Sexual Dysfunction in Uremia

BIFF F. PALMER

Division of Nephrology, Department of Medicine, University of Texas Southwestern Medical School, Dallas, Texas.

Disturbances in sexual function are a common feature of chronic renal failure. Approximately 50% of uremic men complain of erectile dysfunction while an even greater percentage of both men and women complain of decreased libido and a marked decline in the frequency of intercourse (1,2). The genesis of sexual dysfunction is multifactorial and is primarily organic in origin. In addition to the uremic milieu, peripheral neuropathy, autonomic insufficiency, peripheral vascular disease, and pharmacologic therapy all play an important role in the genesis of this problem. In addition, psychologic and physical stresses are also commonly present in this setting.

Sexual Dysfunction in Uremic Men

In men with chronic renal failure, disturbances in the pituitary-gonadal axis can be detected with only moderate reductions in the GFR and progressively worsen as the renal failure progresses. These disorders rarely normalize with initiation of hemodialysis or peritoneal dialysis and, in fact, often progress. By comparison, a well-functioning renal transplant is much more likely to restore normal sexual activity, although some features of reproductive function may remain impaired (3).

Testicular Function

Chronic renal failure is associated with impaired spermatogenesis and testicular damage, often leading to infertility (4). Semen analysis typically shows a decreased volume of ejaculate, either low or complete azoospermia, and a low percentage of motility. These abnormalities are often apparent before the need for dialysis and then deteriorate further once dialytic therapy is initiated. Histologic changes in the testes include evidence of decreased spermatogenic activity with the greatest changes in the hormonally dependent later stages of spermatogenesis. The number of spermatocytes is reduced and there is little evidence of maturation to the stage of mature sperm. In most instances, the number of spermatogonia is normal but on occasion complete aplasia of germinal elements may also be present. Other findings include damage to the seminiferous tubules, interstitial fibrosis, and calcifications.

Correspondence to Dr. Biff F. Palmer, Professor of Internal Medicine, Acting Chief, Division of Nephrology, Department of Medicine, University of Texas Southwestern Medical School, 5323 Harry Haines Boulevard, Dallas, TX 75235. Phone: 214-648-7848; Fax: 214-648-2071; E-mail: biff.palmer@email.swmed.edu

Unlike other causes of severe primary testicular lesions, the Leydig and Sertoli cells show little evidence of hypertrophy or hyperplasia. This later finding suggests a defect in the hormonal regulation of the Leydig and Sertoli cells as might occur with either gonadotropin deficiency or resistance, rather than a cytotoxic effect of uremia where spermatogonia would be most affected (5). The factors responsible for testicular damage in uremia are not well understood. It is possible that plasticizers in dialysis tubing, such as phthalate, may play a role in propagating the abnormalities once patients begin maintenance hemodialysis.

Sex Steroids

In addition to impaired spermatogenesis, the testes also show evidence of impaired endocrine function. Total and free testosterone levels are typically reduced, although the binding capacity and concentration of sex hormone-binding globulin are normal (6–8). Acute stimulation of testosterone secretion with administration of human chorionic gonadotropin (HCG), a compound with luteinizing hormone-like actions, produces only a blunted response in uremic men (9). Lower free testosterone levels and impaired Leydig cell sensitivity to HCG are first detectable with only moderate reductions in the GFR and before basal levels of testosterone fall. Recent studies have shown evidence of a factor in uremic serum capable of blocking the luteinizing hormone receptor, thus providing an explanation for the sluggish response of the Leydig cell to infusion of HCG (10). This blocking activity is inversely correlated with GFR and largely disappears after transplantation. Compared with testosterone, the total plasma estrogen concentration is often elevated in advanced renal failure (8). However, the physiologically important estradiol levels are typically in the normal range. As with the lack of hypertrophy and hyperplasia of Leydig cells, normal levels of estradiol suggest a functional gonadotropin deficiency or resistance in uremia because increased luteinizing hormone levels should enhance the testicular secretion of estradiol (5).

Hypothalamic-Pituitary Function

The plasma concentration of the pituitary gonadotropin, luteinizing hormone (LH), is elevated in uremic men (8). Elevated levels are found early in renal insufficiency and progressively rise with deteriorating renal function. The excess LH secretion in this setting is thought to result from the diminished release of testosterone from the Leydig cells, since testosterone normally leads to feedback inhibition of LH re-

lease. In addition, the metabolic clearance rate of LH is reduced as a result of decreased renal clearance.

The increase in serum LH is variable and modest when compared to that observed in castrate nonuremic subjects. The lack of a more robust response of LH to low levels of circulating testosterone suggests a derangement in the central regulation of gonadotropin release. Infusion of gonadotropin-releasing hormone (GnRH) increases LH levels to the same degree as in healthy subjects; however, the peak value and return to baseline may be delayed (11,12). Since the kidney contributes importantly to the clearance of GnRH and LH, decreased metabolism of these hormones may explain the observed variations. The abnormal LH response to GnRH precedes and is not corrected by dialytic therapy. By contrast, renal transplantation returns the response of gonadotropins back to normal.

