PATHOPHYSIOLOGY COURSE - ENDOCRINE MODULE
Male Gonadal Disorders
(Testicular Disorders & Clinical Conferences)
Dale Childress, MD
Monday, December 6, 2010, 8:00-8:50am

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Goals and Objectives:

1. To understand regulation of the hypothalamic-pituitary-gonadal axis.
2. To become familiar with the etiologic categories of testicular endocrine disorders.
3. To learn the appropriate diagnostic evaluation and interpretation of laboratory results for patients with testicular endocrine disorders.

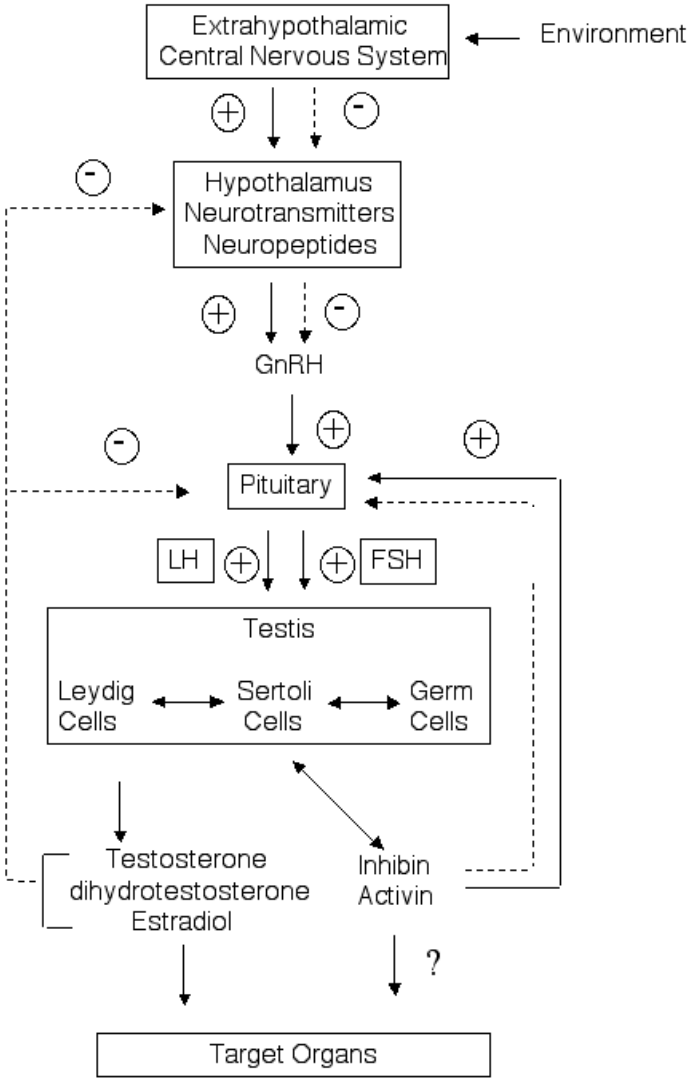
I. THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS

An understanding of the reproductive axis is critical for the assessment of abnormal development of the genitalia (e.g. pseudohermaphroditism), hypergonadism, hypogonadism, infertility and erectile dysfunction. The reproductive hormonal axis in men consists of three main components: (A) the hypothalamus, (B) the pituitary gland, (C) the testis. Regulation of this axis impacts on the steroid-sensitive end organs such as the prostate and penis. This axis normally functions in a tightly regulated manner to produce concentrations of circulating steroids required for normal male sexual development, sexual function and fertility.

A. Hypothalamus

The integrating center of the reproductive hormonal axis is the hypothalamus (Figure 1). The hypothalamus is the site of production of the peptide hormone gonadotropin-releasing hormone (GnRH) which is transported to the adenohypophysis of the pituitary gland by a short portal venous system where it stimulates the synthesis and release of gonadotropic hormones (luteinizing hormone-LH and follicle stimulating hormone-FSH). Both neural input from the central nervous system and humoral factors from the testis modulate the secretion of GnRH. The GnRH neurons receive input from neurons in other parts of the brain including the amygdala and both the olfactory and the visual cortex. The release of GnRH is seasonal (peaks in the spring), circadian (highest testosterone levels are in the a.m.) and pulsatile (peaks occur every 90-120 minutes). GnRH has a very short half-life in the blood (approximately 2 to 5 minutes). The pituitary gland is therefore exposed to high levels of GnRH in hypophyseal-portal blood for brief periods of time. This pulsatile pattern of GnRH release appears to be essential for stimulatory effects on LH and FSH release whereas constant exposure to GnRH results in paradoxical inhibitory effects on LH and FSH release.

Figure 1. (Adapted from Campbell's Urology, 8th Edition)



GnRH has been synthesized and is used for diagnostic studies in humans. When administered intravenously, it acts rapidly, resulting in prompt release of LH and, to a much lesser extent, of FSH into the blood stream. The response of the pituitary to GnRH is influenced by gonadal steroids. Testosterone deficiency in

patients with hypogonadal disorders results in an exaggerated response to GnRH.

Since administered GnRH has a direct effect on the pituitary gland, GnRH testing should distinguish patients with hypogonadotropic hypogonadism of pituitary origin from those with primary hypothalamic disease. Pituitary disease should not respond to GnRH, whereas those with hypothalamic disorders should secrete LH and FSH normally after administration of GnRH. Unfortunately, a single pulse dose of GnRH does not reliably distinguish between these two types of hypogonadotropic hypogonadism. One possible reason for the decreased pituitary response to GnRH in some patients with hypothalamic disorders causing hypogonadotropic hypogonadism is that the pituitary gland is chronically understimulated and has developed neither the stored reserves nor the biosynthetic machinery to respond normally to a single bolus dose of the hypothalamic hormone. This concept has been supported by evidence that repeated GnRH administration to patients with hypothalamic GnRH deficiency results in a greater response to each individual bolus dose of GnRH. This approach with repeated pulsatile administration of GnRH has been used with success in the induction of puberty, maintenance of secondary sex characteristics, and initiation of fertility in patients with hypothalamic GnRH deficiency.

