Approach to the male with infertility

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INTRODUCTION

Infertility in a couple is usually defined as the inability to achieve conception despite one year of frequent, unprotected intercourse; infertility is often defined as failure to conceive within six months of unprotected intercourse when the female partner is >35 years old [1]. However, up to 40 to 50 percent of young, healthy couples that fail to conceive in the first 12 months will conceive in the subsequent 12 months with no specific treatment [2,3]. Therefore, in many circumstances, delay in extensive evaluation and treatment is reasonable. In approximately 35 percent of couples with infertility, a male factor is identified along with a female factor; in approximately 10 percent, a male factor is the only identifiable cause.

While many men with male infertility have oligozoospermia (a low number of sperm cells in the ejaculate compared with reference ranges) or azoospermia (no sperm cells in the ejaculate), some infertile men have normal sperm counts. Over 80 percent of infertile men have low sperm concentrations and poor sperm quality (a decrease in sperm motility [asthenozoospermia] and/or an increase in spermatozoa with abnormal morphology [teratozoospermia]). A small percentage of infertile men have normal sperm concentrations but poor sperm quality, and another small percentage of infertile men have normal sperm concentrations and normal motility and morphology.

This topic will review the evaluation of male infertility. The causes and management of male infertility and an overview of infertility are reviewed separately.

- (See "Overview of infertility".)
- (See "Causes of male infertility".)

CATEGORIES OF MALE INFERTILITY

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

- **Endocrine and systemic disorders** (usually related to secondary [hypogonadotropic] hypogonadism) – 2 to 5 percent.
- **Primary testicular defects in spermatogenesis** – 65 to 80 percent (of which the majority have idiopathic dysspermatogenesis, an isolated defect in spermatogenesis without an identifiable cause).
- **Sperm transport disorders** – 5 percent.
- **Idiopathic male infertility** – 10 to 20 percent. Idiopathic male infertility should be distinguished from idiopathic dysspermatogenesis. Idiopathic male infertility describes an infertile man with a normal semen analysis and no apparent cause for infertility, whereas infertile men with idiopathic dysspermatogenesis have abnormal semen analyses.

The precise epidemiology of prevalence and causes of male infertility has never been accurately assessed for several reasons, including underreporting and lack of systematic data gathering [4]. The noted frequencies represent an estimate of the approximate proportion of men in each category presenting to a tertiary referral center and likely do not represent the prevalence in the broader community in industrialized countries, nor do these estimations reflect likely regional variations around the world [4-6].

DIAGNOSTIC APPROACH

The initial evaluation of the male with infertility is focused on detecting the small percentage of causes that can be treated to restore normal fertility. The remainder of the evaluation of male infertility is focused on determining which couples with male factor infertility might benefit from assisted reproductive technologies (ART).

Molecular biology techniques have increased the ability to identify more genetic causes of male infertility, but only a minority of infertile men have an identifiable cause [7,8] (see "Causes of male infertility"). The disorders in many infertile men are characterized primarily by descriptions of observed abnormalities, such as decreased sperm number, movement, or egg-penetrating and fusion capabilities. Even testicular biopsies rarely shed insight on the underlying etiology; they simply indicate the extent of spermatogenic impairment.

The essential components of the evaluation of the infertile man include (see 'Initial visit' below):

- History
- Physical examination
- Semen analyses

Additional components of the evaluation of the infertile man may include (see 'Additional evaluation' below):

- Endocrine testing
- Imaging of accessory glands and ducts
- Genetic tests

The profile created by the results permits a systematic assessment of the male partner.

Initial visit

History and physical examination — 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. For the male partner, the clinician should inquire about symptoms, prior illnesses, or surgical procedures that are associated with hypogonadism:

- Sexual developmental history, including testicular descent, pubertal development, loss of body hair, or decrease in shaving frequency
- Chronic severe systemic illness and history of major head or pelvic trauma
- 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 or orchiectomy
- Drugs and environmental exposures, including alcohol, tobacco, marijuana, opioids, radiation therapy, anabolic steroids, corticosteroids, cytotoxic chemotherapy (current or past), drugs that cause hyperprolactinemia, and exposure to toxic chemicals (eg, pesticides)
- Sexual history, including libido, frequency of intercourse, and previous fertility assessments of the man and his partner

The physical examination should include a general medical examination to determine overall health, obesity, and overt signs of endocrinopathies that are uncommon causes of male infertility (eg, thyroid dysfunction or Cushing's syndrome).

