
2 Endocrinology of Male Infertility

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INTRODUCTION

Understanding reproductive physiology is pivotal in the evaluation and therapy of endocrine abnormalities. Although an endocrinological cause of male infertility is uncommon (less than 2%) (1) identification is important, as specific hormonal therapy is often successful. The human testis is an organ of dual function: spermatogenesis, occurring in the seminiferous tubules, and secretion of steroid hormones (androgens) by the Leydig cells, present in the interstitial tissue. These testicular functions are intimately related, because testosterone synthesis is required not only for sperm production, but also for the development of secondary sexual characteristics and normal sexual behavior. The anterior

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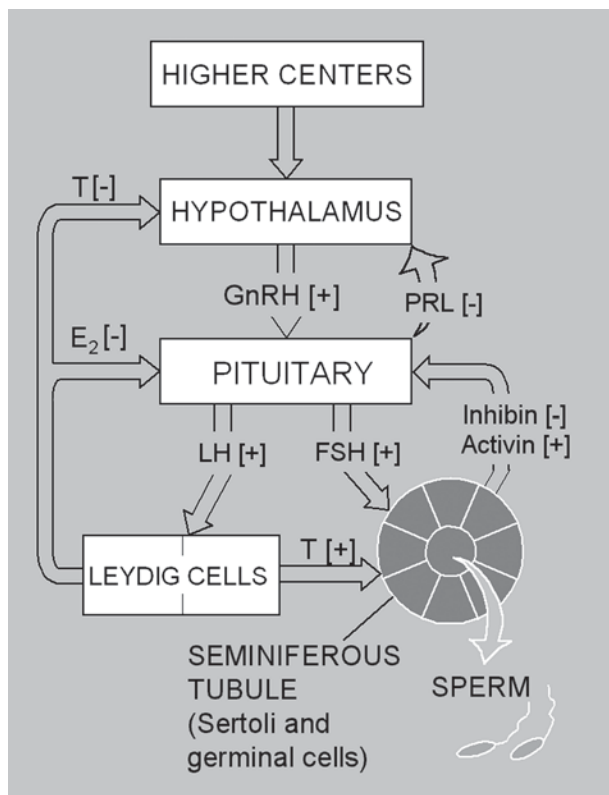


Fig. 1. Hypothalamic-pituitary-gonadal axis. LH, luteinizing hormone; FSH, follicle stimulating hormone; T, testosterone; DHT, dihydrotestosterone; E₂, estradiol; GnRH, gonadotropin-releasing hormone; PR, prolactin; +, positive influence; -, negative influence.

pituitary controls both these functions through the secretion of gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). In turn, the anterior pituitary is regulated by the hypothalamic secretion of gonadotropin-releasing hormone (GnRH). The extrahypothalamic central nervous system then influences the hypothalamus. The hypothalamic-pituitary-gonadal axis consists of a closed-loop feedback control mechanism directed at maintaining normal reproductive function (Fig. 1) (2–5).

REPRODUCTIVE PHYSIOLOGY

The Hypothalamus

The hypothalamus—the integrative center of the reproductive axis—receives neural input from many brain centers and is the *pulse generator* for the cyclical

secretion of pituitary and gonadal hormones (4,5). The function and anatomical association of the pituitary gland with the hypothalamus is accomplished by the hypophyseal portal microvascular system. This portal vascular system provides a direct route for the delivery of hypothalamic-releasing hormones to the anterior pituitary gland. In contrast, reverse flow through this vascular route may allow pituitary hormones direct access to the hypothalamus, e.g., men with pituitary hyperprolactinemia often have problems both with impotence and libido (5). The excess prolactin in these individuals has direct access to, and may affect, higher brain centers.

The single hypothalamic decapeptide, GnRH, has stimulatory effects on the pituitary gland, resulting in the synthesis and release of both gonadotropic hormones, LH and FSH. GnRH is released to the portal circulation in pulses occurring on the average basis of 1 pulse every 70 to 90 min and has a very short half-life in the blood of approx 2 to 5 min. The pulsatile secretion of GnRH appears to be essential for the stimulatory effects on LH and FSH release (3,4). Alternatively, constant exposure of the gonadotropins to GnRH results in paradoxical inhibitory effects on LH and FSH, and the pituitary becomes desensitized through the continuous exposure of GnRH by the downregulation of pituitary receptors.

A variety of influences, including age, diet, stress, and exercise, may affect GnRH secretion (4). Neurotransmitters (norepinephrine, dopamine, serotonin, and acetylcholine) and neuropeptides (endogenous opioid peptides) have both inhibitory and stimulatory effects on the hypothalamus (4,5). Pituitary gonadotropins and gonadal steroids also modulate the pulse frequency and amplitude of GnRH secretion.

ANTERIOR PITUITARY

Binding to high-affinity receptors on pituitary cells (gonadotrophs), GnRH influences the release of the two primary pituitary hormones (LH and FSH) that regulate testicular function. These pituitary hormones are both glycoproteins composed of two polypeptide-chain subunits. The protein component of the α -subunits are identical and similar to other pituitary hormones (thyroid-stimulating hormone [TSH] and human chorionic gonadotropin [hCG]), but biological and immunological activity are conferred by the unique β -subunit (2). Although both hormones are secreted in an episodic manner by the pituitary gland, the longer half-life of FSH in circulation is reflected by a more constant serum level than that of the more rapidly metabolized LH. The peak and trough pattern of blood levels of gonadotropins, particularly LH, is clinically important because a single measurement of circulating LH may be as much as 50% above or below the mean integrated hormone concentrations (6).

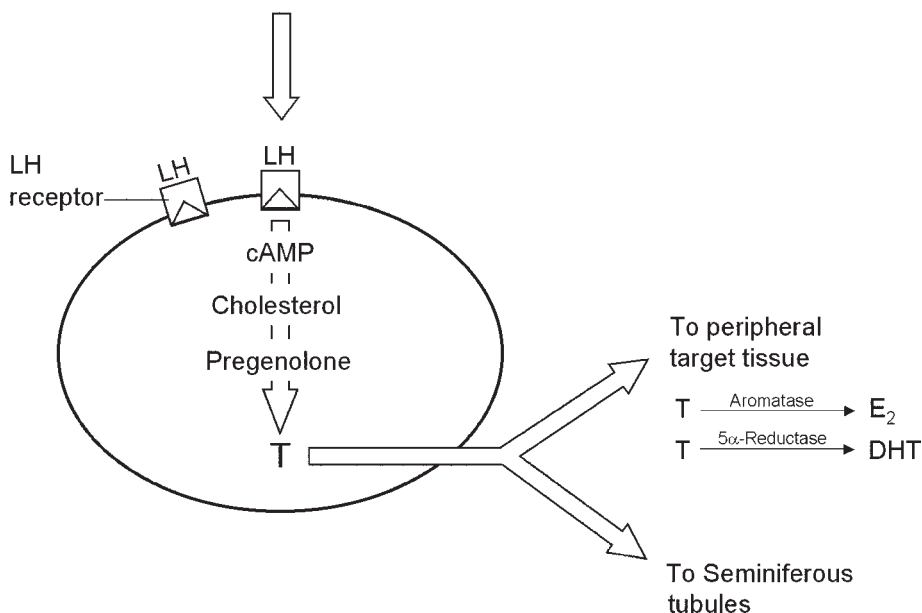


Fig. 2. Testosterone production and metabolism. cAMP, cyclic adenosine monophosphate; T, testosterone; E₂, estradiol; DHT, dihydrotestosterone.

