**Evaluation of male infertility**

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**INTRODUCTION** — Infertility in a couple is defined as the inability to achieve conception despite one year of frequent unprotected intercourse. Use of this time period, while arbitrary, was based upon a study of 5574 English and American women engaging in unprotected coitus who ultimately conceived between 1946 and 1956 [[1](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/1)]. Among these women, 50 percent conceived within three months, 72 percent within six months, and 85 percent within 12 months.

One population-based study found the following distribution of causes when evaluating infertile couples [[2](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/2)]

●Male factor – 23 percent

●Ovulatory dysfunction – 18 percent

●Tubal damage – 14 percent

●Endometriosis – 9 percent

●Coital problems – 5 percent

●Cervical factor – 3 percent

●Unexplained – 28 percent

The causes of male infertility can be divided into four main areas (table 1):

●Hypothalamic pituitary disease (secondary hypogonadism) – 1 to 2 percent

●Primary hypogonadism – 10 to 15 percent

●Post-testicular defects (disorders of sperm transport) – 10 to 20 percent

●Seminiferous tubule dysfunction – 60 to 80 percent including microdeletions of the Y chromosome

**Table 1: Causes of Male Infertility**

|  |
| --- |
| **Hypothalamic-pituitary disorders (GnRH; LH and FSH deficiency)** |
| **Congenital disorders** |
| Congenital GnRH deficiency (Kallmann syndrome) |
| Hemochromatosis |
| Multiorgan genetic disorders (Prader-Willi syndrome, Laurence-Moon-Beidl syndrome, familial cerebellar ataxia) |
| **Acquired disorders** |
| Pituitary and hypothalamic tumors (macroadenoma, craniopharyngioma) |
| Infiltrative disorders (sarcoidosis, histiocytosis, tuberculosis, fungal infections) |
| Trauma, postsurgery, postirradiation |
| Vascular (infarction, aneurysm) |
| Hormonal (hyperprolactinemia, androgen excess, estrogen excess, cortisol excess) |
| Drugs (opioids and psychotropic drugs, GnRH agonists or antagonists) |
| **Systemic disorders** |
| Chronic illnesses |
| Nutritional deficiencies |
| Obesity |
| **Primary gonadal disorders** |
| **Congenital disorders** |
| Klinefelter's syndrome (XXY) and its variants (XXY/XY; XXXY) |
| Cryptorchidism |
| Myotonic dystrophy |
| Functional prepubertal castrate syndrome (congenital anorchia) |
| Varicocele |
| Androgen insensitivity syndromes |
| 5-alpha-reductase deficiency |
| Y chromosome deletions |
| **Acquired disorders** |
| Viral orchitis (mumps, echovirus, arbovirus) |
| Granulomatous orchitis (leprosy, tuberculosis) |
| Epididymo-orchitis (gonorrhea, chlamydia) |
| Drugs (eg, alkylating agents, alcohol, marijuana, antiandrogens, ketoconazole, spironolactone, histamine2 receptor antagonists) |
| Ionizing radiation |
| Environmental toxins (e.g., dibromochloropropane, carbon disulfide, cadmium, lead, mercury, environmental estrogens and phytoestrogens) |
| Hyperthermia |
| Immunologic disorders, including polyglandular autoimmune disease |
| Trauma |
| Torsion |
| Castration |
| Systemic illness (eg renal failure, hepatic cirrhosis, cancer, sickle cell disease, amyloidosis, vasculitis, celiac disease) |
| **Disorders of sperm transport** |
| Epididymal dysfunction (drugs, infection) |
| Abnormalities of the vas deferens (congenital absence, Young's syndrome, infection, vasectomy) |
| Ejaculatory dysfunction (spinal cord disease, autonomic dysfunction, premature ejaculation) |
| **Unexplained male factor infertility** |

The noted frequencies represent an estimate of the approximate proportion of men in each category presenting to a tertiary referral center with capabilities to diagnose subtle defects of Y chromosome microdeletion [[3](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/3)].

