

REVIEW

Gonadal dysfunction in systemic diseases

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Abstract

Gonadal function is significantly affected in many acute and chronic systemic diseases. As the function of the testes and the ovaries is determined by the integrity of the hypothalamic–pituitary–gonadal axis, it is obvious that a systemic disease may affect one or more levels of the axis in such a manner that the gonadal dysfunction may have various clinical and laboratory manifestations. In this brief review, the most common disturbances seen in the main systemic diseases will be discussed.

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Testicular function in systemic diseases

In acute stresses, testicular function is harmed indirectly via gonadotropin suppression and directly by the action of cytokines upon the testes. In chronic stresses, testicular dysfunction is due to primary testicular failure with reduced production of testosterone and semen and elevated gonadotropin levels (1). It is interesting that both types of testicular dysfunction appear to be reversible, since studies performed in patients after kidney or liver transplantation have shown full recovery of testicular function (2, 3). However, primary and secondary hypogonadism may alternate or may be superimposed. For example, a suppression of previously high gonadotropin levels occurs during the terminal stages of cirrhosis with the onset of hepatic coma (4).

Acute illnesses are associated with gonadotropin suppression and secondary testicular failure. There is a common underlying mechanism of reduced secretion of gonadotropin-releasing hormone (GnRH) similar to the seasonal regression of reproductive function in animals. Many toxic mechanisms are implicated, such as fever, drugs, cytokines and stress hormones which act directly upon the testes or indirectly upon the hypothalamus and pituitary. The type of hypogonadism may vary in proportion to the process of the illness. Severe starvation leads to low luteinizing hormone (LH)/follicle-stimulating hormone (FSH) levels, which may rise during refeeding, causing a transient excess of estrogen production and refeeding gynecomastia (5).

The hypogonadism that accompanies most chronic systemic diseases is primary and is characterized by reduced testosterone levels and elevated levels of gonadotropins and inhibin B. It must be noticed that in many cases the derangement is located at both levels.

The pulsatile secretion of LH has been studied in cases with elevated gonadotropin levels and it has been ascertained that the amplitude of the pulsatile wave was reduced while the frequency remained normal (6). In patients with chronic renal failure, apart from the indirect testicular effect, the elevated LH levels are due to insufficient renal excretion (7), while concurrently there is obvious reduction of the amplitude and frequency of the pulsatile waves of LH (8).

In most cases of primary or secondary hypogonadism, Leydig cells present a functional disturbance, as has been demonstrated by the human chorionic gonadotropin (hCG) test. Even if the baseline testosterone levels are within normal limits, the rise after a maximally effective dose of hCG is usually less than the normal doubling of pretreatment levels. Defective Leydig cell function may result from altered paracrine signals by damaged seminiferous tubules (9).

An important factor affecting sex hormone levels and more specifically the efficient relationship between estrogen and androgen is the level of sex hormone-binding globulin (SHBG). Of the circulating testosterone in adult men, approximately 45% is bound with high affinity to SHBG, 50% is loosely bound to albumin and less than 4% is free (not protein bound). SHBG is a carbohydrate-rich β -globulin produced by hepatocytes; it binds testosterone and other steroids with high affinity and prolongs their metabolic clearance. Because of the role of SHBG as a plasma testosterone-binding protein, there is a positive correlation between its level and the level of testosterone in human adult male plasma. It is well known that the production of SHBG by the liver is suppressed by androgens and stimulated by estrogens. An excess of estrogen increases serum SHBG levels, leading to reduced free testosterone

and dihydrotestosterone (DHT), while the metabolic clearance of estrogen is not affected. This has been called the estrogen amplification effect of SHBG and may contribute to the clinical signs of feminization in conditions such as cirrhosis, senescence and thyrotoxicosis, in which serum SHBG levels are elevated (10). Consequently, every factor altering SHBG levels may influence the hormone changes during the process of a systemic disease.

The hormonal control of SHBG in plasma is complex. Table 1 lists those factors that are known to decrease or increase plasma SHBG levels. Only insulin and thyroxine influence SHBG levels through effects on steady-state mRNA levels (11). How other factors increase or decrease circulating SHBG levels remains unknown.

The peripheral metabolism of steroids is altered in many forms of hypogonadism, including cirrhosis, chronic renal failure, thyrotoxicosis, old age, Klinefelter syndrome and testicular atrophy after mumps orchitis. In healthy men, the major quantity of estrogens comes from the biological conversion of testosterone to estradiol and of androstendione to estrone by the enzyme aromatase, which is found in fat, muscles, kidneys and liver. In clinical practice, the features of feminization, such as gynecomastia, are not directly related to the plasma estrogen levels (12). The ratio of estrogen to androgen and the wide range of responsiveness of male breast tissue to estrogen are considered more important factors, as shown by the great variability in the extent of gynecomastia in men given estrogens for metastatic prostatic cancer. Finally, in both men with idiopathic seminiferous tubular failure and patients suffering from celiac disease with an acquired androgen resistance or 5 α -reductase deficiency, defects of androgen receptors have been reported as a different pathophysiological mechanism (13).

Disorders associated with testicular failure

Liver disease Hepatic cirrhosis is associated with hypogonadism and signs of feminization irrespective of the direct toxic effect of ethanol upon the testes. Testicular atrophy, low testosterone levels, decreased libido, infertility, reduced secondary sex hair and gynecomastia are found in men with cirrhosis. Fifty percent of patients

with cirrhosis present reduced spermatogenesis and peritubular fibrosis.

