**CAUSES OF MALE INFERTILITY**

**HYPOTHALAMIC-PITUITARY DISEASE** — Any hypothalamic or pituitary disease can cause gonadotropin-releasing hormone (GnRH) or gonadotropin deficiency (hypogonadotropic hypogonadism) and therefore infertility. These conditions can be subdivided into congenital, acquired, or systemic disorders.

It is important to diagnose secondary hypogonadism as there are specific therapies available (pulsatile GnRH or gonadotropins).

**Congenital disorders** — Congenital idiopathic hypogonadotropic hypogonadism is characterized by isolated gonadotropin deficiency resulting in eunuchoidism (sexual infantilism and eunuchoidal body habitus) and sometimes impaired olfactory function (anosmia). In addition, many of the men have mid-line facial defects, color blindness, hearing difficulties, renal malformations, and cryptorchidism (Kallmann's syndrome). The underlying cause of the hypogonadism is a defect in gonadotropin-releasing hormone (GnRH) secretion.

Some men have gonadotropin subunit mutations causing hypogonadotropic hypogonadism.

Other genetic disorders of gonadotropin secretion include multiorgan genetic syndromes such as the Laurence-Moon-Biedl syndrome, Prader-Willi syndrome, Lowe oculocerebral syndrome, and familial cerebellar ataxia.

**Acquired diseases** — Any hypothalamic or pituitary disease can cause hypogonadotropic hypogonadism and therefore infertility. This can be induced by destruction of GnRH neurons or of the gonadotrophs in the pituitary by interrupting the hypothalamic-pituitary portal circulation or by functional inhibition of GnRH or gonadotropin secretion. Examples include:

**Tumors** — Pituitary macroadenomas (macroprolactinomas and nonfunctioning adenomas) or surgical therapy of macroadenomas or craniopharyngiomas.

**Infiltrative diseases** — Sarcoidosis, histiocytosis, tuberculosis, fungal infections, transfusion siderosis, and hemochromatosis, a genetic disorder of mucosal iron transport that results in increased deposition of iron in many tissues including the pituitary gland. Hemochromatosis-associated hypogonadotropic hypogonadism is nearly always of post-pubertal onset.

**Vascular lesions** — Pituitary infarction and carotid aneurysm.

**Hormonal** — Functional hypogonadotropic hypogonadism and infertility can be induced by hyperprolactinemia, estrogen excess, glucocorticoid excess, and androgen excess.

* While any cause of hyperprolactinemia (drugs, hypothyroidism) may be incriminated, most men have prolactinomas.
* Estrogen excess may be due to estrogen therapy or to estrogen production by a testicular tumor.
* Chronic glucocorticoid therapy in men results in lower serum testosterone concentrations and inappropriately normal serum gonadotropins, suggesting an alteration of hypothalamic GnRH secretion [[29](http://www.uptodate.com/contents/causes-of-male-infertility/abstract/29)].

**Androgens** — Androgen excess may be due to the administration of either exogenous testosterone or other anabolic steroids, androgen overproduction due to congenital adrenal hyperplasia, or tumors of the testis or adrenal glands. Anabolic steroid use should be suspected in men with low sperm counts, low serum LH concentrations, and a well-androgenized phenotype.

**Drugs** — Opioid-like or other central nervous system-activating drugs, including many psychotropic drugs, can inhibit GnRH or gonadotropin secretion, resulting in secondary hypogonadism and infertility. GnRH analogues (agonists and antagonists) usually are given to suppress gonadotropin secretion, as in men with prostatic carcinoma; infertility is an expected effect of treatment with these analogues.

**Systemic illness** — Any serious systemic illness or chronic nutritional deficiency can cause hypogonadotropic hypogonadism, primary hypogonadism, and infertility.