In addition to decreased metabolism, subtle disturbances in LH secretion have also been described. Under normal circumstances, LH is secreted in a pulsatile manner. In uremic subjects, the number of secretory bursts remains normal but the amount of LH released per secretory burst is reduced (13). It is not known whether this decrease in amplitude is the result of a change in the pattern of GnRH release from the hypothalamus or a change in the responsiveness of the pituitary. In either case, the secretory pattern of LH returns to normal with the placement of a well-functioning allograft.

Follicle-stimulating hormone (FSH) secretion is also increased in men with chronic renal failure, although to a more variable degree such that the LH/FSH ratio is typically increased. FSH release by the pituitary normally responds to feedback inhibition by a peptide product of the Sertoli cells called inhibin. The plasma FSH concentration tends 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 suggested that increased FSH levels may portend a poor prognosis for recovery of spermatogenic function after renal transplantation (4,14).

Clomiphene is a compound that acts by competing with estrogen or testosterone for receptors at the level of the hypothalamus and prevents the negative feedback of gonadal steroids on the release of GnRH and subsequently the release of pituitary gonadotropins. When administered to chronic renal failure patients, there is an appropriate rise in the levels of both LH and FSH, suggesting that the negative feedback control of testosterone on the hypothalamus is intact and that the storage and release of gonadotropins by the pituitary is normal (8).

In summary, a number of observations suggest that gonadal failure is an important consequence of chronic renal failure. The finding that LH levels are typically increased is consistent with the presence of testicular damage. However, the lack of Leydig cell hypertrophy and normal estradiol levels also raise the possibility of functional hypogonadism. The finding that LH levels are only modestly increased in chronic renal failure suggests a diminished response of the hypothalamic-pituitary axis to lowered testosterone levels and impaired regulation of gonadotropin secretion. One explanation for the blunted rise in LH in response to low levels of testosterone is that the hypo-thalamic-pituitary axis in chronic renal failure is reset in such a way that it is more sensitive to the negative feedback inhibition of testosterone. In this manner, the axis begins to assume a similar characteristic as seen in the prepubertal state where there is extreme sensitivity to the inhibitory effect of gonadal steroids (5).

Prolactin Metabolism

Elevated plasma prolactin levels are commonly found in dialyzed men (15). Increased production is primarily responsible, since the kidney plays little, if any, role in the catabolism of this hormone. Prolactin release is normally under dopaminergic inhibitory control. Its secretion in chronic renal failure, however, appears autonomous and resistant to stimulatory or suppressive maneuvers. As an example, dopamine infusion or the administration of oral L-dopa fails to decrease basal prolactin levels. On the other hand, procedures that normally increase prolactin secretion such as arginine infusion, insulin-induced hypoglycemia, or thyrotropin-releasing hormone infusion elicit no response or only a blunted response. Again, these abnormalities resolve after a successful renal transplant.

Increased prolactin secretion in chronic renal failure may be related in part to the development of secondary hyperparathyroidism. An infusion of parathyroid hormone (PTH) in healthy men enhances prolactin release, a response that can be suppressed by the administration of L-dopa (16). Furthermore, partial inhibition of PTH release by the administration of calcitriol led in one study to an elevation in plasma testosterone levels, a reduction in plasma gonadotropin concentrations, and improved sexual function (17). However, this benefit could not be confirmed in a controlled trial of calcitriol therapy (18). Depletion of total body zinc stores may also play an etiologic role in uremic hyperprolactinemia (19).

The clinical significance of enhanced prolactin release in uremic men is incompletely understood. Extreme hyperprolactinemia is associated with infertility, loss of libido, low circulating testosterone levels, and inappropriately low LH levels in men with normal renal function. These observations led to the evaluation of therapy with bromocryptine, which reduces prolactin secretion. Although it can lower prolactin levels to near normal in men with advanced renal disease, there has been an inconsistent effect on sexual potency and libido (15). In addition, a high incidence of side effects may be seen, particularly hypotension.

Gynecomastia

Gynecomastia occurs in approximately 30% of men on maintenance hemodialysis. This problem most often develops during the initial months of dialysis and then tends to regress as dialysis continues. The pathogenesis of gynecomastia in this setting is unclear. Although elevated prolactin levels and an increased estrogen-to-androgen ratio seem attractive possibilities, most data fail to support a primary role for abnormal hormonal function. Alternatively, a mechanism similar to that responsible for gynecomastia following refeeding of malnourished patients may be involved.

Evaluation of Sexual Dysfunction in Uremic Men

Sexual dysfunction can be manifest in several ways in uremic men. Perhaps the most common complaint the physician must address is that of impotence (Table 1). In evaluating and ultimately treating the impotent renal failure patient, one must not only consider disturbances in the hypothalamic-pituitary-gonadal axis discussed above, but also abnormalities in the sympathetic nervous system and derangements in the arterial supply or venous drainage of the penis. In addition, the psychologic effects of a chronic illness and lifestyle limitations may have a negative impact on sexual function.