TESTES

LH interacts with specific high-affinity cell surface receptors on the plasma membrane of Leydig cells. Ligand binding stimulates a membrane-bound adenylate cyclase to enhance the formation of cyclic adenosine monophosphate (cAMP), which binds to the regulatory subunits of protein kinase. This, in turn, causes dissociation of regulatory subunit and activation of the catalytic subunit of the enzyme. The activated Leydig cell protein kinase operates through several steps to stimulate the enzyme synthesis of testosterone synthesis (Fig. 2) (2,3).

FSH targets the epithelium of the seminiferous tubule and binds to membrane receptors on the Sertoli's cells. The second messenger is the cAMP, and activation of adenylate cyclase stimulates cAMP-dependent protein kinase and RNA and protein synthesis, including synthesis of the androgen-binding protein and aromatase enzyme that converts testosterone to estradiol (Fig. 3) (2,3).

FEEDBACK CONTROL OF GONADOTROPINS

The hypothalamic-pituitary-gonadal system is a closed-loop feedback system directed at maintaining normal reproductive function (2–5). Gonadal hormones have inhibitory effects on the secretion of LH and FSH. Although testosterone—

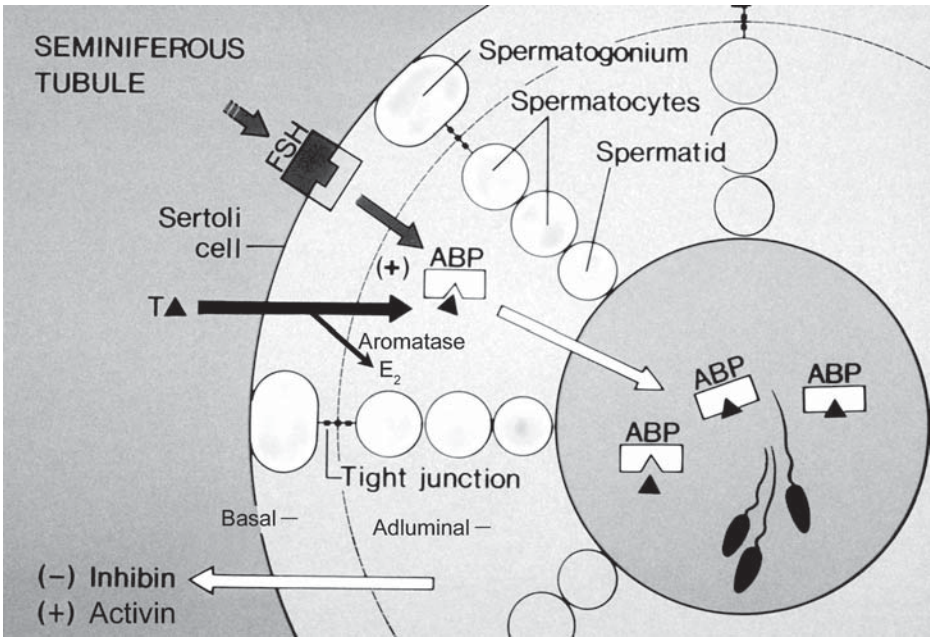


Fig. 3. Schematic representation of the seminiferous tubule. Follicle-stimulating hormone (FSH) and testosterone (T) act on the Sertoli cells to produce androgen-binding protein (ABP), inhibin, activin, as well as estradiol (E₂).

the major secretory product of the testes—is a primary inhibitor of LH secretion in men, other testes products, including estrogens and other androgens, also inhibit LH secretion. Testosterone is metabolized in peripheral tissues to the potent androgen dihydrotestosterone (DHT) or potent estrogen, estradiol.

Both androgens and estrogens *independently* appear to modulate LH secretion. Estradiol is produced both by the testes and from peripheral conversion of androgenic precursors and is a more potent inhibitor of LH and FSH secretion. Infusions of gonadal steroids in amounts that accumulate physiological concentrations of the hormones in the blood demonstrate suppression of LH levels for testosterone and estradiol, suggesting that *both* hormones may have an important role in LH regulation. Gonadal sex steroids influence the *frequency* and/or *amplitude* of LH secretory pulses in men by acting at the level of the GnRH pulse generator in the hypothalamus and partly at the level of GnRH-stimulated LH secretion (2–5).

The mechanism for the feedback control of FSH secretion is even more controversial than that of LH. After castration, FSH increases the indication of a negative feedback from testicular products. Like LH, both testosterone and

estradiol are capable of suppressing FSH serum levels, but the influence of these two gonadal steroids in physiological function is still undefined (2,4).

A nonsteroidal tubular factor may also be significant in the feedback regulation of FSH. *Inhibin* has been isolated and characterized in follicular fluid and is produced by the Sertoli cells of the testes. Inhibin has two subunits: α and β . Two inhibin forms have been isolated—inhibin A (α and β A subunits) and inhibin B (α and β B subunits)—both of which have been shown to cause selective suppression of FSH release in vitro (4). The combination of the two β -subunits led to the formation of *activins*, which increase FSH secretion in vitro. In addition to inhibin, numerous gonadal peptides and growth factors, such as follistatin and transforming growth factor B, are also modulators of FSH secretion (4). Reductions in spermatogenesis are accompanied by decreased production of inhibin, and this decline in negative feedback is associated with reciprocal elevation of FSH levels. Isolated levels of FSH constitute an important and sensitive marker of the status of the germinal epithelium (2).

Even in pathological conditions with marked damage to the germinal tissue, serum FSH is not elevated to castrate levels unless Leydig cell function is also impaired. It appears that *both* gonadal steroids and peptides are important to maintain normal serum FSH concentrations.

PROLACTIN AND GONADOTROPINS

Hyperprolactinemia is linked with disturbed reproductive function reflected by a variety of symptoms and signs of hypogonadism. LH levels are inappropriately low relative to low-serum testosterone levels, indicating that the hypothalamic-pituitary axis fails to respond to reduced testicular testosterone production (4,5). Prolactin may inhibit GnRH secretion either directly or through modulation of the dopaminergic pathways. Although the pituitary responds normally to GnRH administration, the pulse frequency of LH secretion is diminished in hyperprolactinemic individuals. Bromocriptine, a dopamine agonist with prolactin-lowering activities, improves sexual function (7). Excessive prolactin may affect sexual functions by having a direct effect on the central nervous system and also from inhibition of androgen secretion. In individuals with elevated prolactin, libido does not return to normal as long as the prolactin levels remain elevated despite use of androgen therapy (5).

ANDROGEN PHYSIOLOGY

Androgens regulate gonadotropin secretion, initiation and maintenance of spermatogenesis, formation of male phenotype during sexual differentiation, promotion of sexual maturation at puberty, and controlling sexual drive and potency (2).