Because some infertile men have combined defects in testosterone and sperm production, the examination should also focus on findings suggestive of androgen deficiency. The clinical manifestations of androgen deficiency depend upon the age of onset. Androgen deficiency during early gestation presents as atypical 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. (See "Clinical features and diagnosis of male hypogonadism".)

- Skin – Men with iron overload syndromes as the cause of infertility may have diffuse or patchy hyperpigmentation. Men with Cushing's syndrome may have thin skin, ecchymoses, and/or broad purple striae. Loss of pubic, axillary, and facial hair, decreased oiliness of the skin, and fine facial wrinkling suggest longstanding testosterone deficiency.

- External genitalia – Several abnormalities that 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 small testes and other findings of incomplete pubertal development (Tanner stage less than 5). (See "Normal puberty".)

  - Diseases that affect sperm maturation and transport can be detected by examination of the scrotum for absence of the vasa, epididymal thickening, and large varicoceles. (See "Nonacute scrotal conditions in adults", section on 'Varicocele' and "Cystic fibrosis: Clinical manifestations and diagnosis", section on 'Infertility'.)

  - 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 (picture 1). In an adult man, a testicular volume below 15 mL or a testicular length (measured on the longest axis) less than 3.6 cm are considered small.

The Prader orchidometer has been reported to estimate greater testicular volumes than those by ultrasound [9-11]. The difference between the two methods is greater for smaller than larger volumes (eg, approximately 5 mL difference for testicular volumes 5 to 15 mL, but only 1 to 3 mL for volumes 20 to 25 mL) [9]. A systematic review showed that ultrasound is more accurate

than the Prader orchidometer to assess testicular volume, but that measurements by both methods are closely related, indicating that the Prader orchidometer is adequate for assessment of the infertile man in clinical practice [12].

Semen analysis — Semen analysis is the key laboratory assessment of the male partner of an infertile couple. The standard semen analysis consists of the following:

- Semen volume and pH
- Microscopy for:
  - Sperm concentration, count, motility, and morphology
  - Debris and agglutination
  - Leukocyte count
  - Immature germ cells

The semen sample should be collected after two to seven days ejaculatory abstinence. If possible, the patient should collect the sample by masturbation at the doctor's office. If not possible, then the sample may be collected at home and delivered to the laboratory within an hour of collection.

Because of the marked inherent variability of sperm concentrations in semen samples, **at least two samples** should be collected at least one week apart. The semen analysis should be performed using standardized methods, preferably those described in the World Health Organization (WHO) Laboratory Manual for the Examination and Processing of Human Semen [13]. 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 [13-16].

Reference limits — The WHO has published lower reference limits for semen analyses [17]. The following parameters represent the generally accepted 5^{th} percentile (lower reference limits and 95% CIs in parentheses), derived from a study of over 1900 men whose partners had a time to pregnancy of ≤12 months [17]:

- 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 [13]
- Vitality – 58 percent live (95% CI 55-63)
- Progressive motility – 32 percent (95% CI 31-34)
- Total (progressive and nonprogressive) motility – 40 percent (95% CI 38-42)

Additional evaluation — After the initial evaluation (history, physical exam, and two semen analyses), men with infertility should undergo the following evaluation:

Men with a normal semen analysis — Male partners in an infertile couple may have idiopathic male infertility. Other possibilities include infertility of the female partner or a couples' infertility factor. After complete evaluation of the female partner and treatment of reversible causes of female infertility, the couple should consider referral to a specialist in ART, such as in vitro fertilization (IVF).

Men with an abnormal semen analysis — Most infertile men with abnormal semen analyses have abnormalities in sperm concentrations, morphology, and motility.

Normal sperm concentration, abnormal morphology and/or motility — In an infertile couple with a male partner who has a normal sperm concentration but abnormal sperm morphology and/or motility, referral to a specialist in ART such as intracytoplasmic sperm injection (ICSI) might be useful. (See "Treatments for male infertility", section on 'IVF with ICSI'.)