A thorough history and physical can provide useful information during the initial evaluation of a patient with impotence. A history of normal erectile function before the development of renal failure suggests a secondary cause of impotence. Symptoms or physical findings of a neuropathy as in a patient with a neurogenic bladder would indicate a neurologic etiology. Similarly, symptoms or signs of peripheral vascular disease may be a clue to the presence of vascular obstruction to penile blood flow. One should look for the presence of secondary sexual characteristics, such as facial, axillary, and pubic hair. The lack of these findings and the presence of small soft testicles suggest primary or secondary hypogonadism as the cause of the impotence. Neurogenic and vascular causes are more likely to be associated with normal-sized testicles. Even when the history and physical point to a specific abnormality, one must also consider that an individual patient may have more than one factor responsible for the erectile dysfunction and other causes may need to be ultimately evaluated.

A review of the patient's medications may reveal a drug that could be responsible for impairing sexual function. Antihypertensive medications are common offenders, with centrally acting agents and beta blockers being 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 renal failure patients with hypertension. Other drugs commonly implicated include cimetidine, phenothiazines, tricyclic antidepressants, and metoclopramide.

If the history and physical examination reveal no obvious cause, then a psychologic cause of erectile dysfunction may need to be considered. Testing for the presence of nocturnal penile tumescence (NPT) has been done in some centers as a means to discriminate between a psychologic and organic cause of impotence. The basis for this test is that during the rapid eye movement stage of sleep, males normally have an erection. The assumption is that a man with a psychologic cause of impotence would still experience erections while asleep, whereas the absence of an adequate erection would make an organic cause more likely. If a patient is found to have nocturnal erections, then psychologic testing and evaluation is indicated. It should be noted that NPT testing is not infallible and that if a patient has a normal test and no psychologic cause is found then evaluation for an organic cause should still be pursued.

Primary depression may affect sexual function and lead to reduced libido and decreased frequency of intercourse. As a result, it has been suggested that depression may play a role in the genesis of sexual dysfunction in chronic renal failure patients. Studies addressing this issue have produced conflicting results. Procci et al. found no association between the presence or absence of depression and measures of sexual function such as frequency of intercourse or ability to develop an erection as determined by NPT testing (1). In a more recent study, Steele et al. surveyed a randomly selected group of 68 peritoneal dialysis patients that included both men and women and found that 63% of patients reported never having intercourse, 19% had intercourse less than or equal to two times per month, and 18% had intercourse more than two times per month (20). In this study, standard psychologic questionnaires indicated that the patients who never had intercourse were more depressed and anxious, and assessed their overall quality of life at a level that was significantly lower than that of the other two groups. Thus, subclinical depression may be underrated as a contributory cause of sexual dysfunction in both uremic men and women. It is also likely that mental symptoms of fatigue and listlessness associated with the treatment of end-stage renal disease are also major factors in this problem (2).

There are tests that may aid in the discrimination between a neurogenic and a vascular cause of impotence. Tests performed to exclude a vascular etiology of impotence include Doppler studies to measure penile blood flow, measurement of penile BP, and penile pulse palpation. Neurogenic impotence is suggested by detecting a prolonged latency time of the bulbocavernous reflex or confirming the presence of a neurogenic bladder. With the availability of sildenafil (see below) to use in a therapeutic trial, such tests are generally reserved for nonresponders who may eventually be considered for surgical placement of a penile prosthesis.

As discussed previously, hormonal abnormalities are frequently detected in chronic renal failure patients. Endocrine

Table 1. Factors involved in the pathogenesis of impotence in uremic men[a]

Gonadal function
   decreased production of testosterone
Hypothalamic-pituitary function
   blunted increase in serum LH levels
   decreased amplitude of LH secretory burst
   variable increase in serum FSH levels
   increased prolactin levels
Psychologic factors related to chronic disease
Zinc deficiency
Medications
Anemia
Secondary hyperparathyroidism
Impaired arterial inflow and venous drainage of the penis
Autonomic neuropathy

---

[a] LH, luteinizing hormone; FSH, follicle-stimulating hormone.

tests that are useful in the evaluation of an organic cause of impotence include measurement of serum LH, FSH, testosterone, and prolactin levels. It should be noted that only a small percentage of uremic patients will have prolactin levels >100 ng/ml. Imaging studies of the hypothalamic-pituitary region should be performed in patients with levels of greater magnitude to exclude the presence of a microadenoma or macroadenoma.

Treatment of Sexual Dysfunction in Uremic Men

The treatment of sexual dysfunction in uremic men is initially of a general nature (Figure 1). One needs to ensure optimal delivery of dialysis and adequate nutritional intake. Administration of recombinant human erythropoietin has been shown to enhance sexual function in chronic renal failure. It is likely that the associated improvement in well-being that comes with the correction of anemia probably plays an important role in this response. In some studies, erythropoietin therapy has been reported to cause normalization of the pituitary gonadal feedback mechanism with reduced plasma concentrations of LH and FSH and increases in plasma testosterone

levels (21,22). Reductions in elevated plasma prolactin levels have also been noted (23). It is controversial as to whether these endocrinologic changes are solely the result of correction of the anemia or a direct effect of erythropoietin. As mentioned previously, controlling the degree 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.

Patients with normal NPT testing should be evaluated to determine whether there is a psychologic component to the impotence. If a problem is found then a trial of psychotherapy is warranted. The effectiveness of antidepressant medications and/or psychiatric counseling in chronic renal failure patients with sexual dysfunction has not been well studied. In patients with a neurogenic or vascular cause of impotence, therapeutic options include intracavernous injection of alprostadil (synthetic PGE_1), use of vacuum/constriction devices, or urethral suppositories containing alprostadil. Surgical placement of a penile prosthesis is typically considered in patients who fail the less invasive first-line treatments.

