velocity, which is the speed of forward direction; and linearity, which is the straight-line velocity divided by the curvilinear velocity. In addition, the program measures the average path velocity, the amplitude of lateral head displacement, and the flagellar beat frequency, and it is used to evaluate for evidence of hyperactivation. Although CASA produces good qualitative data, it is a labor-intensive procedure that includes a high initial cost and is plagued with inaccuracies when sperm concentrations are very high or very low. It has not been shown to improve patient outcomes but, rather, is very
helpful for research purposes.

- Infection: An increased number of round cells are often observed in patients with infectious or inflammatory processes. While germ cells and white blood cells appear identical on microscopic examination, immunohistochemical stains are used to differentiate between the 2 cell types. Immunohistochemical stains are performed if more than 5-10 round cells per HPF are present. An increased number of white blood cells may signify infection or inflammation of the genital tract.

- Other tests: Semen may be analyzed for levels of zinc, citric acid, acid phosphatase, and alpha-glucosidase. These tests are used to determine gland failure or obstruction.

- Antisperm antibody test

  - Sperm contain unique antigens that are not recognized as self by the body's immune system

because they form after puberty. They are usually protected from the host's immune system by the blood-testis barrier.

- Antisperm antibodies may form when sperm are exposed to the body's defense outside of the blood-testis barrier. These antibodies bind to sperm and may lead to infertility due to a decreased ability to penetrate the cervical mucus, premature acrosome reaction, and decreased ability to bind to the zona pellucida. Known causes include ductal obstruction, infection, testicular torsion, cryptorchidism, testicular or spermatic cord trauma, or varicocele.

- An estimated 60% of patients have evidence of antisperm antibodies after vasectomy, although the clinical significance has not been completely elucidated. In addition, antibodies are present in 35% of patients with CBAVD. Evidence of antibodies found in serum or seminal plasma is less prognostic than antibodies bound to sperm.

- Suspect antisperm antibodies when semen analysis reveals abnormal clumping, agglutination, unexplained decreased motility, or an abnormal postcoital test result.

- Several methods are available to detect antisperm antibodies, such as radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA), but the most specific test is the immunobead test. In this test, rabbit antisperm antibodies are linked to polyacrylamide beads that interact with immunoglobulins attached to sperm. More than 15-20% bound is considered a positive test result.

- Hormonal analysis

  - Fewer than 3% of cases of male infertility are estimated to be due primarily to a hormonal cause.

  - A routine part of the initial evaluation is testing of specific serum hormone levels, which usually includes FSH, LH, testosterone, and prolactin. These 4 hormones are closely related and have an impact on sperm production.

  - Abnormalities may be a sign of a primary hypothalamic, pituitary, or testicular problem.

Imaging Studies:

- Transrectal ultrasound

  - A TRUS is indicated in patients with azoospermia or severe oligospermia to rule out a complete or partial ejaculatory duct obstruction. TRUS is also useful to evaluate for the presence or absence of the seminal vesicles.

  - A 6.5- to 7.5-MHz probe is used with the bladder partially filled, and the prostate, ejaculatory ducts, and seminal vesicles are evaluated. The ejaculatory ducts are normally 3-8 mm wide and 2-3 cm long.

  - Obstruction is suggested by enlarged seminal vesicles, which may be caused by obstructing stones, stenosis, or intraprostatic cysts. Cysts of müllerian origin are in the midline at the utricle and contain no sperm, while those of wolffian duct origin may be part of an ejaculatory duct diverticulum and may contain sperm.

  - Those patients with ejaculatory duct obstruction are candidates for transurethral resection of the ejaculatory ducts.

- Diagnosis may be confirmed by seminal vesicle aspiration, with many sperm per HPF indicating a probable obstruction.

- Scrotal ultrasound

  - A scrotal ultrasound can be used to evaluate the anatomy of the testis, epididymis, and spermatic cord. It is useful for evaluating testicular volume and blood flow, testicular and paratesticular masses, and the presence of varicoceles.