Testosterone is synthesized from pregnenolone within the Leydig cells. Testosterone production in men approximates 5 mg per day and the secretion occurs in an irregular pulsatile manner. There is a diurnal pattern: the peak level is in the early morning, and the nadir is in the evening (8). Inside androgen target cells, testosterone can be converted to DHT by 5 α -reductase. Both these androgens bind to the same high-affinity-androgen receptor protein; subsequently, the hormone receptor complex is attached to acceptor sites in the nuclei to affect the biologic response (3–5).

Estrogens may either be secreted directly by the testes or formed in peripheral tissues. Like other steroid hormones, androgens and estrogens initiate their effect at the cellular level by interacting with high-affinity receptor proteins and are present in the highest concentration in androgen target tissues, e.g., the accessory organs of male reproduction. In the testes, androgen receptors are present both in Sertoli cells and Leydig cells.

In normal males, 2% of testosterone is *free* (unbound), and 44% is bound to a high-affinity sex hormone-binding globulin (SHBG), and the remainder is bound to albumin and other proteins. Free- and albumin-bound portions make up the measure known as *bioavailable testosterone* (2–4). It was formerly believed that the physiologic active androgen moiety was the nonprotein-bound free testosterone. Now it appears that the cellular transfer of steroid hormones is more complicated and can involve hormone dissociation from the binding proteins, such as albumin-bound testosterone, within the microcirculation of the brain and liver (9). SHBG has a higher affinity for testosterone than for estradiol, and changes in SHBG concentration can alter the hormonal milieu. Elevated estrogens, thyroid hormone, and healthy aging increases plasma SHBG and therefore decreases the free testosterone fraction (10). Alternatively, androgens, growth hormone, and obesity depress SHBG levels and increase the active androgen fraction (Fig. 4) (10,11).

HORMONAL CONTROL OF SPERMATOGENESIS

Spermatogenesis is primarily controlled by the gonadotropins—FSH and LH. LH indirectly affects spermatogenesis by stimulating endogenous testosterone production. The Sertoli cells possess specific high-affinity FSH receptors and produce androgen-binding protein, which carries androgens intracellularly, serves as an androgen reservoir within the seminiferous tubule, and transports testosterone from the testes into the epididymal tubule. The physical proximity of the Leydig cells to the seminiferous tubules, and the elaboration by the Sertoli cells of ABP, maintain an extremely high level of androgen concentration within the microenvironment of the developing spermatozoa (2,3,5).

Hormonal requirements for the initiation and maintenance of spermatogenesis appear to be different. The maintenance immediately after hypophysectomy

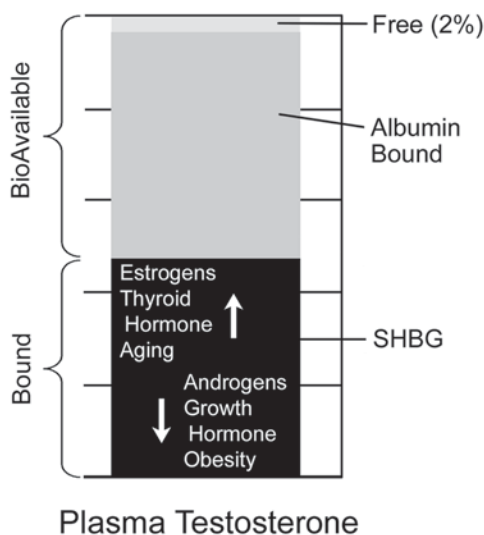


Fig. 4. Plasma testosterone distribution. SHBG, sex hormone-binding globulin.

(pituitary obliteration) requires testosterone alone; however, when the germinal epithelium regresses completely, both FSH and testosterone treatment are required. Qualitatively, testosterone will initiate and maintain spermatogenesis in humans, but quantitative restoration will not be achieved (12). In humans, FSH is necessary for the maintenance of quantitatively normal sperm production (13) and is particularly important for initiating spermatogenesis in pubertal males and reinitiating spermatogenesis in men whose germinal epithelium has regressed after hypophysectomy. *Qualitative* sperm production can be achieved by replacement of either FSH or LH alone. However, both FSH and LH are necessary to maintain *quantitative* normal spermatogenesis in humans (12).

DIAGNOSING ENDOCRINE ABNORMALITIES: CLINICAL FINDINGS

History

Specific childhood illnesses should be sought, including cryptorchidism, postpubertal mumps, orchitis, testicular trauma or pain (torsion), as well as the timing of puberty (14). Precocious puberty may indicate the adrenal genital syndrome (15). A detailed history of exposure to occupational and environmental toxins, excessive heat, and radiation should be elucidated (16,17). Cancer chemotherapy has a dose-dependent, potentially devastating effect on the testicular germinal epithelium and may compromise Leydig cell function (18).

Drug history should be reviewed; anabolic steroids, cimetidine, ketoconazole, and spironolactone may affect the reproductive cycle (1,4,19). Unfortunately, the use of anabolic steroids is very common among potential athletes. Exogenous androgens exert their deleterious effects on the feedback level of the pituitary and hypothalamus by inhibiting gonadotropin release. Chronic use has also been shown to inhibit gonadotropin secretion and lower testosterone levels. Additionally, alcohol, marijuana, and cocaine have been implicated as reversible gonadotoxic agents (14,19,20).

Decreased libido and impotence are the earliest symptoms of low testosterone. Loss of libido that is associated with headaches, visual abnormalities, and galactorrhea may suggest a pituitary tumor. Anosmia may be a symptom in individuals with hypothalamic hypogonadism. Other medical problems associated with infertility include thyroid disease and liver disease (21,22). Chronic systemic diseases (e.g., renal, sickle cell, celiac, and HIV disease) are also related to abnormal reproductive hormonal axis (14,23–25).

Physical Examination

When germ cell failure occurs before puberty, patients have obvious features of eunuchoidism (Table 1). When failure occurs after puberty, the diagnosis is more difficult unless it is linked with adrenal failure, because the regression of secondary sexual characteristics may take years.

Careful examination of the testes is essential in the examination. The seminiferous tubules account for approx 95% of testicular volume. The prepubertal testis measures approx 2 cm in length (2 mL-volume, as assessed by Prader orchidometer) and gradually increases in size with puberty. The normal adult testis is an average of 4.6 cm long (3.6–5.5-cm range) and 2.6 cm wide (2.1–3.2-cm range) with a mean volume of 18.6 ± 4.8 mL standard deviation (SD) (Fig. 5) (2,26). When the seminiferous tubules are damaged before puberty, the testes are small and firm but characteristically small and soft with postpubertal damage.

Gynecomastia is a consistent feature of a feminizing state. Men with congenital hypogonadism may have related midline defects, such as anosmia, color blindness, cerebellar ataxia, hare lip, and cleft palate (2,3,19). Hepatomegaly may be associated with problems of hormone metabolism. Proper neck examination may help rule out thyromegaly, a bruit, or nodularity linked with thyroid disease. The neurologic examination should test the visual field and reflexes.