With the recent approval of sildenafil for the treatment of men with erectile dysfunction, many physicians now utilize
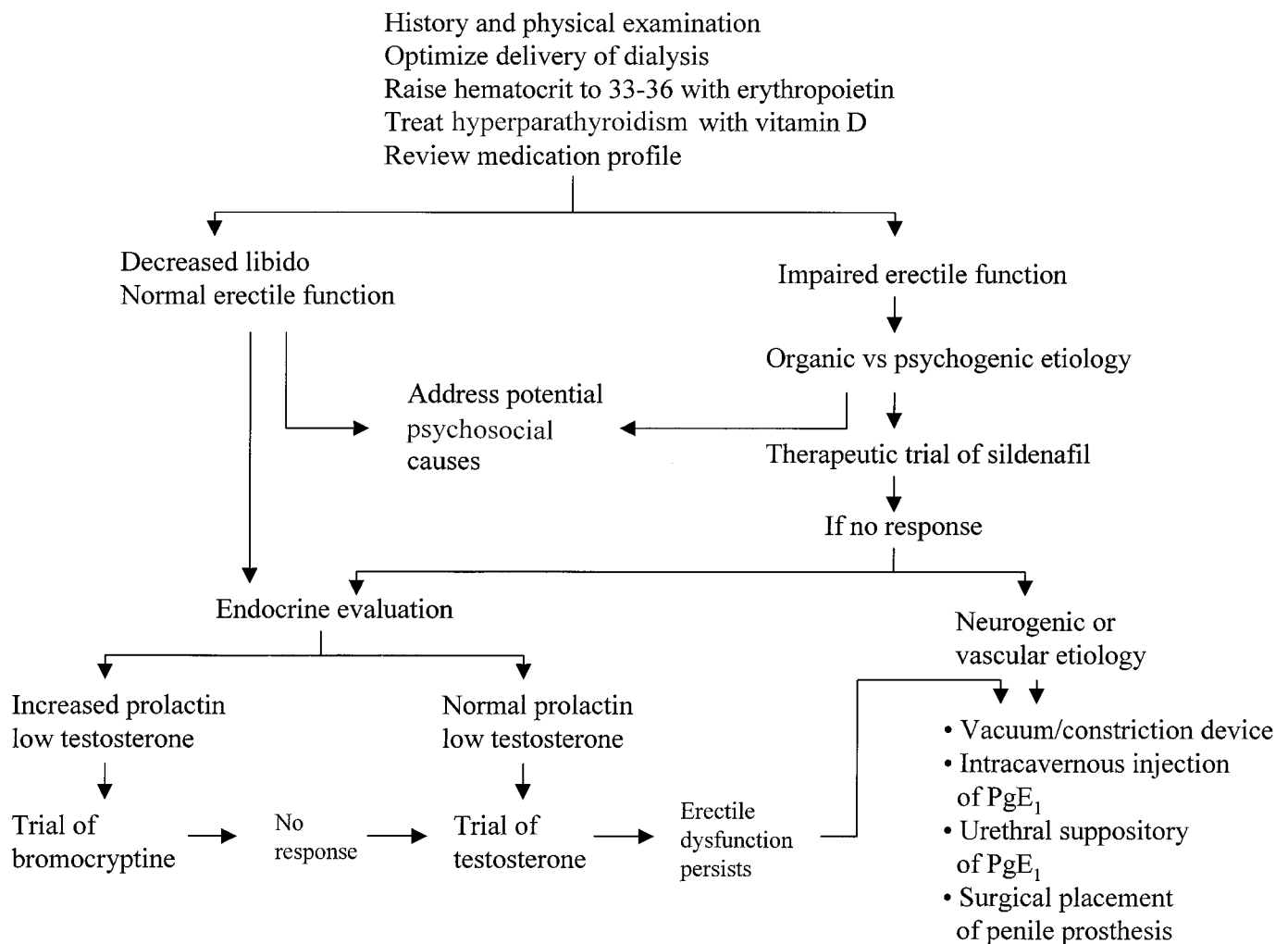

Figure 1. Approach to sexual dysfunction in uremic men.

this agent as the first-line therapy for patients with psychogenic, vascular, or neurogenic causes of impotence. There have been no published studies to date specifically addressing the effectiveness and safety of sildenafil in chronic renal failure patients. However, anecdotally the drug appears effective in such patients. Since the majority of patients receiving renal replacement therapy in the United States are diabetic, it is noteworthy that a recently published randomized controlled trial found that sildenafil was both effective and well tolerated in diabetic men with erectile dysfunction (24). More than 95% of the patients in this study were believed to have either a neurogenic or vascular etiology of erectile dysfunction. Whether diabetic patients with renal disease will experience a similar benefit is not known. It should be emphasized that sildinafil is contraindicated in patients who are currently taking organic nitrates. Caution should also be exercised when prescribing this agent to patients with known coronary artery disease.