B. Pituitary

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are glycopeptides consisting of two peptide chains (alpha and beta). Although named after their function in females, they are produced by both sexes, secreted into the general circulation and thereby transported to the testis. LH and FSH share a common alpha peptide chain (alpha chain) with thyroid- stimulating hormone (TSH) and human chorionic gonadotropin (hCG) and differ from each other by the presence of a specific beta chain, the latter providing specificity of biologic action.

LH and FSH are synthesized in the pituitary gland, released into the systemic blood circulation, and carried to the target end organs the gonads. Both hormones are usually measured in the blood by radioimmunoassay techniques. The LH radioimmunoassay generally available does not distinguish between LH and hCG. Although the latter substance is found only in pregnant women (normal and abnormal), a closely related substance is usually found in high concentrations in the blood of subjects with choriocarcinoma of the testis and may also be produced by a large number of other neoplasms. Neoplastic production of gonadotropin is best assessed by a beta hCG assay, which does not detect the normal endogenous LH levels in men.

The pituitary also secretes prolactin (PRL). The physiologic release of PRL is inhibited by the neurotransmitter dopamine. The hypothalamic peptides thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP) also

stimulate the release of PRL from the pituitary and may be the putative PRL-releasing hormones in men. Therefore, because TRH stimulates prolactin release, hypothyroidism should be ruled out in patients with prolactin excess. Prolactin affects testicular function indirectly by inhibiting GnRH release from the hypothalamus and therefore LH and FSH secretion from the pituitary. Prolactin also directly inhibits pituitary gonadotropic cells and the Leydig cells of the testes.

C. Testis

In the testis, LH stimulates testosterone secretion and FSH is important in the initiation and maintenance of spermatogenesis. The secreted testicular androgen testosterone and its activated form dihydrotestosterone (DHT) act on numerous target end organs causing the development of male secondary sexual characteristics and inhibiting the pituitary secretion of LH and FSH. Peptide secretory products of the testis include inhibin, activin and follistatin which also regulate gonadotropin secretion. Sertoli cell products may serve as the mediators of interaction between germ cells, Leydig cells, peritubular myoid cells and the Sertoli cells of the testis.

The development of the male germ cells in the seminiferous tubule essentially consists of three phases: spermatogonal clonal expansion, meiosis, and spermatogenesis. Spermatogenesis is a 73-day process by which a primitive stem cell, the type A spermatogonium, passes through a series of transformations to give rise to spermatozoa. In the seminiferous epithelium, cells in these developmental phases are arranged in defined in stages. Along the seminiferous tubules, these stages follow one another in a regular fashion, giving rise to the wave of the seminiferous epithelium.

Spermatogenesis is dependent on pituitary FSH and on intratesticular testosterone. FSH and androgens seem to have different preferential sites of action during spermatogenesis. Stages VII and VIII appear to be androgen-dependent, whereas maximal binding of FSH and activation of FSH- dependent enzymes occurs in Stages XIII to XV of the spermatogenic cycle. When the onset of hypogonadotropic hypogonadism is before puberty, the initiation of sperm production generally requires both LH and FSH. LH affects spermatogenesis by increasing intratesticular testosterone levels. The levels of FSH required to initiate spermatogenesis in these patients are low. Thus, both FSH and LH are apparently required for the initiation and completion of spermatogenesis. However, in patients with gonadotropin deficiency acquired after puberty, sperm production can be stimulated with only LH, suggesting that the reinitiation and maintenance of spermatogenesis in adults can be achieved by LH alone. Studies of selective gonadotropin replacement in normal men, in whom hypogonadotropic hypogonadism was induced with exogenous testosterone administration, show that qualitatively normal sperm production can be achieved by replacement of either FSH or LH alone. Both FSH and LH are necessary to maintain quantitatively normal spermatogenesis in man.

LH stimulates testicular steroidogenesis by binding to LH receptors on Leydig cells. In addition to LH, FSH may indirectly affect Leydig cell function by action on Sertoli cells and spermatogenesis. In addition to LH, FSH and androgens many other peptides and growth factors (e.g., inhibin, activin, insulin-like growth factor 1, transforming growth factors) are secreted locally in the seminiferous tubular microenvironment.

D. Feedback Control of Gonadotropins

Negative-feedback of GnRH release is exerted by testosterone through androgen receptors present in the hypothalamic neurons and in the pituitary. This is easily demonstrated by the rise in serum LH and serum FSH that occurs after orchiectomy. LH and FSH blood levels continue to rise for a long period after castration, reaching maximum levels as late as 25 to 50 days after surgery. Although it is generally held that testosterone, the major secretory product of the testis, is the primary inhibitor of LH secretion in men, a number of testicular secretory products, including estrogens and other androgens, have the ability to inhibit LH secretion. Estradiol, a potent estrogen, is produced both from the testis and from peripheral conversion of androgens and androgen precursors and is the predominant regulator of FSH secretion in the male. Although the concentration of estradiol in the blood of men is relatively low compared with testosterone, it is a much more potent inhibitor of LH and FSH secretion (approximately 1000-fold). Testosterone acts primarily to feedback at the level of the hypothalamus whereas estrogens provide feedback to the pituitary to modulate the gonadotropin secretion response to each GnRH surge.