  - Investigators have debated the need to perform a testicular ultrasound on all patients with infertility because of the increased risk of testicular cancer in infertile men (1 out of 200 versus 1 out of 20,000 in the general population). A recent large review reported a 38% rate of abnormalities on testicular ultrasound, including 0.5% with testicular cancer and 29.7% with varicocele.

  - Currently, routine screening ultrasound is not recommended or performed.

  - A color flow ultrasound is used to evaluate for variocele using a 7- to 10-MHz probe.

  - Any spermatic vein greater than 3 mm or an increase in vein size with Valsalva is considered a positive test result. However, Doppler ultrasound may be too sensitive and may detect subclinical varicoceles, which have not been proven to adversely affect fertility.

- Vasogram

  - A vasogram is used to evaluate patency of the ductal system.

  - Indications for vasogram include azoospermia with mature spermatids present on testicular biopsy and at least one palpable vas.

  - Relative indications include severe oligospermia with a normal finding on testis biopsy, antisperm antibodies, and decreased semen viscosity.

  - This test may be performed either as an open procedure at the same time as testicular biopsy (see Image 5) or by a percutaneous puncture.

  - The patient may be placed in a 10- to 15-degree Trendelenburg position to bring the symphysis pubis out of the field.

  - Unilateral patency rules out vasal or ejaculatory duct obstruction as the cause of azoospermia.

Other Tests:

- Postcoital test

  - An abnormal postcoital test result is observed in 10% of infertile couples. Indications for performing a postcoital test include semen hyperviscosity, increased or decreased semen volume with good sperm density, or unexplained infertility.

  - After coitus at mid cycle, the female's cervical mucus is examined for the presence or absence of sperm. Usually, 10-20 sperm per HPF are observed. Abnormal results may also

be due to antisperm antibodies, sperm ultrastructural abnormalities, an abnormal hormonal milieu, male or female genital tract infection, poor semen quality, inhospitable cervical mucus, or male sexual dysfunction. If no sperm are observed, then the couple's coital technique should be analyzed.

  - If the test result is normal, consider a test of sperm function and ability to penetrate the egg.

- Sperm function tests: When a primary sperm defect is suspected or when other tests do not reveal the cause of infertility, perform sperm function tests to determine if a significant sperm factor exists. These tests analyze specific sperm functions such as the ability to undergo capacitation and the acrosome reaction, the ability to bind to the egg, and the ability to penetrate the egg. Results are important because they help guide therapy.

  - Capacitation assay: This test is used to evaluate the ability of sperm to undergo capacitation, which is necessary for fertilization. After capacitation, sperm have hyperactivated motility, which is recognized under microscopy. Sperm that do not undergo capacitation portend a poor response to IVF, and ICSI should be considered.

  - Acrosome reaction: The acrosome reaction assay tests the ability of the sperm to undergo the acrosome reaction when exposed to inducing substances. The acrosome process, which covers the anterior two thirds of the sperm head, contains hyaluronidase and other enzymes used to digest the zona pellucida of the egg. After sperm binding and capacitation, the plasma membrane of the egg induces the acrosome to release its contents. This reaction occasionally occurs spontaneously (<10% of the time), although a spontaneous reaction is more common in infertile men. Under the microscope, acrosome-inducing substances are added to the sample after the sperm have undergone capacitation, which usually takes approximately 3 hours. Usually, 15-40% of the sperm undergo the acrosome reaction when stimulated, and fewer undergo the reaction in infertile men. The results of the test correlate with IVF success; patients with an abnormal test result may need to undergo ICSI.

  - Sperm penetration assay (SPA): First described in 1976 by Yanagimachi et al, the SPA is used to check the ability of sperm to function in vitro by evaluating capacitation, the acrosome reaction, and the ability of the sperm to fuse with the oolemma. Cross-specie fertilization is usually prevented by the zona pellucida. Hamster ova, with the zona pellucida removed, are incubated with the donor's sperm and the number of sperm penetrated per ovum is measured. A normal result is more than 5 sperm penetrations per ovum. Fewer penetrations probably indicate a problem. Patients with a poor SPA should proceed directly to ICSI.