In patients with low circulating levels of testosterone, correcting the deficit generally results in clinical improvement in other forms of gonadal failure. By contrast, administration of testosterone to uremic men usually fails to restore libido or potency, despite increased testosterone levels and reduced release of LH and FSH (25,26). In a recent report of 27 male dialysis patients with biochemically proven hypogonadism, administration of depot testosterone fully restored sexual function in only three patients (27). In those patients unresponsive to medical therapy, use of a vacuum tumescence device completely corrected penile erection dysfunction in the majority of cases. In a hypogonadal patient whose primary complaint is decreased libido, a trial of testosterone may be warranted. In very limited studies, administration of clomiphene citrate has also been reported to cause a normalization of plasma testosterone levels associated with some improvement in sexual function.

Patients found to have increased circulating levels of prolactin may benefit from a trial of bromocryptine. This agent is a dopaminergic agonist that has shown some efficacy in improving sexual function presumably by reducing elevated prolactin levels. However, its usefulness has been limited by a relatively high frequency of side effects. Other dopaminergic agonists, such as parlodel and lisuride, seem to be better tolerated but have only been used in small short-term studies.

Zinc deficiency has also been suggested as a cause of gonadal failure. Uremic patients are often deficient in zinc, probably due to reduced dietary intake, zinc malabsorption, and/or possible leaching of zinc by dialysis equipment. In a controlled trial, supplemental zinc resulted in significant increases in the plasma testosterone concentration and sperm counts, as well as significant declines in LH and FSH levels compared with a control group (28). Potency, libido, and frequency of intercourse also improved in those patients given zinc. It is possible that normalization of total body zinc may also be effective in correcting uremic hyperprolactinemia (19). Thus, the aggregate data suggest that the administration of zinc in a zinc-deficient man is a reasonable therapeutic option.

Sexual Dysfunction in Uremic Women

Disturbances in menstruation and fertility are commonly encountered in women with chronic renal failure, usually leading to amenorrhea by the time the patient reaches end-stage renal disease. The menstrual cycle typically remains irregular with scanty flow after the initiation of maintenance dialysis, although normal menses is restored in some women (29). In others, hypermenorrhagia develops, potentially leading to significant blood loss and increased transfusion requirements.

The major menstrual abnormality in uremic women is anovulation, with affected patients being infertile (30). Women on chronic dialysis also tend to complain of decreased libido and reduced ability to reach orgasm (2,20).

Pregnancy can rarely occur in advanced renal failure, but fetal wastage is markedly increased. Some residual renal function is usually present in the infrequent pregnancy that can be carried to term. The subject of pregnancy in chronic renal insufficiency has recently been reviewed (31).

Normal Menstrual Cycle

The normal menstrual cycle is divided into a follicular or proliferative phase and a luteal or secretory phase. Normal follicular maturation and subsequent ovulation require appropriately timed secretion of the pituitary gonadotropins. FSH secretion exhibits typical negative feedback, with hormone levels falling as the plasma estrogen concentration rises. In contrast, LH secretion is suppressed maximally by low concentrations of estrogen but exhibits positive feedback control in response to a rising and sustained elevation of estradiol. Thus, high levels of estradiol in the late follicular phase trigger a surging elevation in LH secretion, which is responsible for ovulation. After ovulation, progesterone levels increase due to production by the corpus luteum. Progesterone is responsible for the transformation of the endometrium into the luteal phase.

Hormonal Disturbances in Uremic Premenopausal Women

Indirect determination of ovulation suggests that anovulatory cycles are the rule in uremic women (32). For example, endometrial biopsies show an absence of progestational effects, and there is a failure to increase basal body temperature at the time when ovulation would be expected. In addition, the preovulatory peak in LH and estradiol concentrations is frequently absent. The failure of LH to rise in part reflects a disturbance in the positive estradiol feedback pathway, since the administration of exogenous estrogen to mimic the preovulatory surge in estradiol fails to stimulate LH release (32). In contrast, feedback inhibition of gonadotropin release by low doses of estradiol remains intact. This can be illustrated by the ability of the antiestrogen clomiphene to enhance LH and FSH secretion.