The normal function of the hypothalamic–pituitary–gonadal axis is affected in liver diseases. The pulsatile secretion of LH and the response to GnRH and clomiphene are reduced. As has already been mentioned, in late stages of cirrhosis the patients present features of feminization, suggesting altered levels of sex hormones. The clinical signs of hypogonadism are more pronounced in alcoholic patients due to the direct effect of ethanol upon the testes. In cirrhotic patients, the estrogen/androgen ratio is usually increased. The levels of testosterone and dihydroepiandrosterone are reduced, while the estradiol levels are normal or slightly elevated. These alterations are dependent on the severity of the liver disease and are more pronounced in patients with higher Child–Pugh score (14, 15). Several other factors may contribute to these hormonal changes in cirrhosis, including hepatic overproduction of SHBG, changed SHBG isoforms with different steroid-binding affinities, elevated prolactin levels, direct suppression of Leydig cell function by estrogens, increased estrogen receptors in the liver and cyclic variation in the severity of the liver illness producing the hormonal changes of refeeding gynecomastia (16). It must be kept in mind that the gynecomastia and impotence of cirrhotics are augmented by the chronic use of spironolactone, a receptor antagonist of aldosterone and testosterone, which reduces the testosterone levels and slightly increases the levels of estradiol.

Portocaval shunts in normal rats result in testicular atrophy manifested histologically by loss of germinal epithelium due to decreased mitosis and increased apoptosis with loss of spermatogonia, loss of spermatozoa in the lumen of the seminiferous tubules and eventual complete atrophy of the seminiferous tubule, which are then lined only by Sertoli cells (3). The primary event after portocaval shuntings increases estrogen-suppressing LH secretion which leads to decreased testosterone levels and hypogonadism.

Alcoholism – alcoholic cirrhosis Most alcoholics, particularly those with cirrhosis, present features of hypogonadism, such as feminization, impotence, reduced fertility and testicular atrophy. There is a large body of data providing evidence that ethanol reduces the testicular synthesis and serum levels of testosterone, in widely different experimental designs. Both acute and chronic administration of ethanol reduces serum levels of testosterone in rats *in vivo*. Likewise, *in vitro* studies in isolated Leydig cells, isolated perfused rat testes and testicular homogenates have all demonstrated reduced testosterone synthesis and concentrations. Furthermore, acute alcohol intoxication in normal men results in a fall in serum levels of testosterone. In a large series of clinical studies, reduced serum testosterone levels have been found in chronic

Table 1 Factors that influence circulating SHBG levels.

Increase	Decrease
Aging	Prepubertal development
Growth hormone deficiency	Obesity
Estrogens	Hyperinsulinemia
Androgen deficiency	Glucocorticoids
Hyperthyroidism	Androgens
Hepatitis	Progestins
Porphyria	Hypothyroidism
	Growth hormone excess
	Familial

alcoholics. Most of these patients also have decompensated cirrhosis. On the other hand, normal serum levels of testosterone have been found in non-cirrhotic alcoholics and in cirrhotic patients without hepatic decompensation (17).

Several factors affect the testicular biosynthesis caused by alcohol. Ethanol and its metabolite acetaldehyde have a direct toxic effect on Leydig cells but, on the other hand, there is a disruption on the hypothalamic–pituitary–gonadal axis. Chronic alcohol exposure decreases circulating LH levels and the response of LH to GnRH is reduced in alcoholics (18). Thus disturbance of the hypothalamic–pituitary–gonadal axis persists over months of abstinence, with sustained increases in serum free and total testosterone levels in the presence of inadequate raised LH concentrations (19).

Hyperprolactinemia is often found in male alcoholics, particularly those with cirrhosis and may participate in the pathogenesis of hypogonadism by inhibiting gonadotropin secretion.

Alcohol abuse can cause hypogonadism even in the absence of liver disease. It is interesting to note that cirrhosis, acting in concert with alcohol, produces feminization, such as gynecomastia, alteration in body fat distribution and a female escutcheon. The main mechanism is that both alcohol and acetaldehyde stimulate the adrenal cortex to increase the secretion of weak adrenal androgens that serve as estrogen precursors. Alcoholic men with chronic liver disease have elevated circulating estradiol and estrone levels from aromatization of androstendione. Ethanol increases the activity of aromatase, which converts androgens to estrogens.

Successful orthotopic liver transplantation leads to improvement of the sex hormone disturbances. Six months after transplantation, testosterone and gonadotropin levels return to normal values. However, in cases of hypergonadotropic hypogonadism, with elevated FSH and LH levels due to alcohol-induced gonadal injury, the testicular failure is not reversible. Finally, transplanted patients will permanently receive prednisolone and cyclosporine which both tend to reduce testosterone levels in men (17).

An additional mechanism to explain the hypogonadism has been proposed by a series of recent studies examining the role of insulin-like growth factor-I (IGF-I). It is known that IGF-I levels are normal in early stages of cirrhosis but its bioavailability seems to be diminished (20). It is also known that IGF-I stimulates testosterone synthesis and spermatogenesis (21). Its deficiency could contribute to the development of hypogonadism associated with cirrhosis as supported by some experimental data in rats (22). In an experimental model of carbon tetrachloride-induced histologically proven cirrhosis in rats, recombinant IGF-I was administered for 2 weeks (23). This study showed an altered hemato-testicular barrier from an early stage of cirrhosis as was suggested by the reduced

transferrin expression by the Sertoli cells. IGF-I administration increased the expression of this protein in Sertoli cells of cirrhotic rats, showing a dysfunction of these cells and consequently the disruption in blood–testis barrier integrity. The lesion could affect cellular proliferation of spermatogenesis (24). The above findings support the conclusion that the exogenous administration of IGF-I may be useful for the treatment of testicular alterations in cirrhotic patients.