Sperm concentration <10 million/mL — Because Klinefelter syndrome is common in men presenting with infertility and sperm concentrations <10 million/mL, serum total testosterone (on a blood sample obtained between 8 and 10 AM), serum follicle-stimulating hormone (FSH), and luteinizing hormone (LH) measurements should be performed in these men [18,19].

Many clinicians and experts measure these serum hormones in all infertile men with low sperm concentrations (<15 million/mL). The results of the endocrine testing and details from the history and physical examination can help identify the cause of the infertility.

Severe oligozoospermia or azoospermia — Men with azoospermia or severe oligozoospermia also need endocrine testing; further evaluation also depends upon the results (see 'Endocrine testing' below). In addition to undergoing endocrine testing, men with severe oligozoospermia or azoospermia require genetic testing. (See 'Genetic tests' below.)

Some men may require transrectal ultrasound for evaluation of obstructive azoospermia (those who have normal endocrine testing, normal testicular volume, palpable vasa deferentia on examination, and azoospermia). (See 'Scrotal and transrectal ultrasound' below.)

Endocrine testing — The endocrine assessment of an infertile man with a low sperm concentration (<10 million/mL) includes measurements of serum total testosterone, LH, and FSH and other tests as clinically indicated [20,21]. Serum total testosterone should be measured on a blood sample obtained between 8 and 10 AM. The measurement should be repeated in

men with borderline values (see "Clinical features and diagnosis of male hypogonadism", section on 'Serum total testosterone'). The following combinations of serum testosterone, LH, and FSH suggest the following diagnoses:

- Low testosterone, and high FSH and LH – Primary (hypergonadotropic) hypogonadism (affecting both spermatogenesis and Leydig cell function). These men should have a karyotype performed. (See 'Chromosomal anomalies' below.)

- Normal testosterone and LH, and high FSH – Primary (hypergonadotropic) hypogonadism (seminiferous tubule damage without Leydig cell dysfunction). (See "Causes of male infertility", section on 'Primary testicular defects in spermatogenesis'.)

- Low testosterone, but FSH and LH not elevated (normal or low) – Secondary (hypogonadotropic) hypogonadism. Serum prolactin should be measured in men with a low serum testosterone concentration and normal to low serum LH. Some men may need additional evaluation for a sellar mass and secondary hypothyroidism and hypoadrenalism. (See "Clinical features and diagnosis of male hypogonadism".)

- High testosterone and LH, but normal FSH – Partial androgen resistance. (See "Pathogenesis and clinical features of disorders of androgen action".)

- Normal testosterone, LH, and FSH – Further evaluation depends upon findings on semen analysis (eg, azoospermia, oligozoospermia, asthenozoospermia, or teratozoospermia). (See "Treatments for male infertility", section on 'Normal serum T, normal LH and FSH'.)

  Men with normal endocrine testing who also have azoospermia should be evaluated for ejaculatory duct obstruction. (See "Treatments for male infertility", section on 'Obstruction of epididymis or ejaculatory duct'.)

  Most infertile men who have normal serum testosterone concentrations, normal serum gonadotropin concentrations, and a primary defect in spermatogenesis have sperm in the ejaculate, but the numbers of sperm with normal motility and/or normal morphology are low. Clinicians may consider infertile men with oligozoospermia and normal serum hormones in the same category as men with idiopathic infertility (ie, men with normal semen analyses and normal serum hormones). There is no clearly effective medical therapy for these men. Strategies include continuation of attempts at natural conception or ART. (See "Treatments for male infertility", section on 'Assisted reproductive technologies'.)

- Low sperm count and very low LH in a man who is very muscular – Suspicious for androgen abuse. (See "Use of androgens and other hormones by athletes".)

Scrotal and transrectal ultrasound — If a patient has normal testicular volumes, palpable vasa deferentia on examination, normal serum testosterone, FSH, and LH, and azoospermia, the likely diagnosis is **obstructive azoospermia**. Ejaculatory duct obstruction can be diagnosed by a scrotal or transrectal ultrasound showing dilated seminal vesicles [22,23]. Transrectal ultrasound might be modestly more sensitive in detecting obstructive azoospermia [24]. Patients with obstructive azoospermia should be referred to a urologist specialized in infertility for further evaluation and treatment. (See "Treatments for male infertility", section on 'Obstructive azoospermia'.)