It remains unclear whether the disturbances in cyclic gonadotropin production originate in the hypothalamus (via impaired production of GnRH) or in the anterior pituitary (30). It is possible, for example, that endorphins are involved. Circulat-
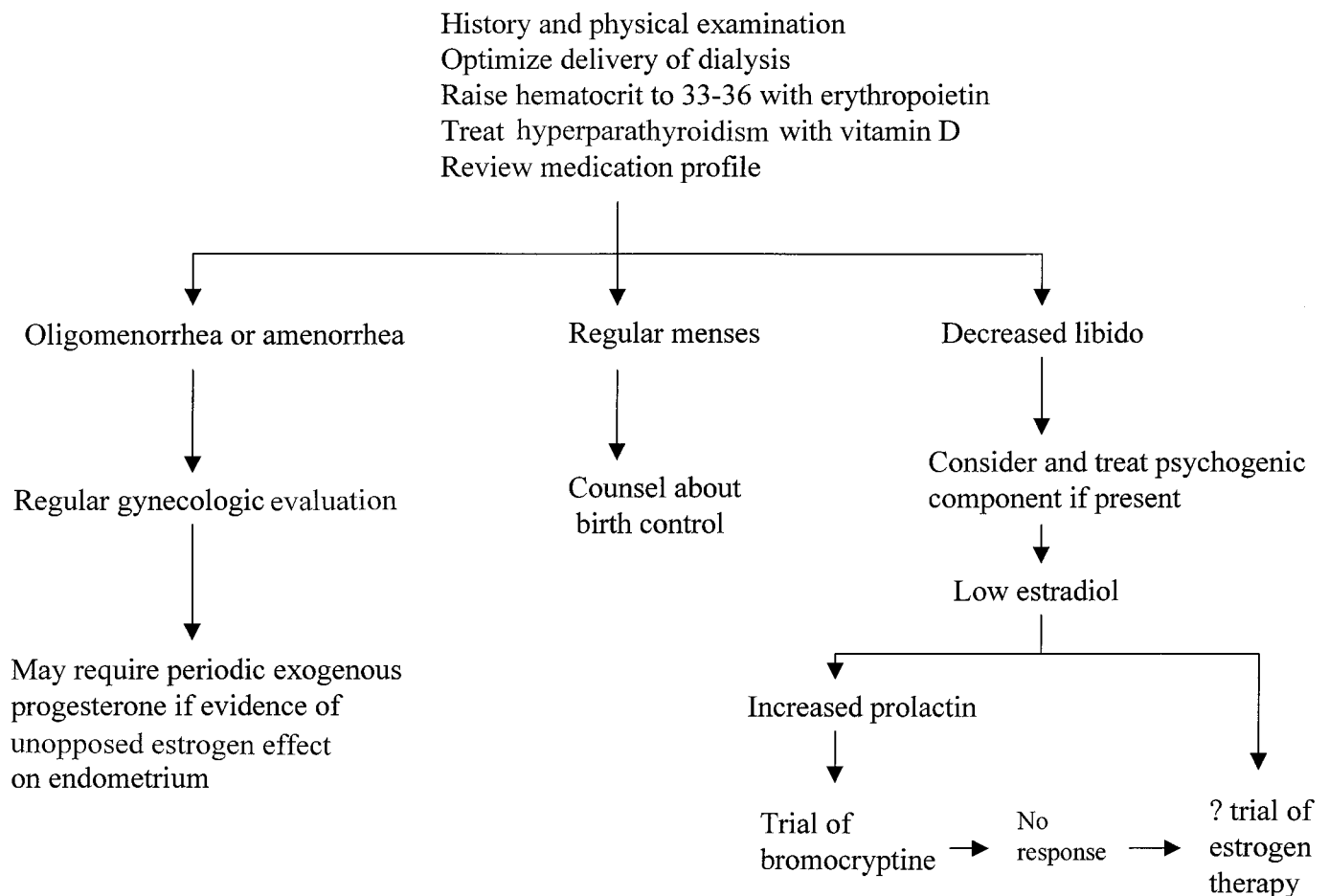
History and physical examination
Optimize delivery of dialysis
Raise hematocrit to 33-36 with erythropoietin
Treat hyperparathyroidism with vitamin D
Review medication profile

Oligomenorrhea or amenorrhea

Regular menses

Decreased libido

Regular gynecologic evaluation

Counsel about
birth control

Consider and treat psychogenic
component if present

May require periodic exogenous
progesterone if evidence of
unopposed estrogen effect
on endometrium

Low estradiol

Increased prolactin

Trial of
bromocryptine → No response → ? trial of estrogen therapy

Figure 2. Approach to sexual dysfunction in uremic women.

ing endorphin levels are increased in chronic renal failure due primarily to reduced renal opioid clearance, and endorphins can inhibit ovulation, perhaps by reducing the release of GnRH.

Prolactin and Galactorrhea

Women with chronic renal failure commonly have elevated circulating prolactin levels. As in men with chronic renal failure, the hypersecretion of prolactin in this setting appears to be autonomous, as it is resistant to maneuvers designed to stimulate or inhibit its release.

It has been suggested that the elevated prolactin levels may impair hypothalamic-pituitary function and contribute to sexual dysfunction and galactorrhea in these patients. It is of interest in this regard that nonuremic women with prolactin-producing pituitary tumors commonly present with amenorrhea, galactorrhea, and low circulating gonadotropin levels. However, uremic women treated with bromocryptine rarely resume normal menses and continue to complain of galactorrhea (if present), despite normalization of the plasma prolactin concentration (32). Thus, factors other than hyperprolactinemia must be important in this setting.

Hormonal Disturbances in Uremic Postmenopausal Women

Postmenopausal uremic women have gonadotropin levels as high as those seen in nonuremic women of similar age (32,33). This observation is consistent with the finding mentioned above in premenopausal women that negative feedback inhibition of estrogen on LH and FSH release is intact in uremia. However, the age at which menopause begins in chronic renal failure tends to be decreased when compared to healthy women.

Treatment

The high frequency of anovulation leads sequentially to lack of formation of the corpus luteum and failure of progesterone secretion. Because progesterone is responsible for transforming the endometrium into the luteal phase, lack of progesterone is associated with amenorrhea. For patients who desire to resume menses, administration of a progestational agent during the final days of the monthly cycle will usually be successful.

On the other hand, ongoing menses can contribute significantly to the anemia of chronic renal disease, particularly in those patients with hypermenorrhagia. In this setting, administration of a progestational agent during the entire monthly

cycle will terminate menstrual flow. Rarely, a patient may require hysterectomy for refractory uterine bleeding.