  - Hypoosmotic swelling (HOS): The HOS test is used to provide functional information to differentiate between viable but immotile sperm and dead sperm. Normal sperm are able to maintain an osmotic gradient when exposed to hypoosmotic conditions, whereas dead sperm cannot. After exposure to a dilute solution (150 mmol/L), sperm are observed under the microscope. Normal sperm swell, with bulging of the plasma membrane and curling of the tail. This test is commonly used clinically to select viable (but nonmotile) sperm for ICSI.

  - Inhibin B: Inhibin B is usually produced by sperm for the acrosome reaction. An increased level or an inability to clear acrosomal enzymes may lead to self-destruction and lipid peroxidation of the sperm membrane. Increased inhibin B levels may be caused by ductal obstruction or abnormalities within the seminiferous tubules.

  - Vitality stains: Vitality stains using substances such as eosin Y and trypan blue help determine whether a sperm is alive and the membrane is intact or if the sperm is dead. Live sperm can exclude dye, while dead sperm cannot. These tests are of little use unless very low numbers of sperm exist or motility is absent and necrospermia must be ruled out. The

Semen   Does not coagulate   TRUS (ejaculatory duct

Medical Care: Limited numbers of medical treatments are aimed at improving chances of conception for patients with known causes of infertility.

- Endocrinopathies
    - A number of patients with hypogonadotropic hypogonadism respond to GnRH therapy or gonadotropin replacement.
    - HCG is an LH analogue that may be used alone of in combination with human menopausal gonadotropin (HMG) for Leydig cell stimulation.
    - Clomiphene citrate and tamoxifen are antiestrogens that block the negative feedback loop at the pituitary level, allowing a potentially increased release of gonadotropins.
    - Patients with CAH may respond to therapy with glucocorticoids, while those with isolated testosterone deficiency may respond to testosterone replacement.
    - Exogenous testosterone decreases intratesticular testosterone production, thus inhibiting Sertoli cell function and spermatogenesis.
    - Treat patients with hyperprolactinemia with bromocriptine, a dopamine antagonist, or cabergoline.

- Antisperm antibodies: Patients with antisperm antibody levels greater than 1:32 may respond to immunosuppression using cyclic steroids for 3-6 months. However, counsel patients regarding the risk of avascular necrosis of the hip, weight gain, and iatrogenic Cushing syndrome.
- Retrograde ejaculation

    - Imipramine or alpha-sympathomimetics, such as pseudoephedrine, may help close the bladder neck to assist in antegrade ejaculation. However, these medicines are of limited efficacy, especially in patients with a fixed abnormality such as a bladder neck abnormality occurring after a surgical procedure.
    - Alternatively, sperm may be recovered from voided or catheterized postejaculatory urine to be used in assisted reproductive techniques. The urine should be alkalinized with a solution of sodium bicarbonate for optimal recovery.
    - More recently, the injection of collagen to the bladder neck has allowed antegrade ejaculation in a patient who had previously undergone a V-Y plasty of the bladder neck and for whom pseudoephedrine and intrauterine insemination had failed.

- Semen processing
    - Patients with poor semen may benefit from having their semen washed and concentrated in preparation for intrauterine insemination.
    - Couples with an abnormal postcoital test result due to semen hyperviscosity may benefit from a precoital saline douche or semen processing with chymotrypsin.

- Lifestyle
    - Encourage patients to stop smoking cigarettes and marijuana and to limit environmental exposures to harmful substances and/or conditions.
    - Stress relief therapy and consultation of other appropriate psychological and social professionals may be advised.

- Infections: Treat infections with appropriate antibiotics.

Surgical Care: Experienced professionals can perform a variety of surgical interventions for the diagnosis and treatment of male infertility.

