Causes of male infertility

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INTRODUCTION

The fertility rate in a couple is influenced by several factors, including the age of each partner; exposure to environmental toxins, drugs, or radiation; severe systemic disease in either partner; and the specific disorders described below.

The causes of male infertility will be reviewed here. The evaluation and treatment of male infertility and issues related to unexplained infertility are discussed separately. (See "Approach to the male with infertility" and "Treatments for male infertility" and "Unexplained infertility".)

EPIDEMIOLOGY

Infertility in a couple is often defined as the inability to achieve conception after one year of frequent, unprotected intercourse [1], but the epidemiological studies vary on the application of this definition. For example, some studies have included only those couples that have consulted a clinician. In addition, some couples that consult clinicians for treatment have not attempted to conceive for one year. (See "Overview of infertility", section on 'Definitions'.)

The distribution of male and female causes of infertility has not been well defined [1,2]. In a 1982 to 1985 World Health Organization (WHO) multicenter study, 20 percent of cases were attributed to male factors, 38 percent to female factors, 27 percent to both, and 15 percent not clearly attributed to either [3]. Additional studies report a prevalence of male fertility of approximately 10 to 15 percent, but a 2017 WHO systematic review concluded that it was not possible to determine accurate estimates because of low quality of evidence [1]. Aging might

affect the prevalence of male infertility. Infertility rates in men ages 15 to 44 years in the United States was 12 percent in one study [2]. Other studies have reported lower fertility rates in men over age 40 years [3,4], but results from assisted reproductive technologies (ART) have not confirmed this observation [5,6].

There is a significant overlap between male infertility and spermatogenic function as measured by seminal fluid analysis. The majority of 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), but some infertile men have normal sperm counts [7].

- Over 80 percent of infertile men have low sperm concentrations associated with a decrease in sperm motility (asthenozoospermia) and spermatozoa with normal morphology.
- A small percentage of infertile men have normal sperm concentrations but poor sperm quality with a decrease in sperm motility and/or abnormal sperm morphology (teratozoospermia).
- A small percentage of infertile men have normal sperm concentrations and normal motility and morphology.

Trends — Reports of declining sperm counts and increasing incidence of urogenital abnormalities and testicular cancer in some regions of the world have stirred public interest and concern [8,9]. Whether there is deterioration of semen quantity or quality is controversial [10-13]. Data in fertile men in Europe and the United States show marked differences in sperm concentration between different countries and different regions of the same country [14-16]. The role of environmental pollutants or toxins remains unclear [17,18]. There are fewer data on sperm parameters in poor, less industrialized countries.

Categories of male infertility — The causes of male infertility can be divided into four main areas (table 1). The prevalence of these etiological categories is based on weak evidence with many confounding factors including variable definitions of male infertility and its causes, selection bias, and variations in evaluations:

- **Endocrine and systemic disorders with hypogonadotropic hypogonadism** – 5 to 15 percent [1,7,19,20].
- **Primary testicular defects in spermatogenesis** – 70 to 80 percent. Klinefelter syndrome is the most common identifiable cause of a primary testicular defect, but the majority in

this category have idiopathic dysspermatogenesis, an isolated defect in spermatogenesis without an identifiable cause [7,20].

- **Sperm transport disorders** – 2 to 5 percent [7].

- **Idiopathic male infertility** – 10 to 20 percent [7]. Idiopathic male infertility must be distinguished from idiopathic dysspermatogenesis. Idiopathic male infertility describes an infertile man with a normal seminal fluid analysis and no apparent cause for infertility, whereas infertile men with idiopathic dysspermatogenesis have abnormal seminal fluid analyses.

The above prevalences represent an estimate of the approximate proportion of men in each category presenting for infertility treatment at a 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 [1,7,20,21].

ENDOCRINE AND SYSTEMIC DISORDERS (HYPOGONADOTROPIC HYPOGONADISM)

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 because gonadotropin treatment often successfully improves spermatogenesis and fertility. All of these disorders are discussed in detail separately. (See "Causes of secondary hypogonadism in males", section on 'Congenital abnormalities' and "Isolated gonadotropin-releasing hormone deficiency (idiopathic hypogonadotropic hypogonadism)" and "Induction of fertility in men with secondary hypogonadism", section on 'Gonadotropin therapy'.)