It is not known whether the usual absence of menses in women with chronic renal failure predisposes to the development of endometrial hyperplasia and possible carcinoma. Since these patients are often anovulatory, there is no disruption of the proliferative effect of estrogen by the release of progesterone. It is therefore recommended that women with chronic renal failure be monitored closely by a gynecologist; it may be desirable in at least some patients to administer a progestational agent several times per year to interrupt the proliferation induced by unopposed estrogen release (Figure 2).

Although pregnancy can rarely occur in women on chronic dialysis, restoration of fertility as a therapeutic goal should be discouraged. In comparison, the abnormalities in ovulation can usually be reversed and successful pregnancy achieved in women with a well-functioning renal transplant. Uremic women who are menstruating normally should be encouraged to use birth control.

Studies addressing the therapy of decreased libido and sexual function in uremic women are lacking. Amenorrheic hemodialysis patients may have low estradiol levels that can secondarily lead to vaginal atrophy and dryness and result in discomfort during intercourse. Such patients may benefit from local estrogen therapy or vaginal lubricants. Low dose testosterone may be effective in increasing sexual desire but is rarely used secondary to potential toxicity. Bromocryptine therapy in hyperprolactinemic patients may help in restoring sexual function but has not been well studied. Estrogen supplementation may improve sexual function in those patients with low circulating estradiol levels. Successful transplantation is clearly the most effective means to restore normal sexual desire in women with chronic renal failure (2).

Summary

In summary, sexual dysfunction is a common finding in both men and women with chronic renal failure. Common disturbances include erectile dysfunction in men, menstrual abnormalities in women, and decreased libido and fertility in both sexes. These abnormalities are primarily organic in nature and are related to uremia as well as the other comorbid conditions that frequently accompany the chronic renal failure patient. Fatigue and psychosocial factors related to the presence of a chronic disease are also contributory factors. Disturbances in the hypothalamic-pituitary-gonadal axis can be detected before the need for dialysis but continue to worsen once dialytic therapy is initiated. Impaired gonadal function is prominent in uremic men, whereas the disturbances in the hypothalamic-pituitary axis are more subtle. By contrast, central disturbances are more prominent in uremic women. Therapy is initially directed toward optimizing the delivery of dialysis, correcting anemia with recombinant erythropoietin, and controlling the degree of secondary hyperparathyroidism with vitamin D. For many practicing nephrologists, sildenafil has become the first-line therapy in the treatment of impotence. In the hypogonadal man whose only complaint is decreased libido, testosterone may be of benefit. Regular gynecologic follow-up is required

in uremic women to guard against potential complications of unopposed estrogen effect. Uremic women should be advised against pregnancy while on dialysis. Successful transplantation is the most effective means of restoring normal sexual function in both men and women with chronic renal failure.

References

1. Procci WR, Goldstein DA, Adelstein J, Massry SG: Sexual dysfunction in the male patient with uremia: A reappraisal. *Kidney Int* 19: 317–323, 1981
2. Toorians AW, Janssen E, Laan E, Gooren LJG, Giltay EJ, Oe PL, Donker AJM, Everaerd W: Chronic renal failure and sexual functioning: Clinical status *versus* objectively assessed sexual response. *Nephrol Dial Transplant* 12: 2654–2663, 1997
3. Holdsworth SR, de Kretser DM, Atkins RC: A comparison of hemodialysis and transplantation in reversing the uremic disturbance of male reproductive function. *Clin Nephrol* 10: 146–150, 1978
4. Prem AR, Punekar SV, Kalpana M, Kelkar AR, Acharya VN: Male reproductive function in uraemia: Efficacy of haemodialysis and renal transplantation. *Br J Urol* 78: 635–638, 1996
5. Handelsman DJ: Hypothalamic-pituitary gonadal dysfunction in renal failure, dialysis and renal transplantation. *Endocrinol Rev* 6: 151–182, 1985
6. De Vries CP, Gooren LJG, Oe PL: Haemodialysis and testicular function. *Int J Androl* 7: 97–103, 1984
7. Levitan D, Moser SA, Goldstein DA, Kletzky OA, Lobo RA, Massry SG: Disturbances in the hypothalamic-pituitary-gonadal axis in male patients with acute renal failure. *Am J Nephrol* 4: 99–106, 1984
8. Lim VS, Fang VS: Restoration of plasma testosterone levels in uremic men with clomiphene citrate. *J Clin Endocrinol Metab* 43: 1370–1377, 1976
9. Stewart-Bentley M, Gans D, Horton R: Regulation of gonadal function in uremia. *Metabolism* 23: 1065–1072, 1974
10. Dunkel L, Raivio T, Laine J, Holmberg C: Circulating luteinizing hormone receptor inhibitor(s) in boys with chronic renal failure. *Kidney Int* 51: 777–784, 1997
11. Schalch DS, Gonzalez-Barcena D, Kastin AJ, Landa L, Lee LA, Zamora MT, Schally AV: Plasma gonadotropins after administration of LH-releasing hormone in patients with renal or hepatic failure. *J Clin Endocrinol Metab* 41: 921–925, 1975
12. LeRoith D, Danovitz G, Trestian S, Spitz IM: Dissociation of pituitary glycoprotein response to releasing hormones in chronic renal failure. *Acta Endocrinologica* 93: 277–282, 1980
13. Schaefer F, Veldhuis JD, Robertson WR, Dunger D, Schärer K, The Cooperative Study Group on Pubertal Development in Chronic Renal Failure: Immunoreactive and bioactive luteinizing hormone in pubertal patients with chronic renal failure. *Kidney Int* 45: 1465–1476, 1994
14. Phocas I, Sarandakou A, Rizos D, Kapetanaki A: Serum α-immunoreactive inhibin in males with renal failure, under haemodialysis and after successful renal transplantation. *Andrologia* 27: 253–258, 1995
15. Gomez F, de la Cueva R, Wauters J-P, Lemarchand-Beraud T: Endocrine abnormalities in patients undergoing long-term hemodialysis: The role of prolactin. *Am J Med* 68: 522–530, 1980
16. Isaac R, Merceron RE, Caillens G, Raymond J-P, Ardaillou R: Effect of parathyroid hormone on plasma prolactin in man. *J Clin Endocrinol Metab* 47: 18–23, 1978
17. Massry SG, Goldstein DA, Procci WR, Kletzky OA: Impotence