Although there is some controversy about the clinical significance of nonpalpable varicoceles in infertile men, it is not necessary to perform scrotal or transrectal ultrasound to detect small varicoceles, because palpation is sufficient to detect large varicoceles that might be associated with male infertility [12,25].

Genetic tests — Depending upon the patient's clinical presentation, genetic testing may include karyotyping, testing for Y-chromosome microdeletions, or testing for cystic fibrosis transmembrane conductance regulator (*CFTR*) mutations. The introduction of ICSI has made it possible for men with severe oligozoospermia and azoospermia to father children, but the genetic risks of this invasive technique must be considered. These include the risks of transferring the *CFTR* gene, somatic and sex chromosome abnormalities, microdeletions of the Y chromosome, X-chromosome defects, and epigenetics influences to the offspring [26-31].

Chromosomal anomalies — Karyotyping is recommended for infertile men with elevated serum FSH and LH concentrations and a sperm concentration less than 10 million/mL [18]. Klinefelter syndrome is the most common sex chromosome anomaly. These men typically have small, firm testes. (See "Causes of primary hypogonadism in males", section on 'Klinefelter syndrome'.)

Chromosomal translocations are much more common in infertile men than fertile men and occur in up to 15 percent of men with severe oligozoospermia or azoospermia [18,32].

Y-chromosome microdeletions, X-chromosome defects, and epigenetics — Approximately 10 to 18 percent of infertile men with sperm concentrations less than 5 million/mL have microdeletions of the Y chromosome [18,33]. These Y-chromosome deletions (and risk of male infertility) may be transmitted from father to son by ICSI [34]. Testing for microdeletion of the Y chromosome should be offered to men with **sperm concentrations ≤5 million/mL**, but it should **not** be offered to men with sperm concentrations >5 million/mL,

because Y-chromosome microdeletions are rare in these men [35]. (See "Causes of male infertility", section on 'Y chromosome and related defects'.)

CFTR gene — Men with cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutations present with obstructive azoospermia with or without manifestations of cystic fibrosis; normal testicular volume; no vas deferens on palpation of the external genitalia; and normal serum LH, 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. (See "Causes of male infertility", section on 'Sperm transport disorders'.)

The likelihood of transfer of a mutant *CFTR* gene was illustrated in a study of 102 men with congenital absence of the vas deferens [27]:

- Nineteen had mutations in both copies of the *CFTR* gene, although none had the 5T allele (a DNA variant in the noncoding region of the *CFTR* gene with reduced CFTR protein).
- Fifty-four 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 deferens [27]. (See "Cystic fibrosis: Genetics and pathogenesis".)

The management of men with *CFTR* gene mutations is reviewed separately. (See "Treatments for male infertility", section on 'Congenital bilateral absence of the vasa deferentia'.)

DESCRIPTION OF SEMEN ANALYSES

Additional details about semen analyses and their interpretation are found in this section.

Semen analysis interpretation — Most infertile men with abnormal semen analyses have abnormalities in sperm concentration, morphology, and motility.

Low volume

- Low semen volume with **normal sperm concentration** is most likely due to incomplete collection of the ejaculate or partial retrograde ejaculation. 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 [17].

- Low semen volume and **low sperm concentration** may also be seen in some men with testosterone deficiency.

  Endocrine assessment of possible testosterone deficiency is reviewed below. (See 'Endocrine testing' above.)

- A low volume with **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). (See 'CFTR gene' above and 'Scrotal and transrectal ultrasound' above.)

  - Congenital absence of vas deferens is suspected by physical examination and low semen pH and confirmed by scrotal or transrectal ultrasound.

  - Ejaculatory duct obstruction is diagnosed by the finding of dilated seminal vesicles on scrotal or transrectal ultrasonography. (See 'Scrotal and transrectal ultrasound' above.)

Low concentration — The lower reference limit for sperm concentration is 15 million/mL (95% CI 12-16) [17] (see 'Reference limits' above). However, some men with sperm counts considered to be low can be fertile, while others above the lower limit of normal can be subfertile [36-40], and, for the purposes of in vitro fertilization (IVF), 10 million/mL or even less can be satisfactory [13].

- Lack of sperm in the ejaculate does not indicate the absence of sperm production; these patients should be evaluated for retrograde ejaculation, congenital absence of the vas deferens, and other causes of obstructive azoospermia. (See "Causes of male infertility", section on 'Sperm transport disorders'.)