**Obesity** — Obesity in women appears to be associated with subfertility and poor reproductive outcomes. Obesity in men results in hypogonadotropic hypogonadism with low serum gonadotropin, total testosterone, and free testosterone concentrations. The obesity-associated decrease in serum sex hormone binding globulin (SHBG) contributes to the low serum total testosterone concentrations. In addition, serum free testosterone concentrations appear to be inversely related to body weight and body mass index (BMI), independent of changes in SHBG. Other factors contributing to the hypogonadotropic hypogonadism seen with obesity include an increase in estrogens through aromatization in adipose tissue, insulin resistance, metabolic syndrome, diabetes mellitus, and sleep apnea.

**PRIMARY HYPOGONADISM** — Primary gonadal deficiency (hypergonadotropic hypogonadism) is an important cause of azoospermia and oligozoospermia. While multiple specific testicular disorders have been identified, the pathogenic basis for testicular dysfunction is often unknown and may reflect an inherited defect in sperm production or response to a more distant event.

**Congenital or developmental disorders of the testes** — Congenital and developmental disorders are found in a substantial proportion of infertile men. These include Klinefelter's syndrome, Y chromosome defects, cryptorchidism, varicoceles, and other less common disorders.

**Klinefelter's syndrome** — One of the most common causes of primary hypogonadism and, therefore, male infertility, is Klinefelter's syndrome, which may occur in up to 1:500 to 700 phenotypic males. It is characterized by sex chromosome aneuploidy with an extra X (XXY) chromosome being the most frequent. These patients often have very small testes and almost always have azoospermia.

**Autosomal and X chromosome defects** — A number of autosomal and X-linked genes have been identified as regulators of spermatogenesis. Gene mutations that have been associated with possible male infertility include:

* Polymorphisms of DAZL (T54A), an autosomal homolog of the DAZ (deleted in azoospermia) gene.
* Polymorphisms of PRM1-PRM2 (protamines responsible for chromatin compaction), TNP1-TNP2 (transition nuclear protein), and USP26 (de-ubiquitinating enzyme family).
* Mutations in the SYCP3 gene that regulates the synapse between homologous chromosomes during meiosis has been associated with azoospermia in rare patients.

**Y chromosome and related defects** — Y chromosome microdeletions and substitutions are increasingly recognized as genetic causes of azoospermia and severe oligozoospermia [[59](http://www.uptodate.com/contents/causes-of-male-infertility/abstract/59)]. Up to 20 percent of infertile men have microdeletions in the long arm of the Y chromosome, many of which map to the Yq11 region of the chromosome, that is named azoospermic factor (AZF). The AZF region of Yq11 contains three regions: AZFa, AZFb, and AZFc. Deletion of the AZFa and AZFb regions results in severe spermatogenesis defects and azoospermia. Testicular biopsies in these men may show germinal cell maturation arrest or Sertoli cell-only syndrome.

Deletions of AZFc that cause infertility have a variable phenotype ranging from oligozoospermia to azoospermia, and represent the largest, well-defined recurrent deletions in the human genome.

The AFZb and AFZc regions contain large sections of duplicate sequences allowing for rearrangements and partial deletions. The gr/gr deletion removes a large segment of the AFZc gene and represents a significant risk factor for oligozoospermia in some [[62,63](http://www.uptodate.com/contents/causes-of-male-infertility/abstract/62,63)], but not all [[64](http://www.uptodate.com/contents/causes-of-male-infertility/abstract/64)], populations.

The focus on candidate genes has been on the AFZa region because this region, unlike the AFZb and AFZc, does not have repeat sequences. DDx3Y (the DEAD [Asp-Glu-Ala-Asp] box polypeptide 3, Y-linked gene) and USP9Y are genes located in the AZFa region of the Y chromosome. USP9Y has been considered to be a candidate gene for male infertility, as deletions in the gene have been observed in men with azoospermia or severe oligozoospermia. However, deletions in USP9Y have also been reported in two men with normal fertility (a normospermic male and his father), suggesting that USP9Y does not have an important independent role in spermatogenesis. When both USP9Y and DDX3Y are deleted, azoospermia is consistently seen, suggesting either that DDX3Y has a critical role in the regulation of spermatogenesis or that the two adjacent genes are necessary for normal sperm development.