SEMEN ANALYSIS

Examination of the seminal fluid provides important information concerning the integrity of the reproductive hormonal network, spermatogenesis, and patency of the reproductive tract. A normal microscopic examination eliminates the need for any further diagnostic studies.

Table 1
Features of Eunuchoidism

<i>Eunuchoid skeletal proportions</i>
Upper body:lower body ratio < 1
Arm span > 2 inches than height
<i>Lack of adult male hair distribution</i>
Sparse axillary, pubic, facial, and body hair
Lack of recession of hair on temporal lobe
<i>Infantile genitalia</i>
Small penis, testes, and prostate
Underdeveloped scrotum
<i>Diminished muscular development and mass</i>

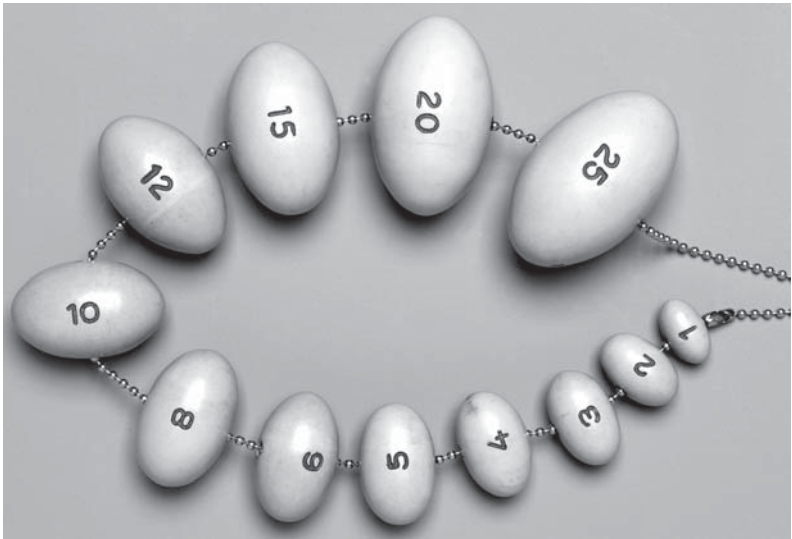


Fig. 5. A Prader orchidometer for measuring testicular volume.

BASELINE HORMONE EVALUATION

The classic hormone evaluation includes a serum testosterone and serum gonadotropins (LH and FSH). An algorithm for diagnosing endocrine causes of male infertility is illustrated in Fig. 6. A low-serum testosterone with inappropriately low LH levels usually warrants the investigation of serum prolactin levels (14). A more recent study showed that obtaining serum FSH and testosterone

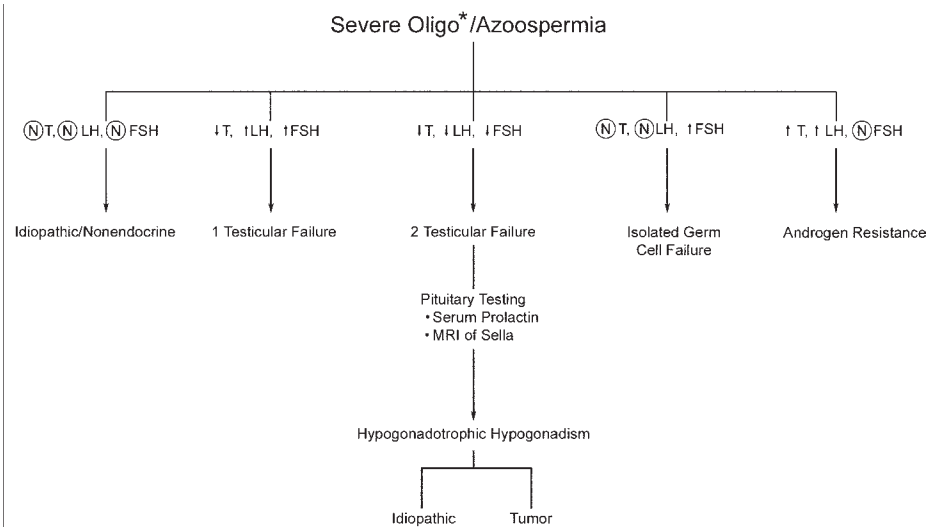


Fig. 6. Algorithm for the diagnosis of endocrine causes of male infertility. *, sperm counts $< 5 \times 10^6/\text{mL}$.

only in men with sperm densities less than 10 million sperm/mL and soft testes will detect virtually all (99%) endocrine abnormalities (27).

A single LH determination has limited prognostic accuracy ($\pm 50\%$) because of the episodic nature of LH secretion and its short half-life (6). In contrast, serum FSH has a longer half-life, and fluctuations in serum levels are less obvious. If an abnormal LH value is obtained in a single sample, then three serum samples can be collected over a 20-min interval and the samples pooled (28). Estradiol levels are measured in patients presenting with gynecomastia, testicular masses, or history compatible with excessive exogenous estrogen exposure.

Testosterone secretion follows a diurnal cycle with an early morning peak around 8:00 AM followed by evening trough at 8:00 PM when the concentration falls to about 70% of the morning peak (4,8,19). Testosterone values should therefore be drawn in the morning. The measurement of total (bound) testosterone usually provides a correct assessment of bioavailable testosterone. Free (unbound) testosterone is a more accurate marker of bioavailable testosterone, particularly when conditions of altered SHBG concentrations exist (10). Elevated estrogens, thyroid hormone, and aging increase plasma SHBG and thus decrease levels of free testosterone. Alternatively, androgens, growth hormone, and obesity depress SHBG levels and increase the active androgen fraction. Measurement of the free-testosterone fraction should be made by equilibrium dialysis. Ultrafiltration or analog immunoassays are currently very unreliable (29).

A low-serum testosterone level is one of the best indicators of hypogonadism of hypothalamic or pituitary origin. Mean serum LH and FSH concentrations are significantly lower in hypogonadotropic patients than in normal men, but they can overlap with the lower limits of normal in some individuals. In patients with hypogonadotropic hypogonadism, the pituitary hormones other than LH and FSH should also be assessed (adrenocorticotrophic hormone, TSH, and growth hormone) to exclude the possibility of hypopituitarism. Thyroid dysfunction is such a rare cause of infertility that routine screening is discouraged.

Elevated serum FSH and LH values help to distinguish primary testicular failure (hypergonadotropic hypogonadism) from secondary testicular failure (hypogonadotropic hypogonadism).

Decreases in spermatogenesis are generally accompanied by reductions in inhibin production, and this decline in negative feedback is associated with a reciprocal elevation of FSH levels. Elevated FSH is usually a reliable indicator of severe germinal epithelial damage and is usually associated with azoospermia or severe oligospermia ($<5 \times 10^6/\text{mL}$). In azoospermic and severely oligospermic patients with normal FSH levels, primary spermatogenic defects cannot be distinguished from obstructive lesions by hormonal investigation alone. Therefore, scrotal exploration and testicular biopsy should be considered. Elevated serum FSH levels related to small atrophic testes implies severe infertility; biopsy is not warranted.