Hemochromatosis Hemochromatosis in its primary form is a genetic disease. The hemochromatosis gene (HLA-H) has been identified on the short arm of chromosome 6 as a single point mutation in which the amino acid cysteine at position 282 changes to a tyrosine. The gene product modulates the uptake of transferrin by cells, and causes excessive iron accumulation and toxicity in the pituitary and the testes (25). Half the patients have hypogonadism with testicular atrophy. The main lesion is hypogonadotropic hypogonadism due to the unresponsiveness of LH to the administration of GnRH. The secondary hypogonadism results from iron deposits in the gonads and gonadotropin secretion is selectively impaired. Patients may present with impotence or infertility, with low testosterone, azoospermia or low semen volume and sperm motility with normal sperm concentration (26).

Patients with chronic anemia, especially sickle cell disease and thalassemia major, and repeated transfusions develop similar disturbances of the hypothalamic–pituitary–testis axis and destruction of testicular tissue due to interruption of the blood supply by the sickling process (27). Patients with sickle cell anemia and thalassemia display characteristics of prepubertal hypogonadism mainly manifested as delayed puberty. The accurate and effective iron chelation can reduce the prevalence of hypogonadotropic hypogonadism, preventing the iron accumulation in the pituitary (28).

Chronic renal disease Chronic renal failure causes major effects on the male reproductive system, notably impairment of spermatogenesis, steroidogenesis and sexual function, through effects at all levels of the hypothalamic–pituitary–testicular axis. Disturbances of the axis can be detected with only moderate reductions in the glomerular filtration rate and progressively worsen as the renal failure progresses. Approximately 50% of uremic men complain of erectile dysfunction while an even greater percentage complain of decreased libido and a marked decline in the frequency of intercourse (29, 30). In addition to the uremic milieu, peripheral neuropathy, autonomic insufficiency, peripheral vascular disease, psychological and physical stresses, and multiple drugs all contribute to the genesis of sexual dysfunction. The disorders of the pituitary–gonadal axis rarely normalize with initiation of hemodialysis or peritoneal dialysis and, in fact, often progress. Transplantation leading to restoration of

normal renal function can reverse most of the hormonal changes of chronic renal failure, although some changes resulting from prolonged dialysis may be irreversible (31).

Chronic renal failure is associated with impaired spermatogenesis and testicular damage, often leading to infertility. A decreased volume of ejaculate combined with low or complete azoospermia and a low percentage of motility has been shown in semen analysis (32). Compared with other causes of severe primary testicular lesions, the Leydig and Sertoli cells show little evidence of hypertrophy or hyperplasia, probably due to a defect in their hormonal regulation. This later effect might occur with either gonadotropin deficiency or resistance, rather than being a cytotoxic effect of uremia where spermatogonia would be most affected (33).

Plasma LH, FSH and inhibin- α levels are slightly elevated along with reduced circulating total and free testosterone levels and normal SHBG levels (34). Although these changes are consistent with a primary defect in testicular function, there is also strong evidence for defective neuroendocrine regulation as an important functional aspect of the reproductive dysfunction in uremia. The increase in gonadotropins is largely explained by the significant reduction (~70%) in renal filtration and whole body clearance rate of LH which, in the presence of decreased testosterone secretion, indicates significantly reduced LH secretion. The hCG test with a single injection is abnormal, but the long-term administration of hCG may restore the testosterone levels, proving that testes retain their reserve secretion (35). There is evidence of a factor in uremic serum capable of blocking the LH receptor, thus providing an explanation for the sluggish response of the Leydig cell to infusion of hCG (36). Plasma levels of estradiol are normal or low, which are consistent with a hypogonadotropic state, because the increased LH levels should enhance the testicular estradiol secretion (37).

Delayed pubertal maturation can occur in children with chronic renal failure. Plasma LH and testosterone levels are normal for their age but the FSH levels are elevated, suggesting damage of the germinal epithelium while the Leydig cell function appears normal (38).

In healthy men, LH is secreted in a pulsatile manner. In chronic renal failure, the number of secretory bursts remains normal, but the amount of LH released per secretory burst is reduced (39). It is unclear whether this derangement is the result of a change in the pattern of GnRH release from the hypothalamus or a change in the responsiveness of the pituitary. Administration of GnRH increases LH levels to the same degree as in healthy subjects; however, the peak value and return to baseline may be delayed (40). The decreased metabolism of LH and GnRH may explain the observed variations, since the kidneys contribute significantly to the clearance of these hormones.

FSH release by the pituitary normally responds to feedback inhibition by inhibin, a peptide product of the Sertoli cells. The plasma FSH levels tend to be highest in those uremic patients with the most severe damage to seminiferous tubules and presumably the lowest levels of inhibin. It has been reported that high FSH levels may portend a poor prognosis for recovery of spermatogenic function after renal transplantation (32). The administration of clomiphene to uremic patients leads to an appropriate rise in the levels of both LH and FSH, suggesting that the negative feedback control on the hypothalamus is intact and that the storage and release of gonadotropins by the pituitary is normal (34).