Congenital disorders

- **Idiopathic hypogonadotropic hypogonadism (IHH)** – Isolated GnRH deficiency, also referred to as idiopathic hypogonadotropic hypogonadism (IHH), is a family of genetic disorders that are associated with defects in the production and/or action of hypothalamic GnRH [22]. IHH can occur either with normal olfaction (normosmic IHH) or with anosmia. This latter clinical presentation of IHH with anosmia is referred to as Kallmann syndrome. In addition, many of the men have midline facial defects, color blindness, hearing difficulties, renal agenesis, synkinesis, and/or cryptorchidism. This disorder is reviewed in

detail separately. (See "Isolated gonadotropin-releasing hormone deficiency (idiopathic hypogonadotropic hypogonadism)".)

- **Gonadotropin subunit mutations causing hypogonadotropic hypogonadism** – In studies of a population of Estonian men, a single nucleotide polymorphism in the follicle-stimulating hormone (FSH) beta gene promoter was associated with lower serum FSH concentrations and abnormal sperm parameters [23-25]. (See "Causes of secondary hypogonadism in males".)

- **Congenital combined pituitary hormone deficiency** – Congenital combined pituitary hormone deficiency syndromes are likely due to genetic defects, but the underlying genetic abnormalities have not been determined in the majority of cases [26]. (See "Causes of hypopituitarism", section on 'Genetic diseases'.)

- **Other** – 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 [27]. (See "Clinical features, diagnosis, and treatment of Prader-Willi syndrome".)

Acquired diseases — Any acquired hypothalamic or pituitary disease can cause hypogonadotropic hypogonadism and therefore infertility by damaging the GnRH neurons in the hypothalamus or the gonadotroph cells of the pituitary, by interrupting the hypothalamic-pituitary portal circulation, or by functional inhibition of GnRH or gonadotropin secretion. These disorders are discussed in detail separately but are listed here (table 2) (see "Causes of secondary hypogonadism in males"):

- Tumors that cause hypogonadotropic hypogonadism include pituitary macroadenomas, craniopharyngiomas, other sellar masses, and surgical or radiation treatment of these lesions. (See "Clinical manifestations and diagnosis of gonadotroph and other clinically nonfunctioning pituitary adenomas" and "Causes, presentation, and evaluation of sellar masses".)

- Infiltrative diseases include sarcoidosis, histiocytosis, tuberculosis, fungal infections, iron overload syndromes (eg, transfusion-related hemosiderosis and hemochromatosis). (See "Causes of hypopituitarism" and "Clinical manifestations and diagnosis of hereditary hemochromatosis".)

- Lymphocytic hypophysitis is an autoimmune condition that affects the pituitary and/or the infundibulum [28]. (See "Causes of hypopituitarism", section on 'Lymphocytic hypophysitis'.)

- Head trauma, intracranial radiation, or surgery. (See "Causes of hypopituitarism", section on 'Traumatic brain injury'.)

- Vascular lesions include pituitary infarction and carotid aneurysm. (See "Causes of hypopituitarism", section on 'Pituitary infarction (Sheehan syndrome)'.)

- Endocrine disorders and their treatment – Functional hypogonadotropic hypogonadism and infertility can be induced by hyperprolactinemia, estrogen excess [29], glucocorticoid excess [30], androgen excess, and overt hypothyroidism or hyperthyroidism [31-37].

  - Lactotroph adenomas and medications are the most likely cause of hyperprolactinemia in men. (See "Causes of hyperprolactinemia".)

  - Estrogen excess may be due to estrogen therapy, secondary exposure (eg, from a female contact who is using topical estrogen), or estrogen production by a testicular tumor [29,36]. (See "Testicular sex cord stromal tumors", section on 'Leydig cell tumors'.)

  - Chronic glucocorticoid therapy or other causes of Cushing's syndrome in men result in lower serum testosterone concentrations and inappropriately normal serum gonadotropins [30]. (See "Causes and pathophysiology of Cushing's syndrome".)