- If few or no spermatozoa per high-power field are observed, there are special techniques to increase the sensitivity of detecting sperm in the ejaculate [17,41]. Identifying even a few spermatozoa in the ejaculate is useful because it indicates that assisted reproductive technologies (ART) might be effective. (See "Treatments for male infertility", section on 'IVF with ICSI'.)

Abnormal morphology — The criteria for sperm morphology are based on length, width, width ratio, area occupied by the acrosome, and neck and tail defects [17,42,43]. Sperm morphology assessment has modest clinical value [44]. It is useful for detecting selected, very rare genetic causes of male infertility [44]. It has been claimed that morphologic assessment has good predictive value for pregnancy rates after IVF [5,42,43,45], but these claims are controversial and not well supported by clinical studies [44].

Round cells in the seminal fluid may be leukocytes, immature germ cells, or degenerating epithelial cells [13]. Presence of immature germ cells in the semen usually indicates disorders of spermatogenesis. White blood cells, mainly polymorphonuclear leukocytes, are frequently present in the seminal fluid. 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 cutoff for the diagnosis of a possible infection is one million leukocytes/mL of ejaculate. However, this cutoff has poor predictive value for bacterial infection [46,47].

Poor motility — In general, motility is not an important factor in independently predicting the probability of natural pregnancy, unless a very high percentage of sperm in ejaculate are immotile [48]. Men with a very high percentage of immotile sperm might still be treatable with intracytoplasmic sperm injection (ICSI) [48]. (See "Treatments for male infertility", section on 'IVF with ICSI'.)

Prediction of fertility — The standard semen analysis provides descriptive data that do not always distinguish fertile from infertile men [48]. In one prospective study of 430 couples, among those with a sperm concentration ≥40 x 10^6/mL, 65 percent achieved pregnancy compared with 51 percent of those with lower sperm concentrations [37]. In a study of male partners in 765 infertile couples in which the female partners had normal infertility workup and in 696 control fertile couples recruited from prenatal classes, there was extensive overlap between fertile and infertile men in sperm concentration, motility, and morphology [40]. However, men who have a "triple" defect of low sperm concentrations, low percentage of normal morphology, and low percentage of motile sperm have a high probability of infertility [48].

At-home test — At-home testing of sperm quality is commercially available. These tests are not recommended in the evaluation of male infertility, because these tests do not assess sperm morphology and they have not been carefully studied for reliability [49,50].

Specialized sperm and semen tests — More specialized semen and sperm tests are not routinely performed but can be used to help determine the cause of male infertility under certain circumstances.

- The presence of agglutination in the initial semen analysis suggests sperm autoantibodies that are present in 4 to 8 percent of infertile men [13]. However, sperm autoantibodies do not appear to cause infertility. (See "Causes of male infertility".)

- 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, and seminal fructose might be low in men with ejaculatory duct obstruction [51]. This test is not routinely used.

- Semen culture is frequently performed in men whose semen samples contain inflammatory cells, but the results are usually not diagnostic.

- There are numerous other specialized sperm and semen tests (including tests of sperm DNA damage) that are used in some fertility clinics and laboratories, but these tests lack standardization and evidence to support their routine use [48,52,53].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Male infertility or hypogonadism".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Male infertility (The Basics)")

- Beyond the Basics topics (see "Patient education: Treatment of male infertility (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

The infertile couple should be evaluated together in an infertility center, if possible. (See "Overview of infertility".)

- The female partner must be evaluated thoroughly before or concurrent with the male partner of an infertile couple. (See 'Initial visit' above.)
- Semen analysis is the fundamental investigation for the infertile man and directs the subsequent evaluation. (See 'Semen analysis' above.)
- If routine semen analysis is abnormal, it should be repeated. If repeated semen analyses demonstrate a sperm concentration less than 15 million spermatozoa/mL, then serum testosterone, serum follicle-stimulating hormone (FSH), and luteinizing hormone (LH) should be measured. (See 'Semen analysis' above.)
- Absence of the vas deferens on physical examination suggest congenital absence of vas deferens. These patients should be tested for the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutations, and, if positive in either the man or the female partner, genetic counseling is necessary before in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). (See 'CFTR gene' above.)
- If seminal fluid pH and volume are low (<1.5 mL) in a man with azoospermia, normal-sized testes, and normal serum testosterone, FSH, and LH concentrations, retrograde ejaculation or ejaculatory duct obstruction is likely and a postejaculatory urine sample analysis and transrectal ultrasound imaging should be performed. (See 'Scrotal and transrectal ultrasound' above.)
- Genetic assessment for Y-chromosomal disorders should be considered in men with normal hormone concentrations or isolated elevation of serum FSH and sperm concentrations <5 million/mL. If a Y-chromosome microdeletion or a chromosomal abnormality is found, genetic counseling is recommended before ICSI is undertaken. (See 'Genetic tests' above.)
- The evaluation of male infertility should focus on identifying treatable causes and factors that might affect the outcome of therapy or the health of offspring. (See 'Diagnostic approach' above.)