Hyperprolactinemia is frequent in uremic patients, due to a functional disturbance in hypothalamic regulation of pituitary prolactin secretion, which appears to be autonomous and resistant to stimulatory or suppressive manoeuvres (41). Insulin-induced hypoglycemia and arginine or thyrotropin-releasing hormone infusions elicit no response or only a blunted response in prolactin secretion. On the other hand, dopamine infusion or the administration of L-dopa fails to decrease basal prolactin levels. In chronic renal failure, increased prolactin secretion may be related in part to the development of secondary hyperparathyroidism (42, 43). Bromocriptine can reduce plasma prolactin levels in patients with chronic renal failure, but there has been an inconsistent effect on sexual potency and libido (41). It should be noted that only a small percentage of uremic patients have prolactin levels >100 ng/ml. In these cases, imaging studies of the hypothalamic-pituitary region should be performed to exclude the presence of a microadenoma or a macroadenoma. Depletion of total body zinc stores may also play an etiologic role in uremic hyperprolactinemia (44).

In addition to the disturbances in the hypothalamic-pituitary-gonadal axis, abnormalities in the sympathetic nervous system, derangements in the arterial supply or venous drainage of the penis and psychologic effects may contribute to the sexual dysfunction in uremic men. Primary depression may affect sexual function and lead to reduced libido and decreased frequency of intercourse (45). Careful consideration of the patient's medications may reveal a drug that could be responsible for impairing sexual function. Centrally acting drugs and β -blockers used as anti-hypertensives are the most commonly implicated agents in causing impotence. The angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are associated with a lower incidence of impotence and represent a useful alternative in uremic patients with hypertension. Other drugs commonly implicated include cimetidine, phenothiazines, tricyclic antidepressants and metoclopramide.

The management of sexual dysfunction in uremia involves a multifactorial approach. One needs to

ensure optimal delivery of dialysis and adequate nutritional intake. Optimal management of the anemia with administration of recombinant human erythropoietin has been shown to improve sexual function in chronic renal failure (46, 47). Control of secondary hyperparathyroidism with 1,25(OH)₂ vitamin D may be of benefit in lowering prolactin levels and improving sexual function in some patients. In uremic men complaining of erectile dysfunction, the first-line therapy is oral sildenafil (48–50). It should be emphasized that sildenafil is absolutely contra-indicated in patients using organic nitrates for coronary artery disease, where lethal hypotension can occur. Caution is also required in men using complex anti-hypertensive regimes. If sildenafil is not effective or is contra-indicated, additional options include cavernosal vasodilator pharmacotherapy (prostaglandin E (PGE) and phentolamine, papaverine), intracavernous injection of alprostadil (synthetic PGE₁) or mechanical devices such as vacuum/constriction devices or implantable prosthesis. Surgical placement of a penile prosthesis is considered in patients who fail the less invasive first-line treatments.

Administration of androgens in patients with chronic renal failure has a proven indication only for the treatment of renal anemia, where it was widely applied for more than three decades before being largely supplanted by recombinant human erythropoietin (51, 52). Uremic patients with hyperprolactinemia may benefit from the administration of bromocriptine. However, its usefulness has been limited by a relatively high frequency of side-effects, particularly hypotension (41). Finally, the administration of zinc in a zinc-deficient uremic man may contribute to improvement of gonadal function (53).

Testosterone and the metabolic cardiovascular syndrome

Circulating testosterone levels are reduced in massively obese men (54) and several studies have confirmed that total testosterone levels decrease as body mass increases. The major reason for the low levels are the reduced levels of SHBG but free and non-SHBG-bound testosterone levels are also reduced in massive obesity (55). As Leydig cell function is normal in obese subjects, the main mechanism responsible are the lower mean LH levels and pulse amplitude (56). The leading hypothesis is that reduced LH pulse amplitude in obesity results from increased estrogen production, because estradiol suppresses the pituitary LH response to GnRH stimulation in males (57). Testosterone is converted to estradiol by aromatase P450, the product of the CYP19 gene (58). Aromatase may be increased in obesity because of increased subcutaneous adipose tissue mass, or adipose-derived factors could upregulate aromatase in selected tissues (59). The plasma estradiol in normal adult men is 20–40 pg/ml and its production rate in blood is 25–40 µg/24 h; both of these values are higher than in postmenopausal women. Mean serum estrone and estradiol levels are

elevated in obese men and urinary estrone and estradiol production rates are positively correlated to the percent above ideal body weight (60).

The association between obesity, low testosterone and SHBG has received considerable attention. Many studies have shown that testosterone levels are inversely correlated with insulin and C-peptide concentrations (61). This association is partly through SHBG, because fasting insulin correlates negatively with SHBG levels (62). The regulation of SHBG expression by insulin has been studied directly using cultures of HepG2 hepatoma cells that express the SHBG gene (63). In these cells, adding insulin reduces SHBG mRNA levels and protein secretion (11). This effect may be mediated by the liver-enriched transcription factor, hepatocyte nuclear factor-4, which transactivates the SHBG promoter (64).

Total testosterone levels are lower than normal in men with type 2 diabetes and much of this difference may result from lower SHBG (65). Several prospective studies found that low SHBG levels predict the development of type 2 diabetes (66). This finding follows logically from the inverse correlation between SHBG and obesity (54) and insulin resistance (61) and the propensity for obese and insulin-resistant individuals to develop type 2 diabetes.