  - Androgen overproduction due to tumors of the testis or adrenal glands suppresses gonadotropin secretion [36,38].

  - Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency – In classic adrenal hyperplasia, chronic glucocorticoid therapy and excessive production of adrenal androgens and estrogens may result in low to low-normal serum testosterone and inappropriately low or low-normal gonadotropin concentrations [35,39]. In addition, growth of adrenal rest tumors in the testis may cause obstruction of sperm transport out of the testes and may directly cause Leydig cell dysfunction due to mechanical damage and local corticosteroid production by the adrenal rest tumors. This topic is reviewed in detail separately [39]. (See "Treatment of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults", section on 'Testicular adrenal rest tumors'.)

  - Overt hypothyroidism or hyperthyroidism is associated with decreased fertility, probably via several mechanisms [37]. Infertility due to hyperthyroidism may present with normal or high serum total testosterone concentrations (due to high sex hormone-binding globulin [SHBG] levels), low free testosterone, and elevated FSH and

luteinizing hormone (LH) concentrations. (See "Clinical manifestations of hypothyroidism", section on 'Reproductive abnormalities'.)

- Drugs, such as opioids or other central nervous system-activating drugs (including cannabinoids), and many psychotropic drugs, can inhibit GnRH or gonadotropin secretion, resulting in secondary hypogonadism and infertility.

  Administration of exogenous testosterone or other androgenic steroids suppress endogenous gonadotropin secretion and thereby reduce spermatogenesis [32-34]. Androgenic steroid use should be suspected in men with low sperm counts; low serum LH, SHBG, and high-density lipoprotein concentrations; and a muscular phenotype. (See "Use of androgens and other hormones by athletes" and "Causes of secondary hypogonadism in males", section on 'Gonadal steroids'.)

  In men, GnRH analogues (agonists and antagonists) are primarily used to treated advanced prostate carcinoma; infertility is an expected effect of this treatment (table 1) [40]. (See "Causes of secondary hypogonadism in males", section on 'Opioids' and "Causes of secondary hypogonadism in males", section on 'GnRH analogs'.)

Systemic disorders

- Any serious systemic illness or chronic nutritional deficiency can cause infertility due to hypogonadotropic hypogonadism [41] that is sometimes combined with primary hypogonadism. (See 'Systemic disorders' below and "Causes of secondary hypogonadism in males", section on 'Chronic, systemic illness'.)

- Obesity in men results in hypogonadotropic hypogonadism with total testosterone, free testosterone, and low or inappropriately normal gonadotropin concentrations. The obesity-associated decrease in serum SHBG contributes to the low serum total testosterone concentrations. Other factors contributing to the hypogonadotropic hypogonadism seen with obesity include metabolic syndrome, diabetes mellitus, and sleep apnea [42-45]. The relationship between obesity and semen parameters and male infertility is less clear [46,47], but we still advise weight loss to obese men seeking infertility treatment, given the known negative effects of obesity on serum SHBG and total and free testosterone concentrations. (See "Overweight and obesity in adults: Health consequences", section on 'Reproductive effects'.)

PRIMARY TESTICULAR DEFECTS IN SPERMATOGENESIS

The most common primary testicular defect is idiopathic dysspermatogenesis, a descriptive term reflecting our general ignorance about male infertility. Primary hypogonadism is an important cause of azoospermia and oligozoospermia. Although multiple specific testicular disorders have been identified, the pathogenic basis for testicular dysfunction is often unknown. These disorders, which can be categorized as congenital/developmental or acquired, are reviewed in detail elsewhere but are described briefly here. (See "Causes of primary hypogonadism in males".)

Idiopathic dysspermatogenesis — In the majority of infertile men who have abnormalities in sperm number, morphology, and/or motility, there is no identifiable cause. The percentage of these men who have either a congenital or acquired abnormality in spermatogenesis is unknown.

Genetic causes of dysspermatogenesis — A number of genetic causes have been identified by a number of techniques, including genome-wide association studies (GWAS) [48-52]. Genetic disorders affecting spermatogenesis have been identified in approximately 5 to 10 percent of cases of male infertility.