The assessment of the male partner of a childless couple is frustrating for both the patient and clinician, because a specific etiology or treatment can be found in only a few of them. The disorders in most men are characterized primarily by descriptions of observed abnormalities, such as decreased sperm number, movement, or egg penetrating and fusion capabilities. Even testicular biopsies have provided little insight; they simply indicated the extent of impaired germ cell maturation. Use of molecular biology techniques has allowed definition of gene deletions and mutations in male infertility [[4,5](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/4,5)].

The components of the evaluation of the man include:

●History

●Physical examination

●Semen analyses

●Genetic tests

●Endocrine testing

**HISTORY** — The evaluation of an infertile man should begin with a detailed history that focuses on potential causes of infertility. A detailed history of the female partner should also be obtained, including history of previous fertility (or infertility), and any prior evaluation or treatment. In the male, the clinician should inquire about:

* Developmental history, including testicular descent, pubertal development, loss of body hair, or decrease in shaving frequency
* Chronic medical illness
* Infections, such as mumps orchitis, sinopulmonary symptoms, sexually transmitted infections, and genitourinary tract infections including prostatitis
* Surgical procedures involving the inguinal and scrotal areas such as vasectomy, orchiectomy, and herniorrhaphy
* Drugs and environmental exposures, including alcohol, radiation therapy, anabolic steroids, cytotoxic chemotherapy, drugs that cause hyperprolactinemia, and exposure to toxic chemicals (eg, pesticides, hormonal disrupters)
* Sexual history, including libido, frequency of intercourse, and previous fertility assessments of the man and his partner
* School performance, to determine if he has a history of learning disabilities suggestive of Klinefelter's syndrome

**PHYSICAL EXAMINATION** — The physical examination should include a general medical examination with a focus on finding evidence of androgen deficiency, which may accompany decreased fertility. The clinical manifestations of androgen deficiency depend upon the age of onset. Androgen deficiency during early gestation presents as ambiguous genitalia; in late gestation as micropenis; in childhood as delayed pubertal development; and in adulthood as decreased sexual function, infertility, and eventually, loss of secondary sex characteristics. The examination of the man should include the following components.

**General appearance** — Eunuchoidal proportions (upper/lower body ratio <1 with an arm span 5 cm >standing height) suggest androgen deficiency antedating puberty. On the other hand, increased body fat and decreased muscle mass suggest current androgen deficiency.

**Skin** — Loss of pubic, axillary, and facial hair, decreased oiliness of the skin, and fine facial wrinkling suggest long-standing androgen deficiency.

**External genitalia** — Several abnormalities that can affect fertility can be recognized by examination of the external genitalia:

* Incomplete sexual development can be recognized by examining the phallus and testes and finding a Tanner stage other than 5
* Diseases that affect sperm maturation and transport can be detected by examination of the scrotum for absence of the vas, epididymal thickening, varicocele, and hernia. The presence of a varicocele should be confirmed with the man standing and performing a Valsalva maneuver.
* Decreased volume of the seminiferous tubules can be detected by measuring testicular size by Prader orchidometer or calipers. The Prader orchidometer consists of a series of plastic ellipsoids with a volume from 1 to 35 mL. In an adult man, testicular volume below 15 mL and testicular length below 3.6 cm are considered small.

The Prader orchidometer has been reported to estimate greater testicular volumes than those by ultrasound, but not all ultrasound instruments use the same formula to calculate volume [[6-8](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/6-8)]. The difference between the two methods is greater for smaller than larger volumes, eg, about 5 mL difference for testicular volumes 5 to 15 mL but only 1 to 3 mL for volumes 20 to 25 mL [[6](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/6)].

**STANDARD SEMEN ANALYSIS** — The semen analysis is the cornerstone of the assessment of the male partner of an infertile couple. In addition to the standard analysis, specialized analyses can be performed in some laboratories [[9](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/9)]. The standard semen analysis consists of the following:

●Measurement of semen volume and pH

●Microscopy for debris and agglutination

●Assessment of sperm concentration, motility, and morphology

●Sperm leukocyte count

●Search for immature germ cells

The semen sample should be collected after two to seven days of sexual abstinence, preferably at the doctor's office by masturbation [[10](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/10)]. If this is not possible, then the samples can be collected with condoms without chemical additives and delivered to the laboratory within an hour of collection.