- Varicocelectomy
    - A variety of techniques for varicocelectomy have been proposed and used, each with advantages and disadvantages.

- The retroperitoneal approach may be performed as an open procedure or laparoscopically, and it is best reserved for patients who have had previous inguinal surgery. General anesthesia is required.
- The inguinal and subinguinal microscopic approach allows for ligation of individual veins with minimal risk of arterial damage. Collateral vessels entering the cord distally may also be directly addressed with this technique.
- The most effective and safest approach appears to be the microsurgical technique (see Image 6). This allows better delineation of the veins and is associated with a lower incidence of inadvertent testicular artery injury. The artery is isolated using intraoperative Doppler ultrasound, allowing safer ligation of the dilated veins.

- Successful varicocelectomy results in improvement in semen parameters in 60-70% of patients. The repair also typically halts further testicular damage and improves Leydig cell function.
- Persistent dilation after repair is not unusual and does not necessarily represent surgical failure. Rather, the veins may remain clinically apparent due to chronic stretching or thrombosis, even if venous reflux is no longer present. Semen analysis may show improvement as early as the 3-month follow-up visit.

- Vasovasostomy or vasoepididymostomy
  - These microsurgical techniques are performed for patients with known epididymal or vasal obstruction, both congenital and acquired (eg, from surgery, trauma, infection). Improved surgical techniques and the use of the operating microscope have improved the outcomes of patients requiring vasectomy reversal or those with primary vas obstruction.
  - After scrotal exploration, the patency of the duct system proximal to the proposed site of anastomosis is confirmed by examination of expressed fluid for the presence of sperm. If no fluid is expressed, a 24-gauge angiocatheter with 0.1 cc of saline should be used to gently barbotage the proximal vas. If no sperm are observed, inspect the vasal fluid aspirated.
  - A thickened, white, toothpastelike fluid usually contains no sperm or nonviable sperm fragments, whereas a watery thin fluid often implies proximal patency. If viable sperm are observed, send an additional sample for cryopreservation prior to vasovasostomy. These sperm may be used for IVF or ICSI if the man remains azoospermic after the repair.
  - The patency of the distal duct system is confirmed by injecting 10 cc of sterile saline through the vas; if no resistance is encountered, the system is deemed patent. Additionally, a radiographic vasogram or a chromogenic vasogram with methylene blue can be performed. Radiographic contrast visualized passing into the bladder or blue coloration of the urine is proof of patency. A 2-0 nylon suture can be passed into the vasal lumen to check the distance to obstruction, if the above tests reveal distal blockage.
  - A vasovasostomy (see Image 7) involves a 2-layer closure, first approximating the inner lining using interrupted 10-0 nylon suture and subsequently closing the outer layer with interrupted 9-0 nylon suture. Optimally, a tension-free, mucosa-to-mucosa, watertight anastomosis is created..

  - A vasoepididymostomy (see Image8) is also closed in 2 layers. Factors that predict a more favorable outcome include a shorter time from the original injury/surgery, undergoing a vasovasostomy on one side rather than bilateral vasoepididymostomies, and reconstruction because of an infectious etiology rather than a surgical or idiopathic etiology.

  - When performing a vasoepididymostomy, an end-to-side technique is easier to perform and has better outcomes than an end-to-end anastomosis. More recently, a triangular technique for vasoepididymostomy has been proposed. Although more motile sperm are present at the proximal epididymis in patients with ductal obstruction, the technique is easier and more successful if it is performed at the distal end.
  - A varicocelectomy and vasovasostomy should never be performed at the same time because

of a risk of testicular atrophy.

- Transurethral resection of the ejaculatory ducts
  - Patients with a known or suspected obstruction of the ejaculatory ducts may be eligible for a transurethral resection of the ejaculatory ducts (TURED).
  - In the operating room, with patients under spinal or general anesthesia, the resectoscope with a 24F cutting loop is used to excise the verumontanum of the prostate. Using the O'Connor drape to enable placement of a finger in the rectum to elevate the prostate may be helpful.
  - The resection is performed with great care to avoid injuring the bladder neck or external sphincter.
  - Risks with this procedure include chemical or bacterial epididymitis due to reflux, bleeding, and retrograde ejaculation.