Various cross-sectional and prospective studies relating testosterone to cardiovascular disease end-points are inconclusive. On the other hand, the findings of several studies raise the possibility that men with relatively low total, particularly bioavailable (non-SHBG-bound), testosterone levels may be related to the progression of aortic atherosclerosis compared with men with higher testosterone levels (67).

The biological mechanisms by which testosterone might influence atherosclerosis in men are unclear. A direct effect of testosterone on the arterial wall is plausible given the presence of androgen receptors in vascular smooth muscle and endothelial cells (68). Other proposed mechanisms are the decrease of vascular adhesion molecule-1 expression in human endothelial cells (68), the upregulation of high-density lipoprotein (HDL) receptors in macrophages (69) and finally the modulation of cardiovascular disease risk factors, such as blood lipids, lipoproteins, coagulation and fibrinolytic proteins.

Several studies have found a positive association between testosterone or SHBG and HDL-cholesterol (HDL-C) levels (70). There is a linear relationship throughout the physiologic range of testosterone concentrations, such that HDL-C increases by 1.0 mg/dl with every 100 ng/dl increase in total testosterone (71). The mechanisms are not clear but one possibility is that testosterone increases the synthesis of apolipoprotein A-1, the major component of nascent HDL particles. There is also evidence that testosterone upregulates the expression of HDL receptors (69). Low HDL-C is found in patients with other metabolic

risk factors which are referred to as the metabolic syndrome. All components of the metabolic syndrome have been related to low testosterone and SHBG in epidemiologic studies, although it is not clear if these relationships are truly causal or indirect.

Testosterone may influence the risk of cardiovascular diseases by affecting hemostatic function and thrombosis. The few population studies that have examined the relationship between testosterone and plasma fibrinogen, factor VII and plasminogen activator inhibitor type I (PAI-I) levels were inconsistent. Low levels of testosterone are associated with higher concentrations of factor VII, fibrinogen and PAI-I, independent of age, central obesity, fasting insulin, glucose and other cardiovascular risk factors (72). Each of these factors predisposes to atherosclerosis and coronary vascular disease.

In conclusion, total testosterone and SHBG levels are reduced in men who are obese and hyperinsulinemic and men with type 2 diabetes. These men have lower levels of HDL-C and triglycerides and higher levels of the thrombotic factors tissue PAI, fibrinogen and factor VII, known to predispose to atherosclerosis and coronary vascular disease. Low testosterone increases the risk for developing type 2 diabetes, whereas the contribution of low testosterone to the metabolic cardiovascular syndrome is less certain.

Starvation Starvation has a profound suppressive effect on gonadotropin secretion and testicular function, independent of its etiology. The main mechanism of gonadotropin suppression is the inhibition of GnRH secretion, as is apparent from the suppression of LH secretion (73). Much evidence indicates that leptin, as a signal for starvation, mediates the under-nutrition-induced alterations of the reproductive axis. It has been found, in mice, that preventing the starvation-induced fall in leptin with leptin administration substantially blunts the changes seen in the gonadal axis in males (74). In studies in primates, it has been shown that intravenous leptin infusion maintains LH pulsatility in fasted male rhesus macaques (75), thereby demonstrating the ability of leptin to counteract the inhibitory effect of fasting on gonadotropin secretion. Serum testosterone levels are low with a poor response to hCG. As body weight is regained, the pulsatile gonadotropin secretion is restored in a manner reminiscent of the changes with puberty.

During the improvement in nutritional status, gynecomastia and, rarely, spider nevi may develop. Breast development, called refeeding gynecomastia, was seen in the starved prisoners of World War II. Anorexia nervosa rarely occurs in men but appears to present the same hormone changes as expected from studies in women, namely low serum LH and FSH levels and a poor response to GnRH administration. These disturbances are normalized with attainment of normal weight (76).

Rheumatic diseases Rheumatic diseases disturb sexual function and reproduction in a multifactorial way;

autoimmunity, impaired function of joints and psychological responses to chronic disease, such as depression and reduced self esteem.

Active rheumatic disease can cause hypogonadism in men and has been reported in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (77, 78). Decreased libido, erectile dysfunction and failure to ejaculate have been reported in 19–35% of men with SLE.

Hypoadrogenicity has been found in men with RA especially in the presence of high-degree activity (79). Basal serum concentrations of total testosterone, SHBG and LH were measured in 104 men with RA and were compared with those of 99 age-matched healthy men (80). Men with RA had lower levels of bioavailable testosterone and a large proportion was considered hypogonadal. A similar study did not find any significant differences in patients with ankylosing spondylitis (81).

Some anti-rheumatic drugs carry a risk for male reproduction. Adverse effects include gonadotoxicity and chromosomal defects. Cytotoxic drugs like methotrexate and cyclophosphamide infer a risk of genotoxicity either by inducing chromosomal aberrations or through single gene mutations.

Oligo- or azoospermia can be induced by sulfasalazine and cyclophosphamide. It occurs rarely during therapy with methotrexate and is reversible after discontinuation of the drug. Azathioprine, cyclosporine and colchicine do not impair male fertility. Salazopyrin-induced sperm alterations are reversible after an average of 2.5 months after discontinuing the drug (82). Treatment with cyclophosphamide carries the risk of irreversible infertility (83). The risk of permanent infertility after treatment with cyclophosphamide can be avoided by the cryopreservation of sperm before start of therapy. Even when sperm counts and quality are reduced, sperm banking is meaningful given the advanced techniques of assisted reproduction which are available.