Inhibin, a peptide growth factor produced by seminiferous tubules, is also important in the feedback regulation of pituitary FSH. Inhibin has also been isolated and characterized in follicular fluid. Two forms of inhibin have been isolated. They have the same alpha subunit, but their beta subunits are different. Inhibin B (alpha subunit and B variant of the beta subunit) is the form secreted by the Sertoli cells. Inhibin B selectively suppresses FSH secretion in the gonadotropes by inhibiting transcription of the gene encoding the beta subunit of FSH. Men who have selective injury to the germinal epithelium (seminiferous tubules) have elevated serum FSH, but normal LH and testosterone levels. Selective damage to the germinal epithelium occurs with testis irradiation, anti-spermatogenic agents, pesticides, chemotherapy, and early cryptorchidism. In addition to inhibin, a number of other gonadal peptide growth factors, such as follistatin and transforming growth factors, are also modulators of FSH secretion.

The activins (closely related to inhibins) are also secreted in the testis, primarily by the Sertoli cells. They are also composed of heterodimers and homodimers of beta subunits. They stimulate transcription of the FSH beta subunit and are in turn negatively regulated by the binding protein follistatin.

II. ETIOLOGIC CATEGORIES OF TESTICULAR ENDOCRINE DISORDERS

A. Hypothalamic Disease

In 1944, Kallmann described a hereditary syndrome of hypogonadotropic hypogonadism associated with anosmia. A failure of GnRH secretion by the hypothalamus is responsible for the gonadotropin deficiency leading to secondary testicular failure. Anosmia may be complete or partial. Kallmann's syndrome occurs in both sporadic and familial forms. The familial part of inheritance is autosomal dominant inheritance with variable penetrance as the most common pattern. Some patients who have Kallmann's syndrome have absent olfactory lobes. Interestingly, anosmia may be transmitted without hypogonadotropism or the hypogonadotropic syndrome may be encountered without anosmia in families with Kallmann's syndrome. Multiple other associated anomalies include cranial facial asymmetry, cleft palate, harelip, color blindness, congenital deafness, cryptorchidism, and renal anomalies. Delayed pubertal development is the hallmark of this syndrome and is the reason that patients present for medical evaluation. As a result of a delay in the androgen dependent closure of the epiphyseal plates, the length of the arms and legs may be greater than that of the trunk. In addition, the testes remain prepubertal, with testicular size smaller than 2 cm in diameter.

In the prepubertal male, differentiating between Kallmann's syndrome and delayed sexual maturation may be very difficult. A family history of Kallmann's syndrome or the presence of somatic midline defects or anosmia may help in the prepubertal diagnosis. Because the first sign of puberty is testicular growth, a patient who has testes greater than 2 cm is experiencing delayed puberty rather than hypogonadotropic hypogonadism. Delayed pubertal males, but not patients with Kallmann's syndrome, respond to clomiphene citrate with a rise in serum LH levels. Although patients who have Kallmann's syndrome have an absent or blunted rise in gonadotropins following GnRH administration, repeated GnRH injections may prime the pituitary resulting in rises of both LH and FSH. Unfortunately, this pattern of response is also found in prepubertal boys. Finally, following doses of 5000 IU of human chorionic gonadotropin (hCG), prepubertal and pubertal boys demonstrate larger rises in testosterone levels than patients with Kallmann's syndrome.

Androgen replacement with testosterone or hCG is adequate treatment for the teenager and usually results in virilization. Exogenous androgens, however, suppress intratesticular testosterone production and consequently, spermatogenesis and testicular growth are not stimulated in these patients. Androgen therapy should be given in parenteral form as testosterone enanthate or cypionate. Intramuscular injections of 200 mg every other week is usually sufficient to induce full virilization in most patients. Although oral androgens are available as fluoxymesterone and fluoxymesterone and 17-α-methyl testosterone, they are less potent and may result in a higher incidence of hepatic abnormalities. Reversible intrahepatic cholestasis resulting in elevations of

plasma transaminases, lactate dehydrogenase, and bilirubin may be noted. The development of hepatomas and peliosis hepatis, a cystic dilatation of the liver venules, has been noted after high androgen dosages. Other side effects include prostatic hypertrophy, acne, priapism, gynecomastia and erythrocytosis.

Gonadotropin therapy is required for the initiation of spermatogenesis. Given as 2000 IU IM three times per week, hCG initiates spermatogenesis in most patients, but only 20% of patients complete spermatogenesis with hCG therapy alone. FSH is required in most patients and is commonly given after 6 months of hCG therapy. FSH is usually given in the form of human menopausal gonadotropin [hMG (Pergonal)], which contains 75 IU of FSH and 75 IU of LH per vial. The intramuscular administration of one-half vial three times per week usually results in the completion of spermatogenesis. Stimulation of the testes with FSH and LH results in testicular growth, although the final testis volume may remain below normal. Although semen motility parameters are usually quite good, oligospermia with counts below 10 million sperm per milliliter are common. In contrast to patients with idiopathic oligospermia who are often infertile with these sperm densities, many patients with hypogonadotropic hypogonadism are able to conceive despite these low sperm densities.

Other Congenital Hypothalamic Hypogonadal Syndromes:
The Prader-Willi syndrome consists of obesity, hypotonic musculature, mental retardation, small hands and feet, short stature, micropenis, and hypogonadism. The syndrome may be associated with abnormalities of chromosome 15. Patients demonstrate LH and FSH deficiencies because of a lack of GnRH. Treatment is identical to that for Kallmann's syndrome. A similar picture is found in Laurence-Moon Bardet-Biedl syndrome, which consists of hypogonadotropic hypogonadism, retinitis pigmentosa, and polydactyly.