Y chromosome and related defects — Infertile men with sperm concentrations <5 million/mL commonly have Y chromosome microdeletions [53]. Most of the microdeletions are found in the Yq11 region of the long arm of the Y chromosome. This region is named azoospermic factor (AZF), and it 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 [54,55]. Y chromosome deletions are also associated with cryptorchidism, varicocele, and obstruction of the vas deferens [56]. Similar results were seen in a second report [57].

A Y chromosome defect in a man is transmissible to his male offspring if assisted reproductive technologies (ART) using his sperm is successful. Thus, genetic testing and counseling should be offered to all men with nonobstructive azoospermia sperm concentrations with <5 million/mL before ART such as intracytoplasmic sperm injection (ICSI) are considered [1]. A 2019 meta-analysis found that a threshold of ≤1 million/mL would be more cost effective because Y chromosome microdeletions were rare in men with sperm concentrations >1 million/mL [58]. (See "Intracytoplasmic sperm injection".)

In Europe, Australia, and many infertility centers in the United States, tests for Y chromosome deletions are offered to the infertile couple. These tests need to be standardized to ensure the

quality of the results so that genetic misdiagnosis can be avoided [59]. (See "Approach to the male with infertility", section on 'Y-chromosome microdeletions, X-chromosome defects, and epigenetics'.)

Autosomal and X chromosome defects — A number of autosomal and X-linked genes have been identified as regulators of spermatogenesis [48-50,60-66].

Epigenetics in male infertility — Sperm in male infertility has only recently been studied. Sperm DNA methylation, histone acetylation, and noncoding RNAs may contribute to defective embryogenesis and idiopathic male infertility [67-73]. Both hypo- and hyper-DNA methylation have been reported with imprinted genes in men with infertility [74-77]. Epigenetic changes in DNA methylation, histone acetylation, or non-coding RNAs [78] may explain infertility due to obesity [79] and environmental toxicants [80], and such changes might prove to be useful predictors of male infertility and for health outcomes of offspring [81,82].

Congenital or developmental disorders associated with primary testicular defects — Congenital and developmental disorders that cause primary testicular defects in spermatogenesis (and sometimes concomitant testosterone deficiency) are found in a substantial proportion of infertile men. These include Klinefelter syndrome, cryptorchidism, and other less common disorders.

Klinefelter syndrome — One of the most common causes of primary hypogonadism with impaired spermatogenesis and testosterone deficiency is Klinefelter syndrome, which may occur in up to 1 out of 500 to 700 phenotypic males and in up to 10 to 15 percent of infertile men with azoospermia. 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. However, mild phenotypes of Klinefelter syndrome are likely more common than previously recognized, and these men may present with low sperm concentrations. This is one of the reasons that many experts recommend karyotyping of all men with sperm concentrations <5 million/mL before ART are considered [1]. (See "Causes of primary hypogonadism in males", section on 'Klinefelter syndrome' and "Clinical features, diagnosis, and management of Klinefelter syndrome".)

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 is probably related to underlying genetic, hormonal, and developmental abnormalities, some of which are partially preventable or 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. (See "Undescended testes (cryptorchidism) in children: Management", section on 'Subfertility'.)

Inactivating mutation in the FSH receptor gene — A rare cause of male infertility is an inactivating mutation in the follicle-stimulating hormone (FSH) receptor gene [83,84]. One report described five men who were homozygous for an inactivating mutation of the FSH receptor [83]. 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. Approximately 20 percent of men with myotonic dystrophy also have low serum testosterone concentrations [85]. (See "Myotonic dystrophy: Etiology, clinical features, and diagnosis", section on 'Endocrine abnormalities'.)

Androgen receptor or biosynthesis disorders — Normal sexual differentiation and spermatogenesis require testosterone and a normal androgen receptor. Polymorphisms of the androgen receptor gene are associated with male infertility [86,87]. Men with partial 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 syndrome) have varying degrees of ambiguous external genitalia, hypogonadism, and infertility [87]. Mild androgen insensitivity can cause infertility alone [87]. (See "Pathogenesis and clinical features of disorders of androgen action" and "Steroid 5-alpha-reductase 2 deficiency".)