- Sperm retrieval techniques: A variety of techniques is used to retrieve sperm to be used in assisted reproductive techniques. More mature sperm are found in the epididymis, although testicular sperm can also be used with good success.
  - Microsurgical epididymal sperm aspiration (MESA): Directly retrieving sperm from the epididymis results in a higher number and higher quality of sperm than observed in testicular sperm extraction. Using a microscope, the epididymis is uncovered and incised to express sperm. Epididymal fluid is aspirated into a tuberculin syringe primed with human tubal fluid (HTF). This is examined under a microscope for sperm presence and quality, and the sperm are cryopreserved appropriately.
  - Percutaneous epididymal sperm aspiration (PESA): Direct sperm aspiration from the epididymis is a convenient and effective procedure that can be performed under local anesthesia in the office setting. While effective in sperm retrieval, this does not allow sampling from multiple sites of the epididymis. With this approach, an associated increased risk of epididymal and testicular injury and secondary epididymal obstruction exists compared to MESA.
  - Autogenous spermatocele: For patients with an unreconstructable ductal system, an autogenous spermatocele may be created. A buttonhole is created within the viscera, and repeated percutaneous aspirations of sperm can be performed using ultrasound guidance. An intact tunica vaginalis with no adhesions is needed, so it is ideal for use in patients with normal spermatogenesis and a congenital absence of the vas. This procedure is rarely used.
  - Alloplastic spermatocele: Similar to the above technique, an artificial silicone sperm reservoir is used in place of the tunica vaginalis for sperm storage and subsequent retrieval. This technique has been unsuccessful so far.
  - Testicular sperm extraction (TESE): Indications for retrieving sperm directly from the testicle include azoospermia, no sperm present in the epididymis, or contraindications to MESA. The technique is the same as open testicular biopsy. Often, careful sampling and inspection of tissue yield viable sperm, even in patients with Sertoli-cell-only syndrome. More recently, the Biopty gun has been used for sperm aspiration for patients with normal spermatogenesis and obstructive azoospermia. This requires only local anesthesia and may be performed in the office setting, but it allows only limited sperm retrieval.

- Electroejaculation
  - Patients with anejaculation because of spinal cord injury, RPLND, neurologic disorders, or other conditions may be candidates for electroejaculation for sperm retrieval.
  - Under general anesthesia, an unlubricated Foley catheter is placed in the bladder and a buffer (ie, HTF) is instilled through the catheter. A rectal probe is inserted, thus positioning its electrodes against the posterior seminal vesicles. Electrical stimulation is begun at 3-5 volts and increased as necessary.
  - Electroejaculation has been reported to achieve up to a 90% sperm retrieval rate and a 40% pregnancy rate in select populations. Using this technique, patients benefit from a full

ejaculate that can be used for either ICSI or IVF. This is important because patients with anejaculation have lower conception rates; the cause is unknown. For instance, using ICSI, patients with ejaculatory dysfunction due to spinal cord injury or RPLND have lower pregnancy rates (29% versus 47%) than subfertile men and men with obstructive azoospermia undergoing MESA or testicular aspiration. This is despite similar fertilization rates (60% versus 58%).

  o The penile vibratory stimulator has been shown to be a useful alternative to electroejaculation in select patients. The Food and Drug Administration FDA has recently approved this device for home use, using 2.2 mm at 100 Hz. This is associated with fewer adverse effects, lower morbidity, and a decreased cost compared to electroejaculation. In addition, collection may occur at home instead of in the operating room.