Miscellaneous illnesses Leydig cell function and spermatogenesis are frequently disturbed in miscellaneous systemic diseases, such as Hodgkin's disease, cancer before and after chemotherapy, cystic fibrosis, chronic respiratory diseases and amyloidosis. These illnesses usually induce low testosterone levels and normal or slightly elevated LH levels, due to the combined attack of testes and the hypothalamic–pituitary axis. After surgery, myocardial infarction or severe burn-elevated SHBG levels are seen, whereas free testosterone, which is the biologically active fragment, is lower than total testosterone (84).

There is a high prevalence of low testosterone levels in patients with HIV infection, resulting from defects at all levels of the hypothalamic–pituitary–gonadal axis. Both hypogonadotropic and hypergonadotropic hypogonadism has been described, the former being more

prevalent. Low testosterone levels are associated with adverse disease outcomes, including weight loss, disease progression and decreased free mass and exercise capacity (85). Testosterone replacement in hypogonadal men with HIV-associated weight loss, physiologic testosterone administration alone or in combination with resistance training has been shown to increase lean body mass, muscle strength and quality of life (86). The role of higher dose testosterone therapy in eugonadal men with HIV-associated weight loss is less clear, given the potential adverse effects on HDL-C and lack of safety data (87).

In thyrotoxicosis, the hypothalamic–pituitary–testis axis alterations are secondary, due to elevated estrogen levels, and consist of reduced semen, elevation of plasma testosterone and normal free testosterone levels (84). The issue of fertility in celiac men is poorly understood, and there are few studies available. Basal serum FSH and LH concentrations are higher in untreated celiac men than in male controls with Crohn's disease (88). Plasma testosterone and free testosterone indices are high, whereas DHT levels are reduced, indicating androgen resistance (89). It was recently reported that the children of celiac men had a lower birth weight than age- and sex-matched non-celiac children (90). It has been suggested that genetic loci outside the human leucocyte antigen complex are implicated (90, 91).

Ovarian function in systemic diseases

Chronic anovulation is a common problem in women with systemic diseases and is displayed with secondary amenorrhea, oligomenorrhea or irregular episodes of metrorrhagia. Chronic diseases affect regular menses through various mechanisms determined by the main illness. In most cases, treatment of the underlying disease restores the normal function of the hypothalamic–pituitary–ovarian axis.

GnRH is produced in the arcuate nucleus of hypothalamus and secreted via the hypothalamic portal vessels to the median eminence in a pulsatile fashion which is a necessary presumption for the secretion of FSH and LH by the anterior pituitary. After depolarization of the GnRH-containing neurons, GnRH is secreted with a frequency which fluctuates between 60 and 200 min in the various phases of the menstrual cycle (92). The frequency of the pulsatile secretion is defined by the feedback of the ovarian steroids and by local regulatory substances of the hypothalamus, such as norepinephrine, dopamine and β -endorphin. This fine function may be influenced by locally developed tumors or genetic diseases as well as by functional disorders. The latter are the most frequent and include strenuous exercise, abrupt weight loss, vigorous emotional conditions and various systemic diseases. The above constitute the clinical setting of functional hypothalamic anovulation, characterized by reduced

plasma gonadotropin and estrogen levels with a common mechanism of the alteration of pulsatile LH secretion. A lack of increase of plasma gonadotropin has been considered to be the main finding despite the shortage of inhibitory factors of ovarian origin in plasma, such as estradiol and inhibin. The disturbance of pulsatile secretion is referred either to the frequency or the amplitude of the pulse wave of LH. In severe cases, the frequency and the wave amplitude are both significantly reduced (93). This normal function of the hypothalamic–pituitary axis is disturbed in conditions of prolonged exposure to chronic stress, such as strenuous exercise or severe emotional states. In all these conditions, the stress hormones, such as corticotropin-releasing hormone, adrenocorticotropin, cortisol, prolactin, oxytocin, vasopressin, epinephrine and norepinephrine, are elevated. These hormones inhibit gonadotropin secretion by various mechanisms provoking hypothalamic anovulation.

Heavy and prolonged training for championships in women is associated with three distinct disorders of reproductive function, namely delayed menarche, luteal dysfunction and amenorrhea. In addition to amenorrhea, these female athletes present disordered eating and osteoporosis (94).

Amenorrhea may occur in women with a definite history of psychological and socio-economic trauma. In depressed women, the incidence of amenorrhea is quite high and hormonal tests reveal low to normal gonadotropin levels with normal responses to GnRH, prolonged suppression of gonadotropins in response to estradiol and failure of a positive feedback response to estradiol (95). In patients with depression, the disturbance of the hypothalamic–pituitary–ovarian axis is similar to the hypothalamic amenorrhea caused by exercise or disordered eating (96).