Because of the marked inherent variability of semen analyses, at least two samples should be collected one to two weeks apart. The semen analysis should be performed using standardized methods, preferably those described in the World Health Organization (WHO) Laboratory Manual for Human Semen and Sperm Cervical Mucus Interaction [[10](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/10)]. In addition, the laboratory should employ internal quality control measures and participate in external quality control programs available from national andrology, clinical chemistry, and pathology societies [[10-13](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/10-13)].

**WHO lower reference limits** — The WHO has published revised lower reference limits for semen analyses [[14](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/14)]. The following parameters represent the generally accepted 5th percentile (lower reference limits and 95% confidence intervals in parentheses), derived from a study of over 1900 men whose partners had a time-to-pregnancy of ≤12 months [[14](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/14)].

* Volume – 1.5 mL (95% CI 1.4-1.7)
* Sperm concentration – 15 million spermatozoa/mL (95% CI 12-16)
* Total sperm number – 39 million spermatozoa per ejaculate (95% CI 33-46)
* Morphology – 4 percent normal forms (95% CI 3-4), using "strict" Tygerberg method [[10](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/10)]
* Vitality – 58 percent live (95% CI 55-63)
* Progressive motility – 32 percent (95% CI 31-34)
* Total (progressive + non-progressive motility) – 40 percent (95% CI 38-42)

**Semen volume** — The mean semen volume in the WHO study was 3.7 mL; the lower reference limit was 1.5 mL [[14](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/14)]. A low volume in the presence of azoospermia (no sperm) or severe oligozoospermia (severely subnormal sperm concentration) suggests genital tract obstruction (eg, congenital absence of the vas deferens and seminal vesicles or ejaculatory duct obstruction). Congenital absence of vas deferens is diagnosed by physical examination and low semen pH, whereas ejaculatory duct obstruction is diagnosed by the finding of dilated seminal vesicles on transrectal ultrasonography.

Low semen volume with normal sperm concentration is most likely due to semen collection problems (loss of a portion of the ejaculate) and partial retrograde ejaculation. Androgen deficiency is also associated with low semen volume and low sperm concentration. The patient should be asked to return for a carefully collected repeat semen sample after emptying the bladder; post-ejaculation urine can be collected to assess whether there is retrograde ejaculation [[14](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/14)]. Endocrine assessment of possible androgen deficiency is reviewed below.

**Sperm concentration** — The lower reference limit for sperm concentration is 15 million/mL (95% CI 12-16) [[14](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/14)]. However, some men with sperm counts considered to be low can be fertile, while others above the lower limit of normal can be subfertile [[15-19](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/15-19)] and, for the purposes of fertilization in vitro, 10 million/mL or even less can be satisfactory [[10](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/10)].

If only a few spermatozoa per high power field are observed, the sensitivity of detecting spermatozoa can be increased by labeling the spermatozoa with a fluorescent nuclei stain and then counting the spermatozoa using a deep chamber. The sensitivity is reduced to 2000 spermatozoa per mL ejaculate [[20](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/20)]. If no spermatozoa are seen, the semen should be centrifuged and the whole pellet should be smeared on a slide and examined for the presence of spermatozoa before the diagnosis of azoospermia is given [[14](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/14)]. The presence of adequate motile sperm in the pellet will allow intracytoplasmic sperm injection (ICSI) to be performed with ejaculated spermatozoa. Identifying even a few spermatozoa in the ejaculate is useful because it indicates that the patient may have spermatogenesis in a few seminiferous tubules even in atrophic testis, and microdissection testicular sperm extraction (TESE) could/should be attempted by experienced urologists and the testicular spermatozoa used for ICSI [[21](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/21)].

Round cells observed in the semen smear may be leukocytes, immature germ cells or degenerating epithelial cells [[10](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/10)]. Presence of immature germ cells in the semen usually indicated disorders of spermatogenesis. Leukocytes can also be seen microscopically and counted with the hemocytometer. Agglutination suggests autoimmunity, which should be confirmed by tests for sperm surface antibodies.