The number of trinucleotide (CAG) repeats in exon 1 of the androgen receptor are inversely correlated with the transcriptional activity of the androgen target gene [86]. In a study of normal, fertile men, those with short CAG repeats had the highest sperm output [88]. Reports of CAG repeat lengths in men with idiopathic infertility have been inconsistent. In some [89-91], but not all [92], 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 [93]. Although androgen receptor CAG repeat length may be a valuable tool for epidemiological studies and pharmacogenomic evaluation of efficacy in treatment trials, it is not useful for clinical assessment of individual patients.

Estrogen biosynthesis or receptor disorders — Estrogen and the estrogen alpha receptor appear to be important for normal spermatogenesis. Case reports of men with decreased estrogen production due to aromatase deficiency or absence of estrogen receptor alpha have

variable degrees of spermatogenesis [94]. Certain polymorphisms of the estrogen receptor are associated with decreased spermatogenesis in men [95].

Acquired disorders of the testes — Virtually all acquired testicular disorders can cause infertility, often without accompanying Leydig-cell dysfunction. Some acquired disorders are reviewed briefly here; they are discussed in detail elsewhere. (See "Causes of primary hypogonadism in males".)

Varicocele — Varicocele is a dilatation of the pampiniform plexus of the spermatic veins in the scrotum. Left-sided varicoceles are 10 times more common than right-sided ones because of difference of the anatomy of the venous drainage of the two sides that results in lower blood flow in the left spermatic vein. Most men with varicocele and infertility have abnormal semen parameters, including low sperm concentration and abnormal sperm. (See "Nonacute scrotal conditions in adults", section on 'Varicocele' and "Treatments for male infertility", section on 'Surgical repair of varicocele'.)

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 [96,97]. In mumps and other viral causes of orchitis (echovirus and arbovirus), germ cell failure is much more common than androgen deficiency. (See "Mumps", section on 'Orchitis or oophoritis'.)

Other infectious causes of orchitis, impaired spermatogenesis and male infertility include tuberculosis and leprosy; the former may also cause epididymal obstruction [98]. Sexually transmitted diseases (STDs) such as gonorrhea and chlamydia can also cause orchitis. Many human immunodeficiency virus (HIV)-infected men have relatively normal semen parameters, but some may have low sperm motility and infertility that is due to HIV infection [99,100].

Drugs and radiation — Many drugs are associated with impaired spermatogenesis and/or Leydig cell dysfunction [101]. Among them, the most important are the alkylating drugs (cyclophosphamide and chlorambucil). Antiandrogens (flutamide, cyproterone, bicalutamide, spironolactone), ketoconazole, and cimetidine may cause dysspermatogenesis by inhibiting testicular androgen production or action [102]. Marijuana may decrease male fertility by decreasing sperm concentrations and sperm quality including motility but there is little evidence to date that it affects male fertility [103]. (See "Effects of cytotoxic agents on gonadal function in adult men", section on 'Impact on the germinal epithelium' and "Effects of antiinflammatory and immunosuppressive drugs on gonadal function and teratogenicity in men with rheumatic diseases".)

Ionizing radiation impairs spermatogenesis. Doses as low as 0.015 Gy (15 rads) may transiently suppress spermatogenesis, while doses above 6 Gy (600 rads) usually cause irreversible azoospermia and infertility [104].

Environmental factors, smoking, and hyperthermia

- **Environmental toxins** – Environmental toxins are potential causes of male infertility [67,68,74,105,106]. The pesticide dibromochloropropane is a well-known cause, as are lead, cadmium, and mercury [107]. 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 [106,108].

  Review of data of men exposed to pesticides indicates that changes in semen quality might be multifactorial, including DNA damage to germ cells and abnormal sperm morphology. Occupational and environmental exposure has been associated with lower-quality semen analyses; limited data suggest that consumption of fruits and vegetables with high pesticide residues might also be associated with lower semen quality [109]. (See "Endocrine-disrupting chemicals", section on 'Men'.)