in patients with uremia: A possible role for parathyroid hormone. *Nephron* 19: 305–310, 1977

18. Blumberg A, Wildbolz A, Descoeudres C, Hennes U, Dambacher MA, Fischer JA, Weidmann P: Influence of 1,25 dihydroxycholecalciferol on sexual dysfunction and related endocrine parameters in patients on maintenance hemodialysis. *Clin Nephrol* 13: 208–214, 1980

19. Caticha O, Norato DYJ, Tambascia MA, Santana A, Stephanou A, Sarlis NJ: Total body zinc depletion and its relationship to the development of hyperprolactinemia in chronic renal insufficiency. *J Endocrinol Invest* 19: 441–448, 1996

20. Steele TE, Wuerth D, Finkelstein S, Juergensen D, Juergensen P, Kliger AS, Finkelstein FO: Sexual experience of the chronic peritoneal dialysis patient. *J Am Soc Nephrol* 7: 1165–1168, 1996

21. Kokot F, Więcek, Schmidt-Gayk H, Marcinkowski W, Gilge U, Heidland A, Rudka R, Trembecki J: Function of endocrine organs in hemodialyzed patients of long-term erythropoietin therapy. *Artif Org* 19: 428–435, 1995

22. Schaefer F, van Kaick B, Veldhuis JD, Stein G, Schärer K, Robertson, WR, Ritz E: Changes in the kinetics and biopotency of luteinizing hormone in hemodialyzed men during treatment with recombinant human erythropoietin. *J Am Soc Nephrol* 5: 1208–1215, 1994

23. Schaefer RM, Kokot F, Wernze H, Geiger H, Heidland A: Improved sexual function in hemodialysis patients on recombinant erythropoietin: A possible role for prolactin. *Clin Nephrol* 31: 1–5, 1989

24. Rendell MS, Rajfer J, Wicker PA, Smith MD, for the Sildenafil Diabetes Study Group: Sildenafil for treatment of erectile dys-

function in men with diabetes: A randomized controlled trial. *JAMA* 281: 421–426, 1999

25. Barton CH, Mirahmadi MK, Vaziri ND: Effects of long-term testosterone administration on pituitary-testicular axis in end-stage renal failure. *Nephron* 31: 61–64, 1982

26. van Coevorden A, Stolear JC, Dhaene M, van Herweghem JL, Mockel J: Effect of chronic oral testosterone undecanoate administration on the pituitary-testicular axes of hemodialyzed male patients. *Clin Nephrol* 26: 48–54, 1986

27. Lawrence IG, Price DE, Howlett TA, Harris KPG, Feehally J, Walls J: Correcting impotence in the male dialysis patient: Experience with testosterone replacement and vacuum tumescence therapy. *Am J Kidney Dis* 31: 313–319, 1998

28. Mahajan SK, Abbasi AA, Prasad AS, Rabbani P, Briggs WA, McDonald FD: Effect of oral zinc therapy on gonadal function in hemodialysis patients. *Ann Intern Med* 97: 357–361, 1982

29. Holley JL, Schmidt RJ, Bender FH, Dumler F, Schiff M: Gynecologic and reproductive issues in women on dialysis. *Am J Kidney Dis* 29: 685–690, 1997

30. Ginsburg ES, Owen WF Jr: Reproductive endocrinology and pregnancy in women on hemodialysis. *Semin Dial* 6: 105–116, 1993

31. Hou S: Pregnancy in chronic renal insufficiency and end-stage renal disease. *Am J Kidney Dis* 33: 235–252, 1999

32. Lim VS, Henriquez C, Sievertsen G, Frohman LA: Ovarian function in chronic renal failure: Evidence suggesting hypothalamic anovulation. *Ann Intern Med* 93: 21–27, 1980

33. Zingraff J, Jungers P, Pélissier C, Nahoul K, Feinstein MC, Scholler R: Pituitary and ovarian dysfunctions in women on haemodialysis. *Nephron* 30: 149–153, 1982