- Artificial insemination
  o Artificial insemination (AI) involves the placement of sperm directly into the cervix (ie, intracervical insemination [ICI]) or the uterus (ie, intrauterine insemination [IUI]). AI is most useful for couples in whom the postcoital test indicated no sperm, those who have very low sperm density or motility, or those who have unexplained infertility.
  o IUI allows the sperm to be placed past the inhospitable cervical mucus and increases the chance of natural fertilization. This results in a 4% pregnancy rate if used alone and a pregnancy rate of 8-17% if combined with superovulation. Both processes require semen processing.
  o Patients in whom IUI has failed 3-6 times should consider proceeding to IVF.

- Assisted reproduction techniques (ART): Patients with severe oligospermia, azoospermia, unexplained infertility, or known defects that preclude fertilization by other means are candidates for ART. ART uses donated or retrieved eggs that are fertilized by the male partner's sperm or donor sperm. The fertilized embryos are then replaced within the female reproductive tract. These techniques result in a 15-20% delivery rate per cycle and may eventually be successful in 50% of cases. However, the high cost and technical difficulty of the procedures generally preclude their routine use as first-line therapy.

  o In vitro fertilization
    ■ IVF involves fertilization of the egg outside the body and reimplantation of the fertilized embryo into the woman's uterus. Indications for IVF include previous failures with IUI and known conditions of the male or female that preclude the use of less demanding techniques. IVF is the best method for women with damaged fallopian tubes (tubal factor).
    ■ IVF requires a minimum of 50,000-500,000 motile sperm, so it cannot be used in patients with severe oligospermia. Harvesting eggs initially involves down-regulating the woman's pituitary with a GnRH agonist and then performing controlled hyperstimulation.
    ■ Follicular development is monitored by ultrasound examination and by checking serum levels of estrogen and progesterone. When the follicles are appropriately enlarged, a transvaginal follicular aspiration is performed.
    ■ A mean of 12 eggs are typically retrieved per cycle, and they are placed immediately in an agar of fallopian tube medium. Unlike sperm and embryos, oocytes do not tolerate freezing. After an incubation period of 3-6 hours, the donor sperm are added to the medium using approximately 100,000 sperm per oocyte. After 48 hours, the embryos have usually reached the 3- to 8-cell stage. Two to 4 embryos are usually implanted in the uterus, while the remaining embryos are frozen for future use. Pregnancy rates are 10-45%.
    ■ Overall, IVF is a safe and useful procedure. Risks include multiple pregnancies and hyperstimulation syndrome. Additionally, an increased risk of hypospadias occurs in

boys (1.5% versus 0.3%), probably because of the increased maternal progesterone used for egg harvesting.
  - Finally, the use of this technology has led to many ethical issues, such as the fate of embryos after divorce.

  - Gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT): These procedures allow the placement of semen (GIFT) or a fertilized zygote (ZIFT) directly into the fallopian tube by laparoscopy or laparotomy. Success rates have been estimated to be 25-30% using these techniques. Unfortunately, these procedures require general anesthesia and have associated risks. Fertilization and implantation within the uterus are not guaranteed, and these procedures cannot be performed in patients with fallopian tube obstruction. GIFT and ZIFT rarely are employed as a therapeutic option.

- Intracytoplasmic sperm injection
  - ICSI is a sophisticated and expensive technique that involves the direct injection of a single sperm into a single egg under the microscope (see Image 9).

  - While the indications for ICSI are not completely agreed upon, in general, ICSI is reserved for patients in whom other techniques have failed or for patients who have known problems precluding IVF. This group generally has less than 500,000 sperm or less than 5% motile sperm, less than 4% normal morphology, and less than 2 million sperm per cc. Patients with sperm extracted directly from the epididymis or testicle proceed to ICSI.
  - Oocytes are processed with hyaluronidase to remove the cumulus mass and corona radiata. A micropipette is used to hold the egg while a second micropipette injects the sperm. The oocyte is positioned with the polar body at the 6 o'clock or 12 o'clock position, and the sperm is injected at the 3 o'clock position because the oocyte is in the second metaphase and the chromosomes are lined up on the metaphyseal plate. This positioning minimizes the risk of chromosomal damage.
  - After incubation for 48 hours, the embryo is implanted as in IVF. Van Steirteghem (1993) reported a 59% fertilization rate and a 35% pregnancy rate using ICSI in 1409 oocytes.