  Because of the rapid increase in cell phone 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 [110-112].

- **Tobacco smoking** – There is some evidence that tobacco smoking is associated with decreased sperm quantity and quality and possibly fertility [1]. The data are inconsistent, but meta-analyses have shown that tobacco smoking is associated with decreases in all semen parameters [87,113].

  In utero exposure to smoking may have a detrimental effect on sperm production (approximately 20 percent decrease) in adulthood [114]. The fertility implication of this difference is not known. In another study, there were no significant differences in mean sperm concentrations in men whose mothers either smoked or did not smoke during pregnancy [115]. However, men whose mothers had smoked ≥10 cigarettes per day while pregnant were at higher risk of having oligozoospermia (defined as sperm concentration $<20 \times 10^6$/mL in this study). Smoking has been shown to change microRNA content in spermatozoa. These microRNAs are associated with cell death and apoptosis [116].

- **Hyperthermia** – Hyperthermia has long been thought to impair spermatogenesis, but there is weak evidence to support this conclusion [1]. Prolonged high testicular

temperature may explain the infertility associated with spinal cord injuries, varicocele, and chronic sauna or hot tub exposure [117]. Studies in men have shown that small increases in testicular temperature accelerate germ cell loss through apoptosis [118]. 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 [119,120].

Antisperm antibodies — Some infertile men have antisperm antibodies in serum or semen, and both could impair spermatogenesis [121]. Whether antibodies occur spontaneously or only after some testicular injury is not known. A systematic review in 2013 concluded that there was little evidence that antisperm antibodies contributed to infertility [122]. (See "Causes of primary hypogonadism in males", section on 'Autoimmune damage'.)

Systemic disorders — Some systemic disorders, such as chronic renal insufficiency or malnutrition of any cause, may cause primary hypogonadism in addition to secondary hypogonadism [41,123-125]. The infertility in men with sickle cell anemia is 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 luteinizing hormone [LH] concentrations) have been reported in men with celiac disease [126-128]. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults", section on 'Menstrual and reproductive issues'.)

SPERM TRANSPORT DISORDERS

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, for successful natural conception, sperm must be ejaculated into the female partner's vagina. Disorders of sperm transport include the following:

- **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 [94,129]. Little is known about functional abnormalities of the epididymis, but drugs used in some countries (eg,

triptolide) and chemical toxins (chlorhydrin) affect the function of metabolism of spermatozoa within the epididymis [130].

- **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 by surgical re-anastomosis, but some men have an immune response to sperm granulomas that form on the proximal side of the ligation and remain infertile [131].

  One to 2 percent of infertile men have bilateral congenital absence of the vasa deferentia. Most have mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [132]. Many infertile men with mutations of *CFTR* present with infertility and absence of the vasa differentia without other manifestations of cystic fibrosis (eg, respiratory and pancreatic disease). (See "Approach to the male with infertility", section on 'Genetic tests' and "Treatments for male infertility", section on 'Congenital bilateral absence of the vasa deferentia'.)

  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 [133-135]). Genetic mutations of dynein proteins or thioredoxin-nucleoside diphosphate kinase have been implicated to cause primary ciliary dyskinesia [136,137]. A similar genetic defect that may lead to abnormal transport of sperm is Young syndrome, in which inspissated secretions within the vas and epididymis interfere with transport of sperm, leading to obstructive azoospermia [138,139].

- **Ejaculatory duct disorders** – Patients with ejaculatory duct obstruction present with a low ejaculate volume and seminal fructose with no sperm count and/or very low sperm motility. Ejaculatory duct obstruction is uncommon but can be treated surgically with minimally invasive techniques. Spinal cord disease or trauma, sympathectomy, or autonomic disease (eg, diabetes mellitus) can cause decreased or retrograde ejaculation and lead to decreased fertility. Some men with severe retrograde ejaculation (eg, due to neuropathy or medications) may also be infertile.

- **Seminal vesicles and prostate** – It is not known if abnormal function of the seminal vesicles and prostate contributes to infertility, but chronic infection of the accessary glands might contribute to infertility.