Hyperprolactinemia is reported to cause oligospermia, but the diagnostic value of routine prolactin measurements is extremely low in men with semen abnormalities unless decreased libido, impotence, and evidence of hypogonadism also exist. Prolactin measurement is warranted in patients with low-serum testosterone without an associated increase in serum LH. Individuals with gynecomastia or suspected androgen resistance (high-serum testosterone and LH with undermasculinization) should have a serum estradiol determination.

Individuals with a rapid loss of secondary sex characteristics, implying both testicular and adrenal failure, should undergo investigation of adrenal function. In men with a history of precocious puberty, congenital adrenal hyperplasia should be considered. In the common variant (21-hydroxylase deficiency), serum levels of 17-hydroxyprogesterone are elevated, as is urinary pregnanetriol. In the 11-hydroxylase deficiency, serum 11-deoxycortisol is elevated (15).

DYNAMIC HORMONAL TESTING

Dynamic tests to determine the physiologic state of the hypothalamic-pituitary axis include stimulation tests with GnRH and hCG. The GnRH test evaluates the functional capacity of pituitary gonadotropins to release LH and FSH. Often, a single GnRH test is nondiagnostic, and chronic testing with GnRH is necessary. The ability of the testes to secrete testosterone is tested with the

administration of hCG, which has a biologic activity similar to that of LH. The stimulation tests are usually in the realm of endocrinology and are used mainly in a research setting (2,14).

CLASSIFICATION OF ENDOCRINE CAUSES OF INFERTILITY

The results of hormone testing can classify patients into primary and secondary hypogonadism. The primary type (hypergonadotropic hypogonadism) where the defect is at the testicular level with elevated serum LH or FSH or both. The secondary type (hypogonadotropic hypogonadism) where the defect is at the hypothalamic or pituitary level with inappropriately low-serum LH and FSH levels. Occasionally, there is selective involvement of LH but rarely of FSH by itself. Most infertile men with seminiferous tubule abnormalities have no detectable endocrinopathy and have normal serum LH, FSH, and testosterone levels. These characteristics typify eugonadotropic hypogonadism (Table 2).

PRIMARY HYPOGONADISM

Chromosomal Abnormalities

SOMATIC

Various somatic chromosomal abnormalities are associated with male infertility, and incidence increases as the sperm count decreases. In a study of 1263 barren couples, Kjessler found the overall incidence of male chromosomal abnormalities to be 6.2%. In a subgroup in which the male partner's sperm count was less than 10 million, the incidence rose to 11%. In the azoospermic subjects, 21% had significant chromosomal abnormalities (30).

Y CHROMOSOME

Approximately 7% of men with severe oligospermia and 13% of men with azoospermia harbor structural alterations in the long arm of the Y chromosome (Yq) (31,32), and gene defects (microdeletions) in this region may lead to defective spermatogenesis. There appears to be a specific region designated as azoospermic factor (AZF), and its absence or mutation accounts for azoospermia. Three nonoverlapping regions with AZF designated as *AZF_a*, *AZF_b*, and *AZF_c* (33) can also be identified. Deletion of the *DAZ* (deleted in azoospermia) gene in the *AZF_c* region is the most commonly observed microdeletion in infertile men. In addition to azoospermia, men with abnormalities in testicular development, e.g., cryptorchidism, may also have Y chromosome microdeletions (34). Testicular sperm extraction in conjunction with assisted reproductive techniques can result in pregnancies in these previously infertile men. Similar genetic defects are likely present in male offspring, and vertical transmission is described (35). Prior to undergoing any

Table 2
Male Hypogonadism

Primary hypogonadism (hypergonadotropic hypogonadism)

Chromosomal abnormalities
 Myotonic dystrophy
 Bilateral anorchia (vanishing testes syndrome)
 Sertoli-cell-only syndrome
 Gonadal toxins (drugs and radiation)
 Orchitis
 Systemic diseases (hepatic, renal, sickle cell disease, and HIV)

Secondary hypogonadism (hypogonadotropic hypogonadism)

Hypogonadotropic eunuchoidism (Kallmann's hypogonadism)
 Isolated LH or FSH deficiency
 Multiorgan genetic disorders (congenital hypogonadotropic syndromes)
 Pituitary disease
 Androgens, estrogens, glucocorticoids (endogenous/exogenous excess)
 Hyperprolactinemia
 Hemochromatosis
 Hypothyroidism or hyperthyroidism

Defective androgen synthesis or action

Reifenstein's syndrome
 5- α reductase deficiency
 Celiac disease

Eugonadotropic syndromes

Adult seminiferous tubule failure

LH, luteinizing hormone; FSH, follicle-stimulating hormone.

assisted reproductive techniques, appropriate genetic testing should be offered to these individuals.

Klinefelter's Syndrome

Klinefelter's syndrome is the most common cause of primary hypogonadism. It occurs in approx 1 in every 500 men and is a genetic disorder resulting from the presence of an extra X chromosome in the male (2,19,36). In classic Klinefelter's syndrome, the karyotype of all cells is XXY as a result of either maternal or paternal meiotic nondisjunction during gametogenesis (2).

Characteristically, these individuals have small firm testes, decreased androgenicity (delayed sexual maturation), azoospermia, and gynecomastia. As features of hypogonadism are often not evident until puberty, diagnosis is usually delayed. The reduction in testicular mass is usually owing to sclerosis and hyalin-

ization of the seminiferous tubules; although the Leydig cells may appear hyperplastic, their total number per testis is normal. The testes are characteristically less than 2 cm long and always less than 3.5 cm (corresponding to volumes of 2 and 12 mL, respectively). These individuals have increased mean body height secondary to a longer lower body segment that is not secondary to the androgen deficiency but caused by the underlying chromosome abnormality (2,3,19).

Gonadotropin levels are characteristically elevated, particularly FSH. Plasma testosterone can range from normal to low, but decreases with age. Serum estradiol levels are often increased secondary to elevated LH levels, and increased serum estradiol levels promote an increase in SHBG. Elevated SHBG results in higher levels of bound testosterone and lower levels of free testosterone, which explains the inconsistency between total serum testosterone levels and degree of androgenicity. Higher estrogen levels relative to testosterone cause the feminized appearance and gynecomastia. As these men have abnormal testosterone to estradiol ratio, aromatase inhibitors have been known to decrease the conversion of testosterone to estradiol, thereby increasing serum testosterone levels (40). In the majority of these men, they will later require androgen replacement for optimal virilization and normal sexual function.

Several medical disorders occur at a greater frequency than normal in Klinefelter syndrome, including chronic pulmonary disease, varicose veins, cerebrovascular disease, glucose intolerance, and primary hypothyroidism (37). There is also a 20-fold increase of breast cancer and these individuals may have mild mental deficiency and/or be socially maladjusted (38). There are also variant syndromes characterized by more than two X chromosomes (Poly X syndrome) associated with more severe abnormalities than classical Klinefelter syndrome.

Approximately 10% of these patients have a chromosomal mosaicism (XXY/XY), which is the result of mitotic nondisjunction that occurs after fertilization. They have less severe features of Klinefelter syndrome and may be fertile when a normal (46,XY) clone of cells exists within the testes (2,3,14,19). In the past, infertility was irreversible in classic Klinefelter syndrome. Presently, techniques using testicular microdissection have identified viable sperm allowing in vitro fertilization and intracytoplasmic sperm injection with resulting pregnancies (39).