Y chromosome deletions may be detectable not only in men with idiopathic "oligozoospermia" or azoospermia, but also in men with identifiable other causes of testicular dysfunction. As an example, in a study of 131 infertile men, Y chromosome deletions were found in 16 of 85 men (19 percent) with idiopathic oligo- or azoospermia, and 3 of 46 men (7 percent) with disorders such as cryptorchidism, varicocele, and obstructive lesions of the vas deferens [[67](http://www.uptodate.com/contents/causes-of-male-infertility/abstract/67)]. Similar results were seen in a second report.

Y chromosome defects are transmissible to male offspring if cases are successfully treated by assisted reproduction methods. Thus, genetic testing and counseling should be done before technologies such as intracytoplasmic sperm injection (ICSI) are considered. In Europe, Australia, and many infertility centers in the United States, tests for Y chromosome deletions are offered to the infertile couple.

**Cryptorchidism** — Men with a history of undescended testes have lower sperm counts, sperm of poorer quality, and lower fertility rates than men with normally descended testes. Impaired spermatogenesis in the undescended testis probably is related to underlying genetic, hormonal, and developmental abnormalities, some of which may be partially reversible through early surgical intervention. Sperm counts in adulthood are directly related to prepubertal germ cell counts and type of cell at the time of orchiopexy.

The degree of germ-cell dysfunction with cryptorchidism is correlated with the duration of suprascrotal location of the testes. Serum FSH concentrations are often high, but serum LH concentrations are usually normal, indicating normal Leydig cell function. Formerly cryptorchid men with low serum inhibin B and high FSH concentrations may be at particularly high risk for infertility.

Bilateral cryptorchidism must be distinguished from the functional bilateral castrate syndrome in which the testes are not detectable in the abdomen or other location; the latter condition is not associated with an increased risk of testicular tumors.

**Testicular cancer** — There is evidence of an increased incidence of testicular cancer in men presenting with infertility (even in the absence of a history of cryptorchidism). As an example, in one observational study of 3847 men with oligozoospermia (using previously published rather than current WHO criteria for normal semen parameters, defined as sperm concentration less than 20 million/mL with concomitant defects in total motility [less than 50 percent]), 10 cases of testicular cancer were seen (8 of 10 with no history of cryptorchidism) [[73](http://www.uptodate.com/contents/causes-of-male-infertility/abstract/73)]. When compared with a control population, this represented approximately an 18-fold greater incidence of testicular cancer (standardized incidence ratio 18.3, 95% CI 18.0-18.8). However, this study is limited by the small number of cases, and thus, routine screening for testicular cancer in men who present with infertility is not warranted at this time.

**Varicoceles** — Varicoceles are dilatations of the pampiniform plexus of the spermatic veins in the scrotum. Left-sided varicoceles are 10 times more common than right-sided ones, perhaps because of anatomic variations that lower blood flow in the left spermatic vein. The mechanisms by which a varicocele might cause infertility and the reversibility of infertility after varicocele surgery are controversial. Varicoceles are found in about 10 to 15 percent of normal men and an even higher percentage of infertile men; the former finding has led many clinicians to question whether a varicocele alone can cause infertility

**Defective androgen receptor or synthesis** — Men with congenital androgen insensitivity due to androgen receptor or postreceptor abnormalities and those with 5-alpha-reductase deficiency are nearly always infertile. Men with partial androgen insensitivity (Reifenstein's syndrome) have varying degrees of ambiguous external genitalia, hypogonadism, and infertility. Mild androgen insensitivity can cause infertility alone.

Normal sexual differentiation and spermatogenesis require androgen and a normal functioning receptor. Polymorphisms of the androgen receptor gene may also be associated with male infertility. The number of trinucleotide (CAG) repeats in exon 1 of the androgen receptor is inversely correlated with the transcriptional activity of the androgen target gene. In a study of normal fertile men, those with short CAG repeats had the highest sperm output.