B. Pituitary Disease

Pituitary function may be impaired in cases of pituitary surgery, infarction, tumors, radiation, or infectious diseases. Patients with prepubertal onset of pituitary disease are usually diagnosed prior to a fertility evaluation as a result of growth retardation or adrenal or thyroid deficiency. Infertility, impotence, visual field abnormalities, and severe headaches may be presenting symptoms in the adult male with pituitary dysfunction. Normal male secondary sexual characteristics are usually present unless adrenal insufficiency exists. Small, soft testes may be demonstrated on physical examination. This is in contrast to cases of primary testicular failure with tubular and peritubular sclerosis, in which case the testes are small and firm to palpation. Plasma testosterone levels are low and gonadotropin levels are low or normal. Thus, a normal LH value associated with a low serum testosterone value is abnormal and further evaluation is required. Evaluation of other pituitary hormones and endocrine functions should be performed in appropriate cases.

1. Fertile Eunuch Syndrome

Isolated LH deficiency occurs rarely in patients with normal FSH levels. These men demonstrate a variably eunuchoid habitus, large testes, and small volume ejaculates containing few spermatozoa. Plasma testosterone and LH levels are low, but FSH levels are in the normal range. *Testicular biopsy specimens demonstrate maturation of the germinal epithelium with Leydig Cell hypoplasia because of insufficient LH stimulation.* A rise in serum testosterone following hCG therapy supports normal Leydig function in these patients. Sufficient intratesticular testosterone is produced for spermatogenesis, but inadequate peripheral androgen levels lead to poor virilization.

2. Isolated FSH Deficiency

This is a rare disorder in which patients have adequate virilization, normal LH- and testosterone levels, and normal-sized testes. Because of a lack of FSH, oligospermia or azoospermia is present. Administration of hMG improves spermatogenesis, but a more specific treatment may be given in the form of pure FSH (Metrodin).

3. Hyperprolactinemia

Hyperprolactinemia interferes with reproductive functions lowering serum testosterone levels resulting in classic symptoms of hypogonadism. The mechanisms by which hyperprolactinemia induces testosterone deficiency are complex. Serum LH levels are suppressed or inappropriately low, indicating that the hypothalamic-pituitary axis fails to respond to reduced testicular testosterone production. Prolactin inhibits GnRH secretion. Prompt and dramatic improvement in sexual function occurs in many hyperprolactinemic men treated with bromocriptine (dopamine agonist with PRL-lowering activity). There is evidence to suggest that hyperprolactinemia may impair sexual function in men both by direct effect on the CNS and by inhibition of androgen secretion. The direct CNS effect is supported by clinical data demonstrating that androgen replacement therapy of hyperprolactinemic hypoandrogenized men did not return libido to normal as long as PRL levels remained elevated. Finally, it must be recognized that some patients with prolactinomas will have hypogonadotropic hypogonadism produced by the mass lesion itself.

C. Primary Testicular Disorders

Approximately 6% of infertile men are found to have chromosomal abnormalities, with the incidence increasing as the sperm count decreases. The highest incidence is found in azoospermic patients, with up to 21 % of cases demonstrating abnormalities of the karyotype. The majority of these cases are

associated with Klinefelter's syndrome or XXY syndrome. One gene locus localized to the long arm of the Y chromosome is a region referred to as AZF (Azoospermic Factor). This locus is subdivided into a, b and c, of which AZFc contains the gene DAZ (deleted in azoospermia). Men with complete deletions of the entire AZFa region uniformly show a Sertoli cell only pattern (see below). The AZFa region contains a gene DBY, a transcriptional regulator. The AZFb region appears to be critical for completion of spermatogenesis. No patients with AZFb deletion have shown completely developed spermatozoa present on testicular biopsy.

1. Klinefelter's Syndrome

The presence of an extra X chromosome is the genetic hallmark of Klinefelter's syndrome. This is due to nondysjunction of the meiotic chromosomes of the gametes from either parent. Hypogonadism, with the classic triad of small, firm testes, gynecomastia, and elevated urinary gonadotropins, has an incidence of 1 of every 600 male births, but clinically may not be identifiable until puberty. Although secondary sexual characteristics begin developing at the appropriate time, the completion of puberty is usually delayed with features of eunuchoidism, gynecomastia, and impotence. Virilization may be complete in some patients and the diagnosis for them delayed until adulthood, at which point the patient may present with infertility (azoospermia) with associated gynecomastia and small, firm testes. Mental retardation and various psychiatric disturbances may also occur. Testicular biopsy reveals seminiferous tubular sclerosis and an occasional Sertoli cells or spermatozoa. Owing to the absence of normal seminiferous tubules, Leydig cells may appear hyperplastic. Plasma FSH levels are usually markedly elevated as a result of the severe seminiferous tubular injury, whereas LH levels may be elevated or normal. Total plasma testosterone levels are decreased in 60% of patients and normal in 40%. The physiologically active free testosterone concentrations are usually decreased. In addition, plasma estradiol levels are usually increased, stimulating increased levels of testosterone-binding globulin and resulting in a decreased testosterone to estrogen ratio resulting in gynecomastia. The diagnosis may be made with a chromatin-positive buccal smear, indicating the presence of an extra X chromosome. Karyotypes usually demonstrate 47 XXY or, less commonly, a mosaic pattern 46 XY/47 XXY. Less severe abnormalities are present in patients with the mosaic form of Klinefelter's syndrome, and occasional patients are fertile.

2. XYY Syndrome

This karyotype occurs in 0.1 % to 0.4% of newborn infants. This karyotype has been linked to aggressive and criminal behavior. Not all investigators agree that this behavior is secondary to the karyotype, but feel it may be secondary to tall stature, which may predispose individuals to this

behavior. Patients are characteristically tall, whereas semen analyses typically reveal severe oligospermia or azoospermia. Testicular biopsy specimens reveal patterns of maturation arrest to complete germinal aplasia as well as occasional cases demonstrating seminiferous tubular sclerosis. Plasma gonadotropins and testosterone levels are most often within the normal range in these patients. However, elevations of plasma FSH levels may be found in association with more severe patterns of testicular dysfunction.