**Sperm motility** — Sperm motility is assessed microscopically and is classified as progressive motility, non-progressive motility, and immotile spermatozoa. At least 40 percent of spermatozoa should be motile and at least 32 percent should have progressive motility. If sperm motility is poor, sperm vitality should be assessed by supravital stains or the hypoosmotic swelling test to determine whether the majority of immotile spermatozoa are dead [[10](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/10)]. The distinction between living, non-moving sperm, and dead sperm influences the type of assisted reproductive treatment that can be used for the induction of pregnancy.

**Sperm morphology** — The criteria for normal morphology were previously based mainly on shape, as observed microscopically. They now also include length, width, width ratio, area occupied by the acrosome, and neck and tail defects [[14,22,23](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/14,22,23)]. These criteria are called “strict” criteria and have good predictive value in terms of fertilization in vitro and pregnancy rates after in vitro fertilization (IVF) [[22-25](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/22-25)]. Based upon these correlations between "strict criteria" sperm morphology and IVF pregnancy rate, the lower limit of normal sperm morphology was estimated to be about 4 percent of spermatozoa [[14,17,18,24,25](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/14,17,18,24,25)].

**Leukocytes** — White blood cells, mainly polymorphonuclear leukocytes, are frequently present in the seminal fluid. Assessment of white blood cells is usually performed by using the peroxidase stain. The peroxidase positive cells are counted using the hemocytometer [[14](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/14)]. Presence of increased white blood cells in the ejaculate may be a marker of genital infection/inflammation and may be associated with poor semen quality because of the release of reactive oxygen species from the leukocytes. The suggested cut-off for the diagnosis of a possible infection is one million leukocytes/mL of ejaculate. However, this cut-off is not evidence-based [[26](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/26)].

**Hyperviscosity** — Hyperviscosity may interfere with the semen analysis, in particular, evaluation of sperm motility. Hyperviscous samples should be treated in the laboratory to reduce viscosity by passing the sample via a large gauge needle, diluting with a physiological solution or use of enzyme digestion before testing for sperm parameters in the laboratory. Although the cause of hyperviscosity is unclear, it is thought to be due to inflammation of the genitourinary tract [[27](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/27)].

**Prediction of fertility** — The standard semen analysis provides descriptive data, which do not always distinguish fertile from infertile men. In one prospective data of 430 couples, among those with a sperm concentration ≥40x10(6)/mL, 65 percent achieved pregnancy, compared with 51 percent of those with lower sperm concentrations [[16](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/16)]. In a study of male partners in 765 infertile couples in which the female partners who had normal infertility workup and in 696 control fertile couples recruited from prenatal classes [[19](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/19)]:

* There was extensive overlap between fertile and infertile men in sperm concentration, motility, and morphology.
* The subfertile ranges were a concentration less than 13.5 million/mL, less than 32 percent motility, and less than 9 percent normal morphology using "strict criteria."
* The fertile ranges included sperm concentration greater than 48 million/mL, greater than 63 percent motility, and greater than 12 percent normal morphology.
* Values in between these ranges were not useful in discriminating fertile from infertile couples (termed intermediate by the authors). The likelihood of infertility generally increased with decreases in any of the three parameters.
* The percentage of sperm with normal morphology had the greatest discriminatory power. It should be noted that none of the semen parameters was a powerful discriminator although each of these helped to distinguish between fertile and infertile men.

Lack of sperm in the ejaculate does not indicate the absence of testicular sperm production; these patients should be evaluated for retrograde ejaculation, congenital absence of the vas deferens, and other causes of obstructive azoospermia.

**At-home test** — An over the counter at-home test for evaluating sperm quality is commercially available (Fertell). The test provides an estimate of the total motile sperm using a "swim-up" technique followed by reaction with a monoclonal antibody against a sperm surface antigen. Data on the reliability of this test or its ability to predict fertility are very limited [[28](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/28)]. A second "dip stick" test that requires dilution of the semen (Sperm Check) has been used to monitor the sperm concentration after vasectomy [[29](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/29)]. However, as these tests do not assess sperm motility and morphology, we do not recommend them in the evaluation of male infertility.

**SPECIALIZED SEMEN ANALYSIS** — More specialized semen tests are not routinely performed, but can be used to help determine the cause of male infertility under certain circumstances.