  - The potential complications, ethical issues, and high costs of ICSI make this a very useful but somewhat involved method.

Consultations:

- Geneticist

  - A genetics consultation may be indicated in patients with a known or suspected genetic cause of infertility and in patients with nonobstructive azoospermia or severe oligospermia (<5 million sperm per cc). In addition, in the era of IVF and ICSI, determining the risks of passing on chromosomal abnormalities to a potential offspring is important.

  - Use a peripheral karyotype and a PCR-based evaluation of the Y chromosome to evaluate for microdeletions. Patients with nonobstructive azoospermia have a 13-17% chance of genetic abnormalities, 4-16% of which are due to Klinefelter syndrome and 9% are due to a partial Y deletion.
  - Patients with CBAVD nearly uniformly have a mutation in the *CFTR* gene. An estimated 50-82% of men with CBAVD have a genital-only form of CF, which may manifest in patients with only one copy of the abnormal CF gene. In contrast, patients with clinical CF usually have 2 copies of the abnormal gene.

  - As for men who do have the digestive and pulmonary complications of CF, technology is allowing them to live longer. These men are now candidates for assisted reproductive

Documented hypersensitivity; severe cardiac or renal

Documented hypersensitivity; ischemic heart

Prognosis:

- Prognosis of a patient with infertility depends on the underlying cause of infertility. The appropriate workup must be performed, and then the appropriate intervention may be employed. Prognosis is individualized depending on these results.

Patient Education:

- Couples should be counseled that the most effective regimen is to perform coitus every 48 hours at mid cycle.

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Medical/Legal Pitfalls:

- With the technological advancements in assisted reproductive techniques, a new host of ethical issues has followed.

  - Gamete donation has enabled infertile couples to conceive, and many use family members as the donors to keep genetic linkages alive. However, laws and published guidelines directing these donations do not exist; rather, decisions are left up to the individual, physician, or program. The legal battles over the rights to embryos from donated eggs or sperm or to embryos, eggs, or sperm after divorce are still being fought.

  - Technology has now proven the ability to clone animals, and future advances may provide the ability to choose a child's sex and physical characteristics.

  - All of these and other issues are still controversial, and the rate of evolution of these technologies hopefully will not exceed society's capacity to deal with the potential consequences.

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Caption: Picture 1. Male infertility. Hypothalamic-pituitary-gonadal axis stimulatory and inhibitory signals. Gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary. FSH stimulates the Sertoli cells to facilitate sperm production, while LH stimulates testosterone release from the Leydig cells. Feedback inhibition is from testosterone and inhibin.
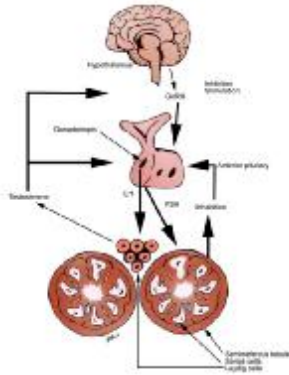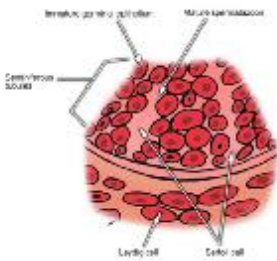
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eMedicine Zoom View (Interactive!)

Picture Type: Image

Caption: Picture 2. Male infertility. Testicular histology magnified 500 times. Leydig cells reside in the interstitium. Spermatogonia and Sertoli cells lie on the basement membrane of the seminiferous tubules. Germ cells interdigitate with the Sertoli cells and undergo ordered maturation, migrating towards the lumen as they mature.
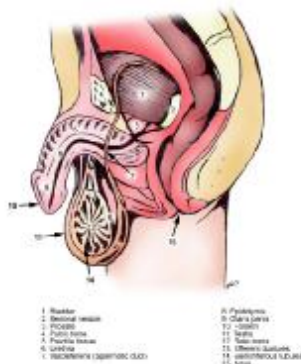

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Picture Type: Image

Caption: Picture 3. Male infertility. Normal male ductal anatomy.