3. XX Disorder

Patients with the XX male syndrome (sex reversal syndrome) have findings similar to those of Klinefelter's syndrome. These patients demonstrate small, firm testes, frequent gynecomastia, small to normal-sized penises, and azoospermia. Testicular biopsy may demonstrate seminiferous tubule sclerosis, resulting in elevated gonadotropins and decreased testosterone levels. In contrast to Klinefelter's syndrome, these individuals have average heights to shorter than normal heights, no mental deficiency, and hypospadias. Although karyotypes are 46 XX, molecular biologic mapping has suggested that portions of the Y chromosome including the testis determining gene SRY are present in some but not all of these individuals. Because none of the AZF region is present, it is unlikely that sperm could be recovered from testicular tissue.

4. Noonan's Syndrome

The appearance of these patients is similar to that of Turner's syndrome (XO). They have short stature, hypertelorism, webbed neck, low-set ears, cubitus valgus, ptosis, and cardiovascular abnormalities. Chromosomal analysis reveals a 46 XY karyotype. A gene on chromosome 12 has been linked to this defect. Cryptorchidism and testicular atrophy results in elevations of gonadotropins. Androgens may be given to complete virilization, but these patients remain infertile.

5. Androgen Insensitivity Syndrome

Androgens act by binding to androgen receptors that travel to the cell nucleus and interact with the nuclear matrix, stimulating messenger RNA synthesis. Abnormalities in this process result in androgen-resistant syndromes. Karyotypically, these patients are 46 XY males, with phenotypes ranging from pseudohermaphroditism to a normal male phenotype with infertility. Since there was a defect in testosterone action, these patients were found to have elevated serum levels of LH and testosterone.

6. Bilateral Anorchia (Vanishing Testis Syndrome)

Vanishing testis syndrome is bilateral anorchia found in genetic XY males with nonpalpable testes. Patients have prepubertal male phenotypes, suggesting that testicular tissue capable of secreting androgens must have been present at one time in utero. It is theoretical that the testes may have been lost in utero secondary to vascular injury or testicular torsion. Low plasma testosterone and elevated gonadotropin levels are present in these males. Virilization may be induced with testosterone administration but the infertility is not treatable.

7. Cryptorchidism

Cryptorchidism is present in about 3% of full term boys. By 1 year of age, approximately 1% of boys demonstrate undescended testes and approximately 0.8% of adult males have undescended testes. After 1 year of age, the undescended testis is unlikely to descend. Two thirds of cases are unilateral, whereas one third of cases are bilateral. Sperm concentrations below 12 to 20 million per milliliter are found in 50% of patients with bilateral cryptorchidism and in 25% of patients with unilateral cryptorchidism. Testicular biopsy of the cryptorchid testis reveals decreased numbers of Leydig cells. Within the first 6 months of life, the number of germ cells in the cryptorchid testis is within the normal range. By 2 years of age, 38% of unilateral and bilaterally cryptorchid testes will have lost their germ cells. The descended testis, in cases of unilateral cryptorchidism, also may demonstrate abnormalities with low numbers of germ cells. The higher the cryptorchid testis, the more severe the testicular dysfunction. Absence of germ cells is found in 20% to 40% of inguinal or prescrotal testes in contrast to 90% of intra-abdominal testes. Both mechanical and hormonal etiologic factors have been suggested to explain the mechanism of cryptorchidism. Increasing evidence points to a defect in the hypothalamic-pituitary-gonadal axis in these patients. Histologic changes in cryptorchid testis within the first year of life has supported the therapy directed toward correction of cryptorchidism by 12 months of age. Retrospective studies report reasonably high fertility rates in patients with surgically corrected unilateral cryptorchidism.

8. Sertoli Cell-Only Syndrome

Although the etiology of Sertoli Cell-Only Syndrome is unknown, patients usually present with bilaterally small testes and azoospermia. Phenotypically, these patients have normal secondary characteristics. Seminiferous tubules are lined by Sertoli cells with a complete absence of germ cells. The testes of patients with Sertoli Cell Only Syndrome are reasonably normal in consistency. Plasma FSH levels are often but not invariably elevated. Plasma testosterone and LH levels are normal.

9. Myotonic Dystrophy

Patients who have myotonic dystrophy have myotonia, a condition of delayed muscle relaxation after contraction. In addition, patients demonstrate premature frontal baldness, posterior subcapsular cataracts, and cardiac conduction defects. Testicular atrophy may develop in up to 80% of patients. Testicular damage usually occurs in adulthood; Leydig cells typically are uninvolved, with biopsy specimens demonstrating severe tubular sclerosis. Serum FSH is elevated with severe tubular atrophy. disease is transmitted as an autosomal dominant trait with variable penetrance. There is no therapy for the testicular dysfunction in these patients.

10. Gonadotoxic Agents

Many physical and chemical agents may injure the germinal epithelium. Since the seminiferous epithelium consists of rapidly dividing cells, it is susceptible to agents that interfere with cell division. In addition, since spermatogenesis is an androgen dependent process, drugs that interfere with androgen production or action may adversely affect fertility.