**Sperm autoantibodies** — Sperm autoantibodies are present in about 4 to 8 percent of subfertile men. The presence of agglutination in the initial semen analysis suggests sperm autoimmunity; this should be confirmed by the mixed antiglobulin reaction or the immunobead test [[10](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/10)], both of which detect sperm surface antibodies. Antibodies are considered clinically important when over 50 percent of the spermatozoa are coated with them and when the spermatozoa fail to penetrate preovulatory human cervical mucus or demonstrate impaired fertilizing capacity. Studies suggest use of new proteomic analyses to assess such antibodies may provide a greater understanding of this disorder [[30](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/30)].

**Semen biochemistry** — Sperm biochemistry is frequently described in semen analyses, but is rarely useful in clinical practice. The most commonly ordered test is fructose, which is a marker of seminal vesicle function. Low or non-detectable semen fructose is associated with congenital absence of the vas deferens and seminal vesicles or with ejaculatory duct obstruction; in comparison, obstruction of the epididymis is associated with normal semen fructose. The diagnosis of ejaculatory duct obstruction can be confirmed by transrectal ultrasonography, which will demonstrate dilated seminal vesicles [[31](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/31)].

**Semen culture** — Semen culture is frequently performed in men whose semen samples contain inflammatory cells, but the results are usually not diagnostic. If semen culture is performed, precautions must be taken by the man during sample collection to prevent skin contamination. The yield of semen culture may be improved by performing a prostatic massage before sample collection.

**Sperm-cervical mucus interaction** — Sperm-cervical mucus interaction identifies whether the problem is in the sperm or in the cervical mucus and is assessed in vivo by the postcoital test and in vitro by the slide or capillary tube tests [[10](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/10)].

* The postcoital test should be done in the doctor's office or laboratory when the female partner is in the preovulatory phase of the cycle. The number and motility of sperm in the cervical mucus is assessed 9 to 24 hours after vaginal intercourse.
* The in vitro tests, such as the slide or the capillary tests, can be performed on sperm and cervical mucus from the infertile couple together with donor semen and cervical mucus. These so-called "crossed tests" identify whether the problem is in the sperm or cervical mucus.

The inability of spermatozoa to penetrate the cervical mucus is correlated with poor sperm motility and the presence of sperm antibodies, and failure of sperm to penetrate zona-free hamster eggs is correlated with failure of in vitro fertilization (IVF) [[32,33](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/32,33)], and in vivo conception [[34](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/34)]. If the sperm-cervical mucus interaction tests are incorporated into the evaluation of an infertile couple, failure of sperm to penetrate a good sample of cervical mucus may suggest that the couple should proceed with assisted reproductive technologies more expeditiously. Thus, sperm-cervical mucus penetration test can be used as a sperm function test.

**Sperm function tests** — Screening male partners of infertile couples with the following advanced andrology diagnostic tests is impractical and costly, but selective use may be justified when the standard semen analysis is normal or near normal [[35](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/35)].

**Computer-aided sperm analysis** — Quantitative measurement of sperm motion characteristics (sperm kinematics) is useful in identifying men with unexplained infertility, predicting in vivo and in vitro fertilizing capacity, and in toxicology studies. Commercially available CASA systems measure sperm kinematics, such as sperm velocity (curvilinear, straight line, average path), amplitude of lateral displacement, and other derived functions [[36-38](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/36-38)]. The predictive value of CASA-derived sperm motility characteristics for in vivo [[39-41](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/39-41)] and in vitro fertility [[42,43](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/42,43)] has been demonstrated. The accuracy of this technique, however, is highly dependent upon the technology, analytic conditions, and technical training of the operators. When conditions are optimized, this technique can be used to assess sperm concentration, motility, and morphology.

**Acrosome reaction** — The acrosome reaction involves the fusion of the acrosome and the plasma membrane, leading to release of the acrosomal enzymes and exposure of the sperm head. This reaction must be precisely timed to occur after sperm binding to the zona pellucida. Premature loss of the acrosome leads to loss of zona pellucida recognition sites from the sperm and compromises sperm binding to the zona [[44](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/44)]. The acrosome reaction can be assessed in human sperm by fluorescein-labeled pea or peanut agglutinins and specific monoclonal antibodies [[10](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/10)] before and after stimulation by calcium ionophore challenge [[45](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/45)].