- **Sexual dysfunction** – Erectile dysfunction, premature ejaculation, and infrequency of vaginal intercourse (less than twice per week [140]) also may be contributing factors to male infertility.

IDIOPATHIC MALE INFERTILITY

Idiopathic male infertility refers to men with repeatedly normal semen analyses who cannot achieve pregnancy with an apparently normal female partner, despite careful assessment of all possible causal mechanisms. (See "Unexplained infertility".)

ASSOCIATION WITH TESTICULAR CANCER

Based upon available data, we do not suggest routine screening for testicular cancer in men with infertility. However, we do suggest careful palpation of the testes on all routine exams. There is evidence of an increased incidence of testicular cancer in men presenting with infertility (even in the absence of a history of cryptorchidism) [141,142]. In one observational study of 3847 men with oligozoospermia (using previously published rather than current World Health Organization [WHO] criteria for normal semen parameters [143], 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) [142]. 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).

In another study in United States fertility centers, 34 cases of germ cell tumors were found in 22,562 male partners of the couples seeking infertility treatment, giving a hazard ratio (HR) of 2.8 (95% CI 1.5-2.8) compared with men without male infertility [144]. However, both studies are limited by the small number of cases. (See "Epidemiology of and risk factors for testicular germ cell tumors".)

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

- The causes of male infertility can be divided into four main categories (table 1):
  - Endocrine and systemic disorders that cause hypogonadotropic hypogonadism (5 to 15 percent) – Many endocrinopathies and any severe systemic disorders may cause hypogonadotropism, decreased spermatogenesis, and infertility. These conditions can be subdivided into congenital, acquired, or systemic disorders. (See 'Endocrine and systemic disorders (hypogonadotropic hypogonadism)' above.)
  - Primary testicular defects in spermatogenesis (70 to 80 percent) – Primary hypogonadism with or without a defect in sex steroidogenesis is an important cause of azoospermia and oligozoospermia. Although multiple specific testicular disorders include genetic abnormalities such as Klinefelter syndrome, specific drugs such alkylating agents, and irradiation have been identified, the pathogenic basis for testicular dysfunction is often unknown. The most common cause of male infertility is an idiopathic testicular defect in spermatogenesis. (See 'Primary testicular defects in spermatogenesis' above.)
  - Sperm transport disorders (2 to 5 percent) – 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. Erectile dysfunction, premature ejaculation, and infrequency of vaginal intercourse (less than twice per week) also may be contributing factors to male infertility. (See 'Sperm transport disorders' above.)

- Idiopathic male infertility (10 to 20 percent) – Idiopathic male infertility is characterized by a normal seminal fluid analysis (unlike idiopathic dysspermatogenesis that is characterized by an abnormal seminal fluid analysis. (See 'Idiopathic male infertility' above.)

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Topic 7473 Version 22.0

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

Causes of secondary hypogonadism in males

Congenital
Isolated gonadotropin deficiency
Kallmann syndrome
DAX1 mutation
GPR54 mutation
Leptin or leptin receptor mutation
Prader-Willi syndrome
Gonadotropin subunit mutation
Idiopathic
Deficiencies of multiple pituitary hormones
Pituicyte differentiation gene mutations
Acquired
Suppression of gonadotropins
Hyperprolactinemia
Gonadal steroid administration
Glucocorticoid treatment
Critical illness
Chronic systemic illness
Opiates
Diabetes mellitus
Idiopathic
GnRH analogs
Damage to gonadotroph cells
Benign tumors and cysts
Malignant tumors
Infiltrative diseases
Infections
Pituitary apoplexy
Trauma
Surgery in the sellar region

GnRH: gonadotropin-releasing hormone.

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Contributor Disclosures

Bradley D Anawalt, MD No relevant financial relationship(s) with ineligible companies to disclose. **Stephanie T Page, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose. **Alvin M Matsumoto, MD** Consultant/Advisory Boards: AbbVie [Testosterone];Partnership for Clean Competition [Anabolic steroid doping and testing];US Anti-Doping Agency [Board of Directors, performance enhancing drug doping and testing]. All of the relevant financial relationships listed have been mitigated. **Kathryn A Martin, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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