11. Chemotherapy

Spermatogenesis is adversely affected by most chemotherapeutic agents. The most susceptible cells are those most actively dividing and consist of spermatogonia and spermatocytes up to the preleptotene stage. Nondividing spermatids and mature spermatozoa are less susceptible. Repopulation of the seminiferous tubules occurs as long as some spermatogonial stem cells remain. These cells slowly divide, eventually resulting in a resumption of spermatogenesis. The specific combination of drugs used for therapy, the dose administered, and the age of the patient at the time of treatment are determinants of the specific effect on the gonads. Studies of large groups of patients who survived cancers in childhood have demonstrated that fertility rates of patients treated with alkylating agents were 60% lower than in nontreated controls. As single drugs, alkylating agents and procarbazine seem to result in the greatest amount of testicular damage. The use of multidrug chemotherapeutic regimens has made it difficult to determine which specific agents are responsible for specific defects. A resumption of spermatogenesis occurs in 50-60% of testis cancer patients treated with combination chemotherapy such as cisplatin, vinblastine and bleomycin. During chemotherapy, most patients demonstrate elevations of serum FSH levels that correlate with azoospermia and then levels decline if and when spermatogenesis resumes.

12. Radiation

Germinal epithelium has a high rate of cell division, making it very radiosensitive. Spermatids are more resistant than spermatogonia or spermatocytes. Leydig cells are reasonably radioresistant; and testosterone levels usually remain normal after radiation exposure. Serum FSH levels may increase and revert to normal after a return of spermatogenesis. Azoospermia results from dosages greater than 65 cGy. At dosages lower than 100 cGy, recovery takes approximately 12 months. Following dosages of 200 to 300 cGy, recovery may take 30 months; at dosages of 400 to 600 cGy, more than 5 years may be required for spermatogenesis to return. Semen quality will usually return to baseline within 2 years of radiation therapy for seminoma, however approximately 25% may become permanently infertile. After radiation therapy, most patients are advised to avoid conception for 2 years, although pregnancies after treatment have revealed no evidence of an increase in the prevalence of congenital anomalies.

13. Alcohol

Both the testes and the liver are directly affected by ethanol. Testicular atrophy is commonly found in chronic alcoholics. Free testosterone levels are often decreased, whereas total testosterone levels may be within the normal range secondary to elevated levels of testosterone-estradiol-binding globulin. Testicular specimens demonstrate peritubular fibrosis and a reduction in the number of germ cells. Patients may demonstrate impotence, gynecomastia, and feminization. Gonadotropin levels may be increased. Acute consumption of alcohol in nonalcoholics also demonstrates a fall in testosterone levels.

14. Systemic Illness

Uremia is associated with decreased libido, impotence, gynecomastia, and defects in spermatogenesis secondary to decreased plasma testosterone levels and elevated gonadotropins. These abnormalities persist even in patients undergoing chronic hemodialysis. The elevated gonadotropin levels and subnormal responses of the testes to hCG administration suggest an impairment of testosterone production. An improvement in spermatogenesis and testicular function occurs following renal transplantation. Testicular failure is also common in patients with cirrhosis of the liver also resulting in impotence, gynecomastia, and testicular atrophy. Patients with sickle cell disease may demonstrate delayed secondary characteristics, small testicles, and oligospermia.

15. Orchitis

Postpubertal mumps results in orchitis in approximately 30% of patients with bilateral involvement in 10% to 30% of cases. Permanent testicular atrophy may develop within several months to several years following infection. An intense interstitial edema and mononuclear infiltration is noted pathologically. This may result in hypergonadotropic hypogonadism and gynecomastia. This entity has become uncommon since the advent of the mumps vaccine. Syphilis may affect both the testis and epididymis, resulting in diffuse interstitial inflammation with endarteritis and gumma formation.

D. Exogenous Hormones

1. Androgen Excess

Production of LH and FSH is inhibited by negative feedback from estrogens and androgens at both the hypothalamus and pituitary levels. Androgen excess may induce a hypogonadal state whether from exogenous sources or endogenous production, such as a metabolic abnormality or an androgen-producing tumor. Congenital adrenal hyperplasia is the most common cause of endogenous androgen excess. A congenital deficiency of 21-hydroxylase is the most common cause of the five enzyme defects responsible for this syndrome. A deficiency of 21-hydroxylase results in a decrease in cortisone synthesis, which leads to increased pituitary production of adrenocorticotropic hormone (ACTH). Elevated levels of ACTH result in hyperstimulation of the adrenal gland and in increased production of adrenal androgens. Excess androgens feed back to the pituitary, inhibiting the production and secretion of gonadotropins and leading to hypogonadism. Short stature and precocious puberty develop in these patients. As a result of androgen stimulation, premature enlargement of the penis may occur - however, because of a lack of gonadotropin stimulation, the testes remain underdeveloped. Basal plasma 17-hydroxyprogesterone levels are often elevated 50 to 200 times above normal levels. In addition, elevated urinary 17-ketosteroid and pregnanetriol levels may occur. Glucocorticoid therapy results in a reduction of ACTH levels, which induces a decrease in peripheral testosterone, thus stimulating endogenous gonadotropin secretion.

Hypogonadotropic hypogonadism has also been identified after the use of anabolic steroids by athletes. This condition is usually reversible after medications are discontinued, but permanent suppression of gonadotropin may occur.

2. Estrogen Excess

Pituitary gonadotropin secretion is suppressed by peripheral estrogens. A state of secondary testicular failure may be induced by estrogen-secreting tumors in the adrenal cortex or in the testis. Testicular Sertoli cell tumors or interstitial cell tumors may produce estrogen. Excess peripheral estrogens may also result from hepatic dysfunction. Peripheral adipose tissue converts androgen into estrogen. Elevated estrogen levels have been identified in morbidly obese patients. Impotence, gynecomastia, and testicular atrophy may result from estrogen excess. Hormonal studies demonstrate low levels of FSH, LH, and testosterone in the presence of elevated estrogens. Treatment is directed at the underlying condition.