The occurrence of acrosome reaction abnormalities as a principal cause of male infertility is probably uncommon, thus acrosome reaction tests should be reserved for couples in whom a specialized procedure such as intracytoplasmic sperm injection (ICSI) and or IVF are contemplated.

**Zona-free hamster oocyte penetration test** — Since its introduction in the 1970s, the hamster oocyte penetration test (HOPT) has been used in clinical andrology laboratories as a predictor of success for in vitro and in vivo fertilization [[35,46](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/35,46)]. This test is based upon the observation that hamster oocytes denuded of zona pellucida can be penetrated by the spermatozoa of several mammalian species, including humans. The HOPT can assess the ability of the spermatozoa to capacitate, undergo acrosome reaction, penetrate the oocyte membrane, and fuse with the oocyte. False positive and false negative rates are high. The test is technically demanding and should be performed only in a specialized laboratory with proven record of good assay repeatability.

**Human zona pellucida binding test** — Two zona binding tests have been used to predict the success of IVF: the hemizona assay [[47](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/47)] and a competitive zona binding assay [[48](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/48)]. In the hemizona assay, human zona pellucida from an oocyte not previously exposed to spermatozoa is bisected; one-half zona is incubated with the test sample, the other half with control spermatozoa. In the competitive binding assay, the test and control spermatozoa are labeled with different fluorochromes [[39](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/39)].

In both tests, the number of spermatozoa bound to the zona from the test sample is compared with a control sample. These tests are technically demanding and are not often used for evaluation of male infertility because of the difficulty in obtaining human oocytes.

**Sperm biochemistry** — Generation of reactive oxygen species may be a cause of sperm dysfunction and a predictor of fertilization in vitro [[49](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/49)]. Reactive oxygen species lead to lipid peroxidation of the sperm membrane and are also deleterious to sperm motility. This is still regarded as a research test and is not often used for diagnosis of a specific sperm defect.

**Sperm chromatin and DNA assays** — A flow cytometric assay of sperm chromatin structure after low pH-induced denaturation has been developed to measure sperm chromatin integrity and sperm function [[50,51](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/50,51)]. Similarly, DNA fragmentation (a measure of sperm apoptosis) has also been utilized as a measure of sperm nuclear integrity [[52,53](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/52,53)]. Flow cytometry to evaluate DNA of sperm can distinguish the mature haploid and the abnormal diploid mature spermatozoa, cellular fragments and immature germ cells [[54](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/54)]. These tests of sperm nuclear chromatin or DNA structure may provide information to semen analysis in male infertility assessment and reproductive toxicology studies, and may have predictive values for assisted reproduction outcome [[55-59](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/55-59)].

The usefulness of tests of DNA integrity for prediction of fertility remains controversial. A meta-analysis reported that DNA integrity was not predictive of pregnancy outcomes in assisted reproduction. However, it is possible that subgroups of infertile men may benefit from assessment of sperm chromatin structure assays or assessment of DNA fragments [[60](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/60)].

**GENETIC TESTS** — The introduction of ICSI has made it possible for men with severe oligozoospermia and azoospermia to father children, but the genetic risks of this highly invasive technique must be considered. These include the risks of transferring the cystic fibrosis conductance regulator (CFTR) gene, somatic and sex chromosome abnormalities, and microdeletions of the Y chromosome [[61-64](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/61-64)].

**CFTR gene** — Men with CFTR gene mutations present with obstructive azoospermia, normal testicular volume, no vas deferens on palpation of the external genitalia, and normal serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone concentrations. In this setting, a family history of cystic fibrosis should be obtained, and both the male and female partner should be tested for CFTR gene mutations.

The likelihood of transfer of a mutant CFTR gene was illustrated in a study of 102 men with congenital absence of the vas deferens [[62](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/62)]:

* 19 had mutations in both copies of the CFTR gene, although none had the 5T allele.
* 54 had a mutation in one copy of the CFTR gene, and 34 of these had the 5T allele in the other CFTR gene.

The 5T allele mutation may result in clinical presentations such as moderate cystic fibrosis and congenital bilateral absence of vas [[62](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/62)].