Reports of CAG repeat lengths in men with idiopathic infertility have been inconsistent. In some but not all reports, a modest association of longer CAG repeat length with male infertility and/or abnormal semen quality has been observed. In a meta-analysis of 33 studies of men with idiopathic infertility and fertile controls, those with infertility had significantly longer CAG repeat lengths than controls. While androgen receptor CAG repeat length may be a valuable tool for epidemiological studies and pharmacogenomic evaluation of efficacy in treatment trials, it is not a practical tool for assessment of individual patients.

Men with 5-alpha-reductase deficiency have pseudohermaphroditism but partially virilize at puberty. Infertility in this disorder may be due to mechanical problems associated with the small phallus, severe hypospadias, cryptorchidism, and poor prostatic secretions.

**Disorders of the estrogen receptor or estrogen synthesis** — In mice lacking a functional estrogen receptor alpha, fluid absorption is impaired in the efferent tubules, resulting in excess accumulation of fluid in the seminiferous tubules and impaired spermatogenesis. In a man with an inactivating mutation of estrogen receptor alpha, sperm count was normal but sperm motility was decreased. Furthermore, aromatase gene knockout older, adult mice are infertile because of impaired spermatogenesis. The generation of estrogen receptor beta knockout mice should provide additional information on the effect of estrogen on fertility in men.

Polymorphisms of the promoter region (variable TA tandem repeats) of the estrogen receptor gene have been shown to be related to sperm production. Men with higher numbers of TA repeats have lower sperm counts. Other polymorphisms of the estrogen receptor may have different effects in different populations.

**Inactivating mutation in FSH receptor gene** — A rare cause of male infertility is an inactivating mutation in the FSH receptor gene. One report described five men who were homozygous for an inactivating mutation of the FSH receptor. These men had variably low sperm counts and serum inhibin B concentrations and high serum FSH concentrations.

**Myotonic dystrophy** — Myotonic dystrophy is an autosomal disorder with delayed onset (age 30 to 40 years) of impaired motor function, cataracts, premature frontal balding, mild mental retardation, and infertility due to impaired spermatogenesis. Only 20 percent of men with myotonic dystrophy have low serum testosterone concentrations.

**Acquired disorders of the testes** — Virtually all acquired testicular disorders can cause infertility, often without accompanying Leydig-cell dysfunction. These acquired disorders will be reviewed briefly here; they are discussed in detail elsewhere.

**Infection** — Viral orchitis, especially mumps, is a well-recognized cause of infertility. Among those with mumps, clinical orchitis is rare in prepubertal males but occurs in 15 to 25 percent of adult men. Some, but perhaps not all, of these men become infertile, due either to germinal cell damage, ischemia, or the immune response to the infection. In mumps and other viral causes of orchitis (echovirus and arbovirus), germ cell failure is much more common than androgen deficiency.

Other infectious causes of orchitis and infertility include tuberculosis and leprosy; the former may also cause epididymal obstruction. Sexually transmitted diseases (STD) such as gonorrhea and chlamydia can also cause orchitis. HIV-infected men may have relative normal semen parameters while others may have low sperm motility and infertility. White blood cells may be present in the semen, especially if the HIV was associated with other STDs such as gonorrhea.

**Drugs** — Many drugs are associated with impaired spermatogenesis and/or Leydig cell dysfunction. Among them, the most important are the alkylating drugs (cyclophosphamide and [chlorambucil](http://www.uptodate.com/contents/chlorambucil-drug-information?source=see_link)). Antiandrogens ([flutamide](http://www.uptodate.com/contents/flutamide-drug-information?source=see_link), [cyproterone](http://www.uptodate.com/contents/cyproterone-drug-information?source=see_link), [bicalutamide](http://www.uptodate.com/contents/bicalutamide-drug-information?source=see_link), [spironolactone](http://www.uptodate.com/contents/spironolactone-drug-information?source=see_link)), [ketoconazole](http://www.uptodate.com/contents/ketoconazole-drug-information?source=see_link), and [cimetidine](http://www.uptodate.com/contents/cimetidine-drug-information?source=see_link) cause testicular dysfunction by inhibiting testicular androgen production or action.