3. Prolactin Excess

Impotence and infertility have been associated with hyperprolactinemia. In patients with pituitary adenomas, prolactin levels are elevated and gonadotropins and testosterone levels are depressed. The majority of patients with hyperprolactinemia, however, demonstrate mild elevations and investigations reveal no evidence of pituitary tumors. These patients are classified as having idiopathic hyperprolactinemia which may be caused by microadenomas that are too small to be detected by current imaging techniques. Hypoglycemia, hyperaminoacidemia, and dopaminergic antagonists and agonists, as well as other neurotransmitters, stimulate prolactin release. Pathologic stimuli include chronic renal failure, cirrhosis, intercostal nerve stimulation, and pituitary and hypothalamic tumors. Gynecomastia and galactorrhea are uncommon findings in men. Although most women present with microadenomas, most men presenting with prolactinomas have macroadenomas (≥1.0 cm). Patients who have persistent elevation of prolactin should undergo a CT scan or a MRI study of the head. Bromocriptine, cabergoline, surgery, and radiation therapy have been used for the treatment of macroadenomas. Bromocriptine therapy alone is usually successful for the treatment of microadenomas.

III. ASSESSMENT OF HYPOGONADAL PATIENTS

Hypergonadotropic hypogonadism and hypogonadotropic hypogonadism

Patients who have low serum testosterone levels usually fall into one of two pathophysiologic classes: those with primary testicular disease (hypergonadotropic hypogonadism) or those with secondary hypothalamic-pituitary disorder (hypogonadotropic hypogonadism). These two classes can be differentiated by the measurement of serum levels of LH and FSH.

Patients who have primary Leydig cell damage exhibit diminished feedback inhibition of gonadotropin secretion resulting in high serum LH and FSH concentrations. In

hypergonadotropic hypogonadism, these patients have a diminished Leydig cell reserve and a blunted testosterone response to administered LH or to the LH-like effects of hCG.

Patients who have low serum testosterone and low or inappropriately low-normal serum LH are classified as having hypogonadotropic hypogonadism. This may result from an abnormality of either the hypothalamus or the pituitary gland. In general, this defect can be 1) structural, such as a hypothalamic or pituitary tumor, 2) secondary to the administration of drugs that inhibit the hypothalamic axis, such as tranquilizers or estrogens; 3) the congenital inability to synthesize GnRH or LH and FSH; or 4) altered hypothalamic control mechanisms such as starvation or anorexia nervosa.

EVALUATION

A. Fertility Status

Throughout early childhood, gonadotropin and testosterone levels remain low. LH and FSH levels begin increasing from approximately 6 to 8 years of age. Testosterone levels begin increasing at 10 to 12 years of age. During the reproductive years, gonadotropin and testosterone levels remain relatively constant. Later in life, testosterone levels, particularly free testosterone levels, decrease and gonadotropin concentrations rise. Degeneration of seminiferous tubules and decreased numbers of Leydig cells are thought to be partly responsible for these changes.

Male infertility may be a manifestation of a primary hormonal abnormality. Such abnormalities are rare in patients with sperm concentrations greater than 5 million sperm per milliliter. In most cases, 2-3 semen analyses spaced over a 2-3 month period are recommended to adequately assess baseline parameters. According to the World Health Organization, a normal semen analysis is defined as: 1) volume 2.0 ml or more 2) pH 7.2 or more 3) sperm concentration 20 million/ml or more 4) total sperm number per ejaculate 40 million or more 5) motility 50% or more Grade A + B 6) morphology 15% or more normal and 7) viability 75% or more. In the presence of normal spermatogenesis, FSH secretion is regulated by negative inhibition from inhibin. With primary testicular failure, inadequate Leydig and Sertoli cell function result in elevated gonadotropin levels with normal or low testosterone levels. Hypothalamic or pituitary dysfunction resulting in inadequate levels of gonadotropins causes low peripheral levels of testosterone and an absence of spermatogenesis. As a result of the pulsatile secretion of GnRH, gonadotropins are secreted episodically, resulting in variation in the serum concentrations of these hormones, particularly LH.

B. Clinical Studies

A single test dose of GnRH does not distinguish hypothalamic from pituitary disease. However, a GnRH challenge test preceded by a period of "priming" the

pituitary gonadotrophs by repeated low-dose stimulation has been used to diagnose hypothalamic disorders. The GnRH test with prior priming can demonstrate that low or absent LH responses to a single dose of GnRH in hypothalamic disorders can be augmented to give normal LH levels, whereas priming has no effect in pituitary disorders.

The clomiphene test is based on the observation that an increase in FSH and LH occurs after clomiphene administration. Although the mechanism of action of clomiphene is not absolutely clear, most evidence indicates that it interferes at a hypothalamic level with steroid feedback inhibition of gonadotropin secretion. Since an intact pituitary is required for normal LH and FSH secretion, adult patients with either hypothalamic or pituitary defects will demonstrate an impaired response to clomiphene.

Patients with severe germinal-epithelial damage without concomitant loss of androgen function may show modest isolated elevation of serum FSH levels. Such an isolated increase in FSH in patients with azoospermia or severe oligospermia is believed to be due to a decrease in the production of inhibin from the germinal epithelium.

In rare instances, phenotypic male patients with clinical evidence of under-virilization may have normal, high-normal, or elevated serum testosterone levels. Such patients have a partial peripheral defect in testosterone responsiveness. Serum LH levels in such patients may be either elevated or normal, depending on whether hypothalamic response to testosterone is also impaired.