**Sex chromosome and somatic mutations** — Approximately 10 to 18 percent of infertile men, previously classified as having idiopathic oligozoospermia, have microdeletions of the Y chromosome. Complete deletions of the AZFa or AFZb regions lead to azoospermia and Sertoli cell only syndrome. Partial deletions of these regions or complete deletion of the AFZc regions result in a variable phenotype varying from hypospermatogenesis to Sertoli cell only syndrome and present with severe oligozoospermia or azoospermia.

A substantial number of men with known causes of infertility also have Y chromosome microdeletions [[65](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/65)], but such deletions are rare in men with sperm concentrations over 5 million/mL [[66](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/66)]. Using sufficient number of markers (primers) allows the detection of over 95 percent of clinically relevant deletions [[67,68](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/67,68)]. Genetic diagnosis is important because ISCI with testicular derived spermatozoa would not be possible in men with complete deletions of the AZFa or AZFb regions.

These Y chromosome deletions may be transmitted from father to son by ICSI [[69](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/69)]. In addition, low-level sex chromosome mosaicism has been reported in infertile couples [[70](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/70)]. Most recently, a gr/gr deletion at the AFZc region of the Y chromosome was associated with male infertility in epidemiological studies with a possible increase in risk of testicular germ cell tumor [[71](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/71)]. The results have not been confirmed. Other gene polymorphisms have been reported to be associated with male infertility but the assessment can only be done in qualified laboratories [[68,72](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/68,72)].

Therefore, genetic counseling and chromosome and other molecular genetic tests are undertaken before ICSI is undertaken [[65,73](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/65,73)]. Routine karyotyping is recommended for infertile men with spermatogenic failure and a sperm concentration less than 10 million/mL [[74](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/74)]. In Europe and many infertility centers in the United States, tests for Y chromosome deletions are offered to the infertile couple when the male partner has severe oligospermia or azoospermia. These men usually have small testicular volumes. Some may have elevated serum FSH concentrations but normal serum LH and testosterone levels. In some infertility centers, all men with “idiopathic” oligozoospermia are screened for Y chromosome microdeletions. In other centers, these tests are only done in men with severe oligozoospermia and azoospermia.

**Androgen receptor** — There is renewed interest in the androgen receptor (AR) transcriptional activity with male infertility. The trinucleotide (CAG) repeats in exon 1 of the AR regulates the functional activity of the AR. In some reports, long CAG repeats are associated with lower AR activity and azoospermia in infertile men [[75-77](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/75-77)] and may have implications for selection of patients for ICSI.

**ENDOCRINE TESTS** — The endocrine assessment of an infertile man includes measurements of serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), and perhaps other tests [[78](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/78)]:

**Serum testosterone** — Measurement of a morning serum total testosterone is usually sufficient. In men with borderline values, the measurement should be repeated and measurement of serum free testosterone may be helpful.

**Serum LH and FSH** — When the serum testosterone concentration is low, high serum FSH and LH concentrations indicate primary hypogonadism and values that are low or normal indicate secondary hypogonadism.

Men with low sperm counts and low serum LH concentrations who are well-androgenized should be suspected of exogenous anabolic or androgenic steroid abuse.

**Other** — Serum prolactin should be measured in any man with a low serum testosterone concentration and normal to low serum LH concentration. Although inhibin assays are not widely available outside of research laboratories, low serum inhibin concentrations may be an even more sensitive test of primary testicular dysfunction than high serum FSH concentrations, provided the assay is specific for inhibin B [[79-82](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/79-82)].

**OBSTRUCTIVE AZOOSPERMIA** — If a patient has normal testicular volumes, normal serum follicle-stimulating hormone (FSH), and luteinizing hormone (LH) and testosterone and azoospermia, the likely diagnosis is obstructive azoospermia. Bilateral congenital absence of the vas can be detected on physical examination and confirmed by a low fructose level in the semen. Ejaculatory duct obstruction can be diagnosed by a transrectal ultrasound showing dilated seminal vesicles [[83,84](http://www.uptodate.com/contents/evaluation-of-male-infertility/abstract/83,84)]. Patients with obstructive azoospermia should be referred to a urologist specialized in infertility for further evaluation and treatment.

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