**Radiation** — Ionizing radiation impairs spermatogenesis. Doses as low as 0.015 Gy (15 rads) may transiently suppress spermatogenesis, while doses above 6 Gy (600 rad) usually cause irreversible azoospermia and infertility.

**Environmental factors** — Environmental toxins may be an underappreciated cause of infertility. The pesticide dibromochloropropane is a well-known cause, as are lead, cadmium, and mercury. The possibility that chemicals with estrogenic or antiandrogenic activity ("endocrine disruptors"), including insecticides and fungicides, may lower sperm counts has attracted much attention lately, although direct proof of an effect in men is lacking. The suspicion of such an effect originated with observations that sperm counts had decreased over the last several decades. However, a meta-analysis suggested that while decreases in sperm counts have occurred on a local basis, there has been no world-wide decline.

Because of the rapid increase in cell phones use around the world, studies have been done to investigate whether cell phone usage has any detrimental effects on sperm parameters. This issue is controversial and definitive data are not yet available.

**Smoking** — Data on cigarette smoking and its possible effect on sperm counts are inconsistent. However, in a meta-analysis of 20 observational studies, men who smoked cigarettes were more likely to have low sperm counts.

The possibility that in utero exposure to smoking may have a detrimental effect on sperm count in adulthood was studied in 1770 young, healthy, potential military recruits and the results showed the possibility of a small effect. Exposure to smoking in utero (after adjusting for some confounding factors, eg, the man's present smoking habits, but not others, eg, alcohol intake) was associated with mean sperm concentrations which were 20 percent lower (95% CI 7 to 34 percent) when compared with unexposed men. The fertility implication of this small difference is not known. In a second study, there were no significant differences in mean sperm concentrations in men whose mothers either smoked or did not smoke during pregnancy. However, men whose mothers had smoked ≥10 cigarettes per day while pregnant were at higher risk of having oligozoospermia (sperm concentration <20 x 10(6)/mL).

**Hyperthermia** — Hyperthermia has long been thought to impair spermatogenesis. Prolonged high testicular temperature may explain the infertility associated with spinal cord injuries, varicocele, and chronic sauna and Jacuzzi exposure. Studies in rodents, monkeys, and men have shown that small increases in testicular temperature accelerate germ cell loss through apoptosis. Similarly, febrile illness, prolonged sitting during work or truck driving, welding, baking, tight fitting underwear, and laptop use with increased heat to the testes have been proposed to adversely affect male fertility. The data to support these associations are inconsistent and may be a very weak risk factor for infertility.

**Antisperm antibodies** — Some infertile men have antisperm antibodies in serum or semen and both presumably could impair spermatogenesis. Presence of sperm agglutination in the semen should trigger the laboratory to test for anti-sperm antibodies. Whether antibodies occur spontaneously or only after some testicular injury is not known. Primary hypogonadism occasionally occurs in men with type 2 autoimmune polyglandular syndrome.

**Systemic disorders** — Men with debilitating illnesses such as chronic renal insufficiency, cirrhosis, or malnutrition of any cause may have primary as well as secondary hypogonadism. Infertility is common in men with sickle cell anemia, presumably due to intratesticular ischemia.

Abnormalities in sperm motility and morphology as well as a biochemical picture of androgen resistance (high serum testosterone and high LH concentrations) have been reported in men with celiac disease.

**DISORDERS OF SPERM TRANSPORT** — The epididymis is an important site for sperm maturation and an essential part of the sperm transport system. The vas deferens then transports sperm from the epididymis to the urethra, where they are diluted by secretions from the seminal vesicles and prostate. Abnormalities at any of these sites, particularly the epididymis and vas deferens, can cause infertility. Finally, sperm must be ejaculated.