C. Endocrine

In addition to serum testosterone, LH, and FSH, serum prolactin levels should be measured in these patients. However, in men with pituitary tumors, serum prolactin concentration may be normal. Most men with prolactin-secreting tumors present with macroadenomas (greater than 1 cm). Prolactin levels in these patients are usually higher than 200 ng/ml. Hypogonadotropism, coupled with low androgen levels, is commonly found in these patients. A hypothalamic or pituitary lesion should be ruled out by computed tomography (CT) scan or magnetic resonance imaging (MRI). Impaired visual fields or severe headaches suggest the presence of a central nervous system tumor. However, mild prolactin elevation is more frequent in infertile patients. Evaluation of the central nervous system often fails to identify a tumor. These patients with idiopathic hyperprolactinemia have normal gonadotropin and testosterone levels. Indirect evidence has suggested that prolactin may have a direct detrimental effect on the testes.

Estrogen levels should be measured as estrogen excess may be endogenous or exogenous. Patients with estrogen excess may present with bilateral gynecomastia, impotence, and atrophic testes. Normal levels of plasma FSH, LH, and testosterone are usually found in cases of elevated levels of plasma

estrogens. Thyroid function studies do not need to be determined unless there is clinical evidence of thyroid abnormalities. Finally, buccal smears and chromosomal analyses (karyotype) may be indicated in some patients with a history or physical findings suggestive of a genetic basis.

D. Testicular Biopsy

The testicular biopsy is performed primarily for azoospermic patients with normal-sized testes to differentiate ductal obstruction from abnormal spermatogenesis. In cases of symmetric testes, unilateral biopsies should be performed. However, in patients with asymmetric testes in which the physician suspects different lesions (such as primary testicular failure on one side and ductal obstruction on the other), bilateral biopsies or biopsy of the more normal testis may be performed. In cases of bilaterally atrophic testes associated with markedly elevated FSH values, testicular specimens usually demonstrate an absence of germ cells. Biopsies in these cases are usually unnecessary but at times may be performed to give the couple a definitive diagnosis and avoid unnecessary treatments. Similarly, biopsy is not indicated in most cases of oligospermia, since the results will not alter therapy. A biopsy very occasionally is performed to rule out partial ductal obstruction in patients with severe oligospermia, normal-sized testes, and normal FSH values. Partial ductal obstruction is suggested in these cases if the biopsy specimen demonstrates normal spermatogenesis. A testicular biopsy may be performed under local or general anesthesia. The examination should evaluate the size and number of seminiferous tubules, the thickness of the tubule basement membrane, the relative number and types of germ cells within the seminiferous tubules, the degree of fibrosis in the interstitium, and the presence and condition of Leydig cells. The testicular biopsy will determine hypospermatogenesis, maturation arrest, and general aplasia (Sertoli cell only syndrome).

IV. REPRESENTATIVE CASES

The following table may be helpful as you think about the clinical cases.

Hormonal Status as a Function of Clinical Diagnosis

Clinical Status	FSH (mIU/ml)	LH (mIU/ml)	Testosterone (ng/100ml)
Normal men	Normal	Normal	Normal
Germinal aplasia	↑	Normal	Normal
Testicular failure	↑	↑	Normal or ↓
Hypogonadotropic hypogonadism	↓	↓	↓

Case I

History: 48-year-old white male presented to his family doctor with the complaint of decreased sexual interest, gradual onset of impotency, and breast enlargement. The patient denied any blurred vision, headaches, weight loss, fever, or night sweats. Past medical and surgical history were not significant. He does not smoke and has only an occasional drink. He is married with 3 children. His family history is significant for cardiovascular disease and diabetes.

On physical exam, he is a well-developed white male with a normal male habitus and secondary sexual characteristics. Cranial nerve and neurologic examinations were normal. Bilateral, nontender breast enlargement was noted bilaterally. He had a normal abdominal examination. The genitourinary examination revealed a normal circumcised phallus. Both testes were palpable and atrophic. No lymphadenopathy was evident. Laboratory values revealed a normal CBC and electrolytes, a screening total testosterone was 100 ng/ml (reference range 280-1070 ng/ml). Urinalysis was negative.

I. In addition to serum LH and FSH, what other tests would be appropriate?

1. Serum estrogen
2. Serum thyroid profile
3. Liver function studies
4. Serum prolactin
5. None of the above

II. The clinical evaluation of this patient should include:

1. EKG
2. Mammography
3. Chest x-ray
4. CT or MRI of the abdomen and pelvis
5. CT or MRI of the head

III. Which of the following drugs would you consider using for the treatment of this condition?

1. Testosterone patch
2. Dopamine agonist
3. Estrogen
4. GnRH
5. Propranolol

Case II

A 19-year-old white male presented with delayed onset of puberty. The patient has undergone a previous psychological analysis which revealed low to moderate intelligence. The patient has no significant past medical or surgical history. He takes no medication. He lives at home with his mother. He does not smoke or drink alcohol. His family history is significant for diabetes.

On physical examination, he was a eunuchoid appearing white male. He has bilateral gynecomastia and incomplete virilization. His abdominal examination is normal. His genitourinary examination reveals a infantile phallus with bilateral small firm testes, each measuring less than 2 cm. Neurologic examination was normal. Laboratory values including CBC and electrolytes were normal. Serum LH and FSH were markedly elevated with the serum FSH at least 2 times normal. Serum testosterone level was less than 50 ng/ml (normal reference range).

I. Which of the following studies will help confirm the diagnosis?

1. CT scan of the head
2. Karyotype
3. GnRH challenge test
4. Serum prolactin
5. Cystic fibrosis analysis

II. A testicular biopsy would reveal:

1. Normal histology
2. Absence of normal seminiferous tubules with peritubular fibrosis and Leydig cell hyperplasia
3. Sertoli cell only pattern
4. Maturation arrest
5. None of the above

III. This patient has which endocrine abnormality?

1. Diabetes Mellitus
2. Hypergonadotropic hypogonadism
3. Hypogonadotropic hypogonadism
4. Hyperprolactinemia
5. Acromegaly