XX Disorder (Sex Reversal)

This is a rare (1/9000) variant of Klinefelter syndrome (2,14,19). The signs are similar, except that the average height is less than normal, hypospadias is common, and the incidence of mental impairment is not increased. Although these patients have a 46,XX chromosome complement, this paradox is explained by the translocation of the testes determining factor normally found in the Y chromosome to the X chromosome. This is a result of frequent XY recombination that occurs during normal male meiosis.

Noonan's Syndrome (Male Turner's Syndrome)

This disorder occurs when genotypic XY males manifest features similar to those of Turner's syndrome (41). Men typically have dysmorphic features like web neck, short stature, low-set ears, wideset eyes, and cardiovascular abnormalities. Most cases are sporadic, but affected families have been described in which inheritance is autosomal-dominant. Of these individuals, 75% have cryptorchidism at birth that may limit their future fertility. However, if testes are fully descended, fertility is possible and likely. FSH and LH levels depend on the degree of testicular function (14,19).

Myotonic Dystrophy

Myotonic dystrophy is an autosomal-dominant disorder characterized by prolonged contraction of skeletal muscles (myotonia). Aside from the progressive muscle atrophy and weakness, associated abnormalities include lenticular opacities, frontal baldness, and impaired spermatogenesis (testicular atrophy) (42). Pubertal development is usually normal, and testicular failure occurs in approx 80% of affected men between the ages of 30 and 40. Leydig cell function remains normal, and there is no gynecomastia. The serum FSH level is elevated proportionate to the degree of testicular atrophy. There is no therapy for the infertility; because testosterone levels are normal, androgen replacement is not required (14).

Bilateral Anorchia (Vanishing Testes Syndrome)

This extremely rare disorder occurs in approximately 1 of every 20,000 males, presenting with nonpalpable testes and sexual immaturity owing to the absence of testicular androgens. The karyotype is normal, but serum LH and FSH levels are elevated, and serum levels of testosterone are extremely low. The absent testes can be from testicular torsion, trauma, vascular injury, or infection (43). These patients have eunuchoid proportions but no gynecomastia, and therapy is directed at treating the underlying androgen deficiency.

These patients usually present with suspected bilateral cryptorchidism before puberty or with sexual infantilism during adulthood. To differentiate between anorchia and bilateral undescended testes, the testosterone response to human chorionic gonadotropin is extremely useful. Men with anorchia do not respond to hCG, whereas those with functioning testes do (14).

Sertoli-Cell-Only Syndrome (Germinal Cell Aplasia)

This disorder is indicated by the absence of germ cells and presence of only Sertoli cells on testicular biopsy. The most likely cause of the syndrome is con-

genital absence or early neonatal loss of germ cells, but it may also be secondary to genetic defects or androgen resistance. Clinical findings include azoospermia associated with normal virilization, testes of normal consistency but slightly smaller size, and no gynecomastia (14). Serum testosterone and serum LH levels are normal, but serum FSH is usually elevated (44). With other testicular disorders (mumps, cryptorchidism, damage from radiation or toxins, and adult seminiferous tubule failure), the seminiferous tubules may also only contain Sertoli cells, but in these men, the testes are small, the histological pattern is not as uniform, and severe sclerosis and hyalinization are prominent features.

Gonadotoxins

DRUGS

The germinal epithelium, a rapidly dividing tissue, is susceptible to agents that interfere with cell division. Cancer chemotherapy causes a dose-dependent, potentially devastating effect on the testicular germinal epithelium and may damage the Leydig cells. Effects vary with drug class and age of the patient (18,45).

Drugs may cause infertility by directly inhibiting testosterone synthesis, blocking peripheral androgen action, inhibiting pituitary gonadotropin secretion, or enhancing estrogen levels. Cyproterone, ketoconazole, spironolactone, and alcohol all interfere with testosterone synthesis (19). The most commonly administered drug known to be an androgen antagonist is cimetidine (46). Men treated with cimetidine present with gynecomastia and may have decreased sperm density. Recreational drugs (marijuana, heroin, and methadone) are associated with lower serum testosterone levels without a concomitant elevation in plasma LH, suggesting a central abnormality as well as a testicular defect (19,20).

RADIATION

Germ cells are particularly sensitive to radiation, whereas Leydig cells are relatively resistant. A single exposure below 600 rad to germ cell damage is reversible, but above this level, permanent damage is likely (2,17). Spermatogenesis may recover in some men, but it may take 2 to 3 yr. Elevated serum FSH levels reflect impaired spermatogenesis, which may return to normal with the recovery of spermatogenesis.

ENVIRONMENTAL TOXINS

A variety of chemical agents are toxic to spermatogenesis, including pesticides (e.g., dibromochloropropane), industrial solvents (e.g., carbon disulfide), and metals (lead, cadmium, and mercury) (19,48). Other toxins are cigaret smoke, and it is likely that as yet unidentified toxins may contribute significantly to male factor infertility.

Orchitis

Approximately 15 to 25% of adult men who contract mumps (epidemic parotiditis) develop orchitis, which is commonly unilateral. Bilateral involvement occurs in only 10% of affected men and less than one-third of men with bilateral orchitis recover normal semen parameters (47). Testicular atrophy can develop within 1 to 6 mo or can take years. With the advent of the mumps vaccine, the incidence of mumps and associated orchitis is becoming increasingly rare.

Systemic Disease

CHRONIC RENAL FAILURE

Uremia is associated with decreased libido, impotence, altered spermatogenesis, and gynecomastia. Serum testosterone is decreased, and serum LH and FSH levels are increased. The cause of this dysfunction is multifactorial, with contributions from nutrition deficiency, estrogen excess, hyperprolactinemia, and nondialyzable uremic toxins (23). In patients who have undergone successful renal transplantation, uremic hypogonadism improves.

CIRRHOSIS OF THE LIVER

A large percentage of men with liver cirrhosis have testicular atrophy, impotence, and gynecomastia (22). Serum testosterone levels and metabolic clearance rates are reduced, and testosterone binding to plasma proteins is increased secondary to increased SHBG. Serum estradiol rises because of decreased hepatic extraction of androgens and increased peripheral conversion of androgens to estrogen, resulting in gynecomastia. Independent of its effect on the liver, ethanol also acutely reduces testicular testosterone synthesis (19,22).

SICKLE CELL DISEASE

Many men with sickle cell disease have evidence of hypogonadism (delayed sexual maturation, impaired skeletal growth, reduced testicular size, and, in some, reduced sperm density). Serum testosterone is low, but studies have shown basal serum LH and FSH levels to be normal, elevated, or reduced. These discrepancies make it impossible to state definitively whether the hypogonadism of sickle cell disease is primary (testicular), secondary (pituitary-hypothalamic), or a mixture of both (14,19).

Androgen Resistance Syndromes

Congenital androgen insensitivity results from either an androgen receptor abnormality or a defect in the enzyme responsible for peripheral androgen conversion (5- α reductase) (49). These men are nearly always infertile.