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Topic 7453 Version 19.0

GRAPHICS

Causes of male infertility

Endocrine and systemic disorders (hypogonadotropic hypogonadism)
Congenital disorders
▪ Congenital GnRH deficiency (Kallmann syndrome) ▪ Iron overload syndromes ▪ Multiorgan genetic disorders (Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, familial cerebellar ataxia)
Acquired disorders
▪ Pituitary and hypothalamic tumors (pituitary macroadenoma, craniopharyngioma) ▪ Pituitary and hypothalamic infiltrative disorders (sarcoidosis, histiocytosis, tuberculosis, fungal infections) ▪ Pituitary and hypothalamic lymphocytic infundibulitis or hypophysitis ▪ Head trauma, intracranial radiation, or surgery ▪ Vascular (pituitary infarction, aneurysm) ▪ Hormonal (hyperprolactinemia, androgen excess, estrogen excess, cortisol excess) ▪ Drugs (exogenous androgens, opioids and psychotropic drugs, GnRH agonists or antagonists)
Systemic disorders
▪ Severe systemic illness ▪ Nutritional deficiencies ▪ Morbid obesity
Primary testicular defects in spermatogenesis
Congenital disorders
▪ Klinefelter syndrome (XXY) and its variants (XXY/XY, XXXY) ▪ Cryptorchidism ▪ Myotonic dystrophy ▪ Functional prepubertal castrate syndrome (congenital anorchia) ▪ Androgen insensitivity syndromes ▪ 5-alpha-reductase deficiency ▪ Estrogen receptor or synthesis disorders
Acquired disorders
▪ Varicocele (large, palpable without Valsalva maneuver)

- Infections – Viral orchitis (mumps, echovirus, arbovirus), granulomatous orchitis (leprosy, tuberculosis), epididymo-orchitis (gonorrhea, chlamydia)
- Drugs – Alkylating agents, alcohol, marijuana, antiandrogens, ketoconazole, spironolactone, histamine-2 receptor antagonists, ionizing radiation
- Environmental toxins – Dibromochloropropane, carbon disulfide, cadmium, lead, mercury, environmental estrogens, and phytoestrogens; smoking; hyperthermia
- Immunologic disorders, including polyglandular autoimmune disease and antisperm antibodies
- Trauma
- Testicular torsion

Systemic illness

- Idiopathic dysspermatogenesis
- Renal failure, hepatic cirrhosis, cancer, sickle cell disease, amyloidosis, vasculitis, celiac disease

Genetic causes of dysspermatogenesis

- Y-chromosome microdeletions and related disorders
- Autosomal and X-chromosome defects
- Mutations causing severe defects in sperm morphology

Sperm transport disorders

- Epididymal dysfunction (drugs, infection)
- Abnormalities of the vas deferens (congenital absence, Young syndrome, infection, vasectomy)
- Seminal vesicles and prostate
- Ejaculatory ducts disorders

Sexual dysfunction

- Infrequent vaginal intercourse, erectile dysfunction, and premature ejaculation

Idiopathic male infertility

GnRH: gonadotropin-releasing hormone.

Graphic 54356 Version 5.0

Prader orchidometer

Photo of a Prader orchidometer for measuring testicular size. On physical examination, the patient's testicul volume is estimated by palpation and comparison with the models on the orchidometer. Each of the beads i labeled with its volume, ranging from 1 to 25 mL. Prepubertal sizes are 1 to 3 mL, pubertal sizes are 4 to 12 r and adult sizes are 12 to 25 mL.

Graphic 117431 Version 1.0

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