In anorexia nervosa, severe undernutrition is associated with extremely low plasma and cerebrospinal fluid leptin levels, low and apulsatile gonadotropins, altered menstrual function and amenorrhea (97). Leptin levels below 1.85 ng/ml have been found to be associated with amenorrhea in underweight females with eating disorders (98). In addition, the resumption of menses is associated with leptin levels above this threshold. However, in underweight patients, the rapid increment in serum leptin with weight gain is not concomitant with menstruation, which suggests that the normalization of menstrual periods might depend on additional factors, such as the GH–IGF-I axis (99). Various experimental data strongly suggest that leptin acts centrally to influence reproduction and that a stimulatory effect is exerted over a relatively narrow range of leptin concentrations. Leptin stimulates the release of GnRH from the hypothalamus. Double labeling studies failed to demonstrate the expression of the leptin receptor Ob-R in GnRH-secreting neurons. However, strong immunoreactivity for Ob-R has been shown in pro-opiomelanocortin and

neuropeptide Y, and cocaine- and amphetamine-related transport neurons in the arcuate nucleus. Together with functional studies, these findings suggest that these peptides might be involved in the stimulatory effects of leptin on GnRH (100). The administration of recombinant human leptin to underweight women or those taking strenuous exercise results in an increase in mean and pulsatile LH levels, enlargement of the ovaries and dominant follicles and estradiol levels. Three out of eight patients had ovulatory menstrual cycles (101).

Systemic diseases and ovarian dysfunction

The metabolic syndrome Central obesity combined with elevated blood pressure, impaired fasting glucose, high triglycerides and low HDL-C concentrations are the main criteria for diagnosing the metabolic syndrome. The syndrome is called the insulin-resistant syndrome and increases the likelihood that one or more abnormalities will be present (102). Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality in premenopausal women and compelling evidence indicates that the prevalence of insulin resistance/hyperinsulinemia is significantly increased in patients with this syndrome. In this instance, the clinical features of PCOS result from an increase in testosterone secretion by ovaries that are at least normally insulin sensitive, secondary to the higher circulating insulin concentrations seen in these patients. Conversely, PCOS cannot be a simple function of insulin resistance. Nevertheless, not all insulin-resistant women have PCOS and vice versa (103). Family studies suggest that there is a genetic susceptibility to hyperandrogenemia and insulin resistance in PCOS. Consistent with this hypothesis, there is evidence for linkage and association of marker locus near the insulin receptor with the hyperandrogenemia phenotype (104).

Chronic renal failure The disturbances of ovarian function occur frequently in women with end-stage renal failure, leading to amenorrhea and infertility (105). Menstruation may present various abnormalities, such as oligomenorrhea or menorrhagia, which may occasionally require hysterectomy. In some women, normal menses are restored after initiation of hemodialysis (106). Moreover, women may present decreased libido and a reduced ability to reach orgasm (45). Pregnancy might rarely occur in chronic renal insufficiency, but fetal wastage is significantly increased (107).

The hormonal profile of uremic women includes elevated prolactin levels, normal FSH and modestly elevated LH levels, along with an increased LH/FSH ratio and relatively low estradiol, estrone, progesterone and testosterone levels (33). The normal pulsatile release of gonadotropins is disturbed, but the response to GnRH is preserved and may be excessive and prolonged.

It has been suggested that increased plasma prolactin levels may impair hypothalamic–pituitary function and contribute to sexual dysfunction and galactorrhea. As in men with chronic renal failure, the hypersecretion of prolactin appears to be autonomous, as it is resistant to manoeuvres designed to inhibit or stimulate its release. In selected cases, the administration of bromocriptine may help.

The first steps for the management of sexual dysfunction in uremic women are to optimize delivery of dialysis, raise haemoglobin to 11–13 g/dl with recombinant human erythropoietin, and control the degree of secondary hyperparathyroidism with 1,25(OH)₂ vitamin D. A review of the patient's medications may reveal that a drug could be responsible for the impaired sexual function, as has been already described for uremic men.

Low estradiol levels in amenorrhic hemodialysis women can secondarily lead to vaginal atrophy and dryness resulting in discomfort during intercourse. These women may benefit from local estrogen therapy or vaginal lubricants. Administration of testosterone in low doses may be effective in increasing sexual desire, but is rarely used secondary to potential toxicity. Successful renal transplantation is the most effective means to normalize sexual desire in women with chronic renal insufficiency (30).

Careful gynaecologic follow-up is recommended because the risk of endometrial hyperplasia and/or carcinoma, associated with unopposed estrogen effects on the uterus, has not been assessed properly. In some patients, it may be desirable to administer a progestational agent several times per year to interrupt the proliferation induced by unopposed estrogen release.

Because of poor pregnancy outcomes, restoring ovulatory cycles is not a therapeutic goal in women on chronic dialysis. For uremic women who are menstruating normally, birth control is recommended. In women with a well-functioning renal transplant, the abnormalities in ovulation can be reversed and a successful pregnancy may be achieved.

Liver diseases – alcoholism Alcohol abuse provokes profound disturbances in the hormonal status and the reproductive performance of women. Chronic alcohol abuse is associated with hypogonadism, as manifest by the loss of secondary sexual characteristics, amenorrhea and early menopause, because the secretion of estrogens and gonadotropin is reduced. Ovary failure results in lack of ovulation and infertility (108). The precise mechanism of alcohol action upon the hypothalamic–pituitary–ovarian axis is not known and relative studies are limited. Long-term administration of alcohol to female rats reduces ovarian size, destroys the corpora lutea and induces changes in estrogen deficiency in the uterus and the salpinxes. There are no specific studies on the effect of ethanol on women's ovaries, even though it seems that the

addition of ethanol in cultures of theca cells inhibits the progesterone and estradiol response (109).