Androgen-resistant syndromes constitute a category of phenotypic disorders in which 46,XY males with bilateral testes fail to develop as completely normal men. The clinical spectrum extends from infertility alone to pseudo-hermaphrodisism. These patients have elevated rates of testosterone production and therefore high-baseline testosterone secondary to high-serum LH. The elevated LH levels are a consequence of the lack of feedback regulation from the resistance or absence of androgen receptors at the hypothalamic pituitary level to the androgen action. Diagnosis of androgen resistance is made by genital skin fibroblast culture and measurement of androgen receptor function.

Individuals with 5- α -reductase deficiency at birth have ambiguous genitalia, but at puberty, increased testosterone secretion from the testes results in incomplete virilization. Spermatogenesis is impaired because the testes are usually undescended, and these men are infertile (14).

Celiac Disease

Individuals with celiac disease have been shown to have infertility (abnormalities in sperm motility and morphology) associated with a biochemical picture of androgen resistance (24); that is, high-serum testosterone and high-LH concentrations. Dietary modification led to the normalization of biochemical abnormalities.

SECONDARY HYPOGONADISM (HYPOGONADOTROPIC SYNDROMES)

Isolated Gonadotropin Deficiency (Kallmann's Syndrome)

Although uncommon (1:10,000 men), this is second to Klinefelter's syndrome as a cause of hypogonadism (2,3,19). The original report described the familial form associated with anosmia, but the eponym now refers to both variants, with and without anosmia. This syndrome may be associated with other congenital anomalies (congenital deafness, hare lip, cleft palate, craniofacial asymmetry, renal abnormalities, and color blindness) (50). The hypothalamic hormone, GnRH, appears to be absent, as exogenous GnRH administration stimulates the release of both LH and FSH from the pituitary (51,52). Except for the gonadotropin deficiency, anterior pituitary function is intact. Congenital GnRH deficiency can be inherited as autosomal-dominant, autosomal-recessive, or an X-linked condition. More than two-thirds of cases, however, are sporadic (19).

During childhood, patients may present with a microphallus, cryptorchidism, or both, but a delay in sexual maturation is the usual presentation. The differential diagnosis includes constitutionally delayed puberty, but anosmia, somatic mid-line defects, or a positive family history may imply that sexual maturation may not proceed normally. Other distinguishing features of Kallmann's syndrome

include a normal growth curve, a height age greater than bone age, and testes that are almost invariably less than 2 cm in diameter. Although basal serum testosterone levels are low, baseline serum LH and FSH in prepubertal patients may be within the lower limits of normal for their age group and thus will not aid the diagnosis. The GnRH stimulation test results in a rise of both serum gonadotropins. With severe deficiency, GnRH may have to be administered chronically to elicit a response.

Isolated Leutinizng Hormone Deficiency (“Fertile Eunuch”)

These individuals have eunuchoid proportions with variable degrees of virilization and often gynecomastia. They also characteristically have large testes with an ejaculate that may contain a few sperm (53). Serum FSH levels are normal, but both serum LH and serum testosterone concentrations are low normal. Serum testosterone increases after hCG administration indicating hypogonadotropic hypogonadism. The cause appears to be partial gonadotropin deficiency with adequate LH to stimulate high-intratesticular testosterone and resultant spermatogenesis but insufficient testosterone to promote virilization. These patients may be treated with hCG for virilization and full spermatogenesis (14).

Isolated Follicle-Stimulating Hormone Deficiency

In this rare disorder, patients are normally virilized and have normal testicular size and baseline levels of LH and testosterone. Sperm counts range from azoospermic to severely oligospermic. Serum FSH levels are low and do not respond to GnRH. The use of gonadotropins may improve spermatogenesis and fertility (2,14).

Congenital Hypogonadotropic Syndromes

These syndromes are associated with secondary hypogonadism and a multitude of other associated somatic findings (54). The Prader-Willi Syndrome is characterized by hypogonadism, hypopentia, hypotonia at birth, and obesity. The Laurence-Moon-Bardet-Biedle Syndrome is characterized by mental retardation, retinitis pigmentosa, polydactyly, and hypogonadism. Other congenital hypogonadotropic syndromes are Lowe’s Syndrome and congenital oculofacial paralysis (Möbius’ Syndrome).

Pituitary Disease

Pituitary insufficiency may result from tumors, infarction, iatrogenic damage (surgery or radiation), or one of several infiltrative and granulomatous processes. If pituitary insufficiency occurs before puberty, growth retardation associated with adrenal and thyroid deficiency is a major clinical presentation.

Hypogonadism occurring in a sexually mature man usually has its origin in a pituitary tumor. The symptoms of decreasing libido, impotence, and infertility may be present years before the appearance of other signs of an expanding tumor, such as headache, visual field abnormalities, and deficiency of thyroid or adrenal hormones (19,55). Once an individual has passed through normal puberty, it takes a long time for the secondary sexual characteristics to disappear unless adrenal insufficiency exists. Physical examination demonstrates small and soft testes, and the diagnosis is based on the finding of low-serum testosterone levels with low or normal plasma gonadotropin concentrations. Depending on the degree of panhypopituitarism, serum corticosteroids are reduced, as will serum TSH and growth hormone levels.

Estrogen Excess

Adrenal cortical, Sertoli cell, or interstitial cell tumors of the testes all may at times produce estrogen (56). Similarly, hepatic cirrhosis has been associated with increased endogenous estrogen. Excessive estrogen acts primarily by suppressing pituitary gonadotropin secretion, resulting in secondary testicular failure.

Androgen Excess

Like estrogens, excessive androgen levels also suppress pituitary gonadotropins, leading to secondary testicular failure. The current use of exogenous androgens (anabolic steroids) by professional and nonprofessional athletes may cause temporary sterility (57). Elevated endogenous androgen secretion may occur in men with testosterone-secreting tumors (e.g., Leydig cell tumors) or in individuals with congenital adrenal hyperplasia (e.g., 21-hydroxylase or 11 β -hydroxylase deficiency) (15).

Hyperprolactinemia

Excessive serum prolactin levels cause both reproductive and sexual dysfunction (58,59). Prolactin-secreting tumors of the pituitary gland, whether from a microadenoma (< 10 mm) or macroadenoma, result in loss of libido, impotence, galactorrhea, gynecomastia, and altered spermatogenesis. Patients with a macroadenoma first present with visual field abnormalities and headaches, should undergo magnetic resonance imaging of the pituitary and laboratory assessment of anterior pituitary, thyroid, and adrenal function (55).

Men with pituitary adenomas have low-serum testosterone levels, but basal serum levels of LH and FSH are either low or low normal and reflect an inadequate pituitary response to depressed testosterone, implicating impaired GnRH secretion. Signs and symptoms of other derangements in pituitary trophic hor-

mones (hypothyroidism and hypoadrenalism) should be sought, particularly in individuals with a macroadenoma.

Other causes of elevated serum prolactin include central nervous system (CNS)-active drugs (antipsychotics, opiates, sedative hypnotics, and antidepressants) (60). Antihypertensive drugs, such as α -methyldopa, reserpine, and verapamil, may also stimulate prolactin levels. Strenuous exercise, stress, nipple stimulation, and high-protein meals may also elevate serum prolactin. A slightly high prolactin level (21–40 ng/mL) warrants reconfirmation.