**Abnormalities of the epididymis** — Absence, dysfunction, or obstruction of the epididymis leads to infertility even though testicular sperm production is normal. Intrauterine exposure to estrogens may cause epididymal dysfunction. Little is known about functional abnormalities of the epididymis, but some drugs used in other countries (eg, triptolide) and chemical toxins (chlorhydrin) affect the function of metabolism of spermatozoa within the epididymis. While poorly documented, it is presumed that some men with isolated asthenospermia (impaired motility) have defects of epididymal function.

**Abnormalities of the vas deferens** — Male infertility can result from acquired or congenital abnormalities of the vas deferens. Bilateral obstruction, ligation, or altered peristalsis of the vas deferens results in infertility. Obstruction may result from infection (gonorrhea, chlamydia, tuberculosis), while ligation of the vas deferens (vasectomy) is an intentional, medically-induced cause of infertility. It may be reversible, but some men have an immune response to sperm granulomas that form on the proximal side of the ligation and remain infertile after adequate reanastomosis of the vas.

One to 2 percent of infertile men have congenital absence of the vas deferens. Most have mutations of the cystic fibrosis transmembrane conductance regulator, CFTR, gene. Many infertile men with mutations of CFTR present with infertility in the absence of many of the other findings (eg, respiratory and pancreatic disease). A primary ciliary dyskinesia is a genetically heterogeneous disease that affects cilia function and structure. The clinical presentations include recurrent sinopulmonary infections, bronchiectasis, situs inversus and male infertility (with asthenozoospermia or oligozoospermia. Genetic mutations of dynein proteins or thioredoxin-nucleoside diphosphate kinase have been implicated to cause primary ciliary dyskinesia. A similar genetic defect may lead to abnormal transport of sperm is Young's syndrome, in which inspissated secretions within the vas and epididymis interfere with transport of sperm, leading to obstructive azoospermia; impaired axonemal structures are sometimes found.

**Seminal vesicles and prostate** — It is not known if abnormal function of the seminal vesicles and prostate contributes to infertility.

**Defective ejaculation** — Spinal cord disease or trauma, sympathectomy, or autonomic disease (eg, diabetes mellitus) all can interfere with normal ejaculation and lead to decreased fertility. Erectile dysfunction, mechanical obstruction (condoms and diaphragm use), premature ejaculation, and infrequency of intercourse also may be contributing factors.

**IDIOPATHIC MALE INFERTILITY** — Despite careful assessment of all possible causal mechanisms, a cause of abnormal sperm number, morphology, or function cannot be identified in a substantial proportion of infertile men [[20](http://www.uptodate.com/contents/causes-of-male-infertility/abstract/20)]. There are also men who have repeatedly normal semen analyses but cannot impregnate an apparently normal female partner.

**SUMMARY** — The causes of male infertility can be divided into four main areas:

● Hypothalamic pituitary disease (secondary hypogonadism; 1 to 2 percent). Any hypothalamic or pituitary disease can cause gonadotropin-releasing hormone (GnRH) or gonadotropin deficiency (hypogonadotropic hypogonadism), and therefore infertility. These conditions can be subdivided into congenital, acquired, or systemic disorders.

● Testicular disease (primary testicular defect including Y microdeletions; 30 to 40 percent). Examples include congenital or developmental disorders, disorders of the androgen receptor, Y chromosome defects, and acquired disorders such as infection, drugs, environmental toxins, and smoking.

● Post-testicular defects (disorders of sperm transport; 10 to 20 percent). The epididymis is an important site for sperm maturation and an essential part of the sperm transport system. The vas deferens then transport sperm from the epididymis to the urethra, where they are diluted by secretions from the seminal vesicles and prostate. Abnormalities at any of these sites, particularly the epididymis and vas deferens, can cause infertility. Finally, sperm must be ejaculated.

● Idiopathic male infertility (40 to 50 percent).