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Picture Type: Image

Caption: Picture 4. Male infertility. Varicocele. A - Physical examination revealing the characteristic "bag of worms." B - Anatomy of the dilated pampiniform plexus of veins.
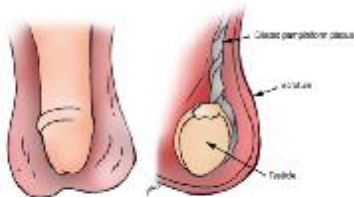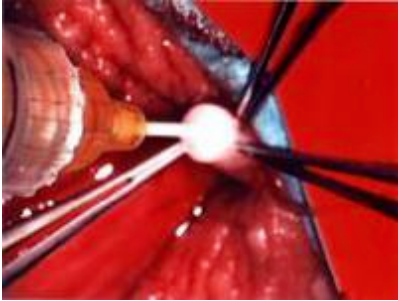

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Picture Type: Image

Caption: Picture 5. Male infertility. Technique of open vasogram: The vas distal to the site of incision is determined to be patent if saline is injected without resistance. Alternatively, radiographic contrast dye is injected through the vas deferens and a radiograph is performed, or blue dye may be injected and visualized in the urine to confirm patency. A vasovasostomy or vasoepididymostomy then may be performed at this level.

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Picture Type: Photo

Caption: Picture 6. Male infertility. Technique of microscopic varicocelectomy. The individual veins of the pampiniform plexus are isolated (top) and ligated, taking care to preserve the testicular artery (bottom) isolated using the intraoperative Doppler.
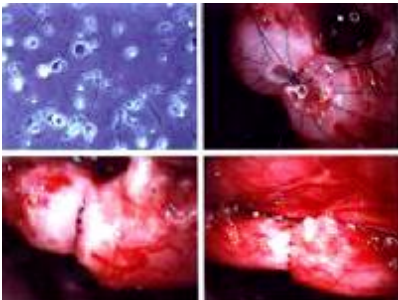

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Picture Type: Photo

Caption: Picture 7. Male infertility. Technique of vasovasostomy: Upper left is confirmation of sperm from the proximal vas deferens, proving proximal patency. Upper right is the inner layer anastomosis using interrupted #10-0 Prolene. Lower left is the inner layer anastomosis completed. Lower right is the outer layer anastomosis using #9-0 Prolene completed.
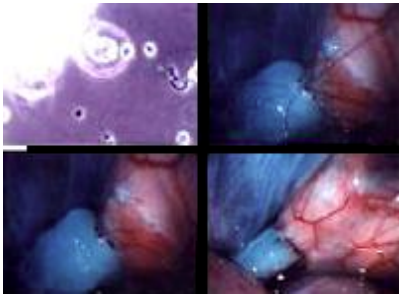

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Picture Type: Photo

Caption: Picture 8. Male infertility. Technique of vasoepididymostomy. Left upper is confirmation of mature sperm in epididymis. Right upper is the inner layer anastomosis of the end of the vas to the side of the epididymal tubule using interrupted #10-0 Prolene. Left lower is the inner layer completed. Right lower is the

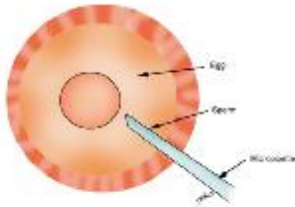outer layer anastomosis using interrupted #9-0 Prolene completed.

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Picture Type: Photo

Caption: Picture 9. Male infertility. Technique of intracytoplasmic sperm injection (ICSI). A micropipette is used to inject a single sperm directly into an egg.

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Picture Type: Image

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NOTE:

Infertility, Male excerpt

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