Fifty percent of women suffering from alcoholic cirrhosis present amenorrhea. Moreover, they may present oligomenorrhea, metrorrhagia or menorrhagia. In some cases with obvious signs of malnutrition, women manifest hypogonadotropic hypogonadism. In other cases, the portosystemic bypass of adrenal androgens leads to elevated estradiol and testosterone levels, due to peripheral conversion of androgens to estrogens in fat and other tissues (108). In the final stages of the disease, where there is hepatic encephalopathy, the central secretion of neurotransmitters (norepinephrine, dopamine) is influenced, resulting in modification of the pulsatile gonadotropin secretion by the hypothalamus. This factor may be responsible for the hyperprolactinemia seen in some cases.

Normal postmenopausal women who drink moderately (one drink per day or less) have higher estradiol levels than women who do not drink. It is unclear whether this phenomenon is due to alcohol or to the phytoestrogens which are contained in the alcoholic beverages.

Postmenopausal women suffering from alcoholic cirrhosis have slightly higher estradiol and lower testosterone levels than control women. The underlying mechanism is that the conversion of androgens to estrogens is enhanced by alcohol abuse. The elevated estrogen levels suppress gonadotropin secretion. However, despite the relatively increased levels of estrogens, alcoholic cirrhotic women have profound signs of defeminization with loss of secondary sexual characteristics (110). Finally, in addition to other harmful effects of alcohol on the female reproductive system, it must be noticed that alcoholic pregnant women are at risk of intra-uterine growth retardation of their newborns (111).

After successful orthotopic liver transplantation, women achieve normal menstrual function and fertility. The return of menses can occur in 2 or 3 months after transplantation. Pregnant transplant recipients are treated with the same doses of immunosuppressive drugs as the non-pregnant women, resulting in the successful outcome of the pregnancy, both for the mother and the newborn.

Rheumatic diseases Different rheumatic diseases can cause specific sexual problems related to the nature of prevailing symptoms. In primary and secondary Sjögren's syndrome, decreased cervical mucus production and atrophic vaginitis can result in dyspareunia, which occurs in 40–50% of patients (112). Vaginal dryness and dyspareunia are also frequently encountered in women with systemic sclerosis, systemic lupus erythematosus and RA.

Several studies have investigated serum concentrations of hypophyseal gonadal and adrenal hormones in women with rheumatic diseases. No significant

abnormalities in estrogen and progesterone levels have been found with RA compared with controls (113, 114). Studies on androgens have been contradictory, although a meta-analysis confirmed the finding of lowered dehydroepiandrosterone sulfate in premenopausal women with RA (113).

In a population-based study, lower numbers of births and a reduced period of reproduction were found in women with rheumatic diseases compared with healthy controls (115). Two other studies have suggested that fertility or fecundity may be decreased among women with RA (116, 117), whereas others have found that fertility or fecundity do not differ from healthy controls (112). Although fertility is normal in SLE, increased fetal loss either as miscarriage or stillbirth has been reported (118–122). Active lupus nephritis, a previous history of fetal death and the presence of anti-phospholipid antibodies (aPLs) are predictive factors for pregnancy loss in lupus pregnancies.

aPLs were shown to be connected not only with pregnancy losses, but with inhibition of implantation and possibly with failures of *in vitro* fertilization (IVF) implantation. Auto-antibodies may exert actions on the trophoblast via interference with membrane surface hemostatic reactions or by reacting with antigens or cell surfaces, resulting in altered cell activity. Effects may include direct cellular injury or microvascular thrombosis (123). The presumed thrombotic effects have led to the use of heparin and aspirin for women with aPLs and recurrent abortion or IVF implantation failure. Despite the experimental evidence that aPLs interfere with implantation and thrombotic development, the question as to whether some of these antibodies are mere epiphenomena remains.

Most anti-rheumatic drugs have no effects on the gonads. However, some drugs can cause reversible infertility, such as the non-steroidal anti-inflammatory drugs in women and salazopyrin or methotrexate in men. Irreversible infertility has been reported exclusively after treatment with alkylating agents, such as cyclophosphamide and chlorambucil (112, 124).

Celiac disease Celiac disease has been ascertained to be the cause of infertility in 4–8% of women with unexplained infertility. In some cases, fertility was restored after treatment of the underlying disease. Menarche is delayed while menopause appears earlier, resulting in a shorter duration of the reproductive period. Women suffering from celiac disease who do not follow a proper diet present more frequently spontaneous abortions and other complications of pregnancy in relation to women following a gluten-free diet (125). The above disturbances cannot be completely interpreted by the malabsorption of food. However, it seems that women who do not follow a gluten-free diet have an increased risk of a poor outcome of their pregnancy (90).

Conclusions

In conclusion, gonadal function, both in men and women, is seriously affected in a variety of acute and chronic diseases. In most cases, the pathophysiological mechanisms are hypothalamic dysfunction in conjunction with direct gonadal involvement. Hormonal changes in acute illnesses rarely reach the stage of inducing clinical manifestations and they are reversible in the majority of cases, following regression of the main disease. In chronic illnesses, like cirrhosis and end-stage renal disease, hormonal changes provoke severe systemic manifestations and worsen prognosis. In these cases, the correction of hypogonadism neither affects the progress of the disease nor improves prognosis. In cases of successful management of the underlying disease, such as organ transplantation, gonadal dysfunction is restored.

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