Because prolactin release by the pituitary lactotrophs is under tonic inhibition by the catecholamine dopamine, the dopamine agonist, bromocriptine, will lower prolactin concentration and can restore gonadotropin secretion and normal gonadal function in patients with prolactin-producing tumors. The usual dose is 5 to 10 mg per day. Side effects are dizziness, hypertension, headaches, nausea, and vomiting. Cabergoline, another dopamine agonist, can be administered once or twice a week and has less tendency toward nausea than bromocriptine. In certain individuals, surgical ablation may be required (7). In the rare patient in whom infertility is the sole manifestation of elevated prolactin, treatment has resulted in normalization of sperm counts.

Glucocorticoid Excess

Whether glucocorticoid excess is exogenous (e.g., from treatment of ulcerative colitis, asthma, or rheumatoid arthritis) or endogenous (Cushing's syndrome), the result is decreased spermatogenesis (19,61). Elevated plasma cortisol levels depress LH secretion and cause secondary testicular dysfunction. Even short-term therapy may result in lower serum testosterone levels. Correction of the glucocorticoid excess results in improvement of spermatogenesis.

Hyperthyroidism and Hypothyroidism

Both elevated and depressed levels of serum thyroid hormone alter spermatogenesis (14,19,21). Hyperthyroid men may develop gynecomastia, a depressed sperm count and/or motility, and sexual dysfunction. Hyperthyroidism is evidenced by effects at both the pituitary and testicular levels with alterations in the secretion of releasing hormones and increased conversion of androgens to estrogens. Men with hypothyroidism may experience a decreased libido as well as other CNS effects. Decreased SHBG levels and lower total testosterone in these patients may indicate testicular failure. Either hypothyroidism or hyperthyroidism are extremely rare causes of infertility.

Hemochromatosis

Approximately 80% of men with this disease have testicular dysfunction. Their hypogonadism may be secondary to iron deposition in the liver or may be

primarily testicular because of iron deposition in the testes (62). Recently, iron deposits have been identified in the pituitary, implicating this gland as the major site of abnormality.

CASE PRESENTATION

Medical Treatment of Hypogonadotropic Hypogonadism

GS was a 32-yr-old gentleman with a known diagnosis of Kallman's syndrome presenting for treatment of infertility. At birth, he was found to have a small phallus and was bilaterally cryptorchid. Orchidopexy was performed and he subsequently received exogenous testosterone therapy to stimulate penile growth and for virilization. The diagnosis of Kallmann's syndrome had been made with the clinical findings of anosmia, color blindness, and the response of GnRH stimulation with a rise in both serum LH and FSH from previously undetected levels as well as an increase in serum testosterone.

Previous androgen therapy will not affect the testicular responsiveness to gonadotropins. The androgens, however, must be withdrawn for at least 2 mo prior to gonadotropin stimulation. Human gonadotropin has the biological activity of LH and stimulates Leydig cells to synthesize and secrete testosterone. Human chorionic gonadotropins (Pregnyl, Profasi, APL; 2000 IU intramuscularly 3 times/wk) were given to stimulate testosterone and obtain full androgenization (Fig. 7). Over a 4-mo period, hCG increased the testicular volume from 3 to 8 cc, but for full testicular growth, FSH needed to be added (63). Serum testosterone was measured every month and kept between 300 and 600 ng/dL. The hCG dose was changed accordingly. Higher testosterone levels should be avoided as they may elevate serum estrogen levels and cause gynecomastia. If plasma testosterone concentration fails to respond to hCG, antibodies to hCG should be suspected (64).

After 4 mo, the patient was well-virilized, but the testicular volume had only increased to 8 cc, and monthly semen analysis still revealed azoospermia. At this time, FSH was initiated (14). FSH is available as human menopausal gonadotropin. The commercial preparation of Pergonal contains 75 IU of FSH and 75 IU of LH per vial. The initial dose was one vial intramuscularly three times per week given with hCG. Both solutions are compatible, and the same syringe may be used.

As it may take months for sperm to appear in the ejaculate after FSH administration, monthly semen analyses were performed (65,66). After 5 mo of hCG and FSH, the patient achieved a volume of 12 cc and had a sperm count of 6 million per cc. At 12 mo, his testicular volume had increased to 14 cc, and his sperm count had risen to 12 million per cc. Pregnancy occurred 4 mo later. The sperm counts in most individuals receiving gonadotropin therapy are usually less

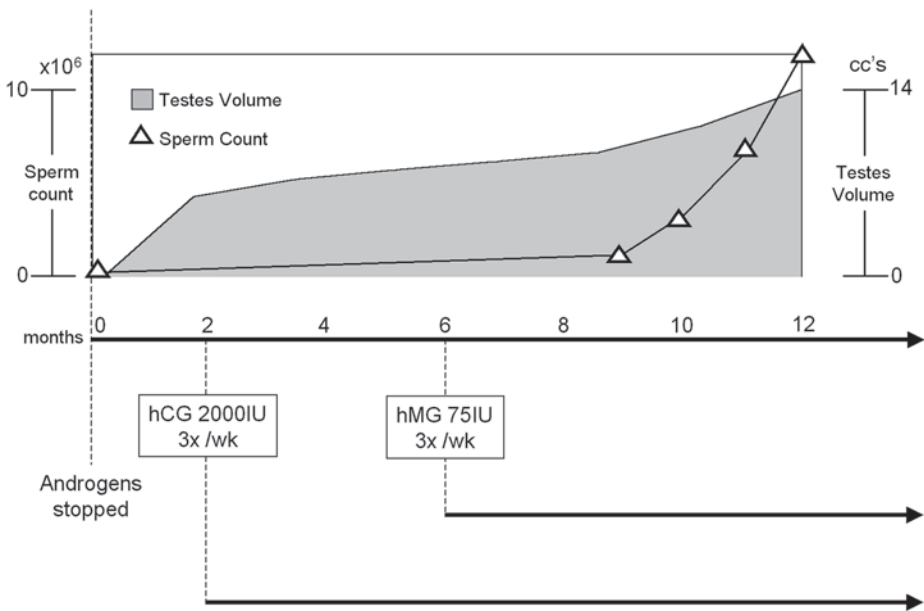


Fig. 7. Course of treatment of an individual with hypogonadotropic hypogonadism.

than 20 million. Burris found that 71% of 22 individuals who initiated a pregnancy had sperm counts less than 20 million per milliliter, indicating the quality of spermatogenesis as well as sperm function in these males are relatively normal (67).

Once pregnancy occurs, if the patient wants further children, FSH can be stopped and spermatogenesis can be maintained on hCG therapy alone (65). An alternative therapy would be to give GnRH subcutaneously in a pulsatile manner (68). Unfortunately, this requires an infusion pump, which is expensive and is not proven to be superior to the combined hCG/FSH therapy. It is also not approved by the FDA. Therapy is monitored by its effect on gonadotropins, testosterone, and eventually on spermatogenesis.

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