Gonadotropin Therapy in Androgen Deficiency

It is known that hCG binds to Leydig cell LH receptors and stimulates the production of testosterone. Peripubertal boys with hypogonadotropic hypogonadism and delayed puberty can be treated with hCG instead of testosterone to induce pubertal development. The initial regimen of hCG is usually 1,000 to 2,000 IU administered intramuscularly two to three times a week (65). The clinical response is monitored, and testosterone levels are measured about every 2 to 3 months. Dosage adjustments of hCG may be needed to determine an optimal schedule. Increasing doses of hCG may reduce testicular stimulation by down-regulating the end-organ; thus, a more optimal result may occur with less frequent or reduced dosing. The half-life of hCG is long.

The advantages of hCG over testosterone in this setting include the stimulation of testicular growth, which may be an important issue for some men. Use of hCG may also yield greater stability of testosterone levels and fewer fluctuations in hypogonadal symptoms (66). In addition, hCG treatment is necessary for stimulating enough intra-testicular testosterone to allow the initiation of spermatogenesis. The disadvantages of hCG include the need for more frequent injections and the greater cost.

Gonadotropin Therapy for Induction of Spermatogenesis

Male patients with onset of hypogonadotropic hypogonadism before completion of pubertal development may have testes generally smaller than 5 mL. These patients usually require therapy with both hCG and human menopausal gonadotropin (or FSH) to induce spermatogenesis. Men with partial gonadotropin deficiency or who have previously (peripubertally) been stimulated with hCG may initiate and maintain production of sperm with hCG therapy only. Men with postpubertal acquired hypogonadism and who have previously had normal production of sperm can also generally initiate and maintain spermatogenesis with hCG treatment only (67). Fertility may be possible at sperm counts much lower than what would otherwise be considered fertile. Counts of less than 1 million/mL may be associated with pregnancies under these circumstances. It is imperative that the female partner undergo assessment for optimal fertility before or concurrently with consideration of therapy in the man.

Therapy with hCG is generally begun at 1,000 to 2,000 IU intramuscularly two to three times a week, and testosterone levels should be monitored monthly to determine whether any therapeutic adjustments are needed to normalize the levels. It may take 2 to 3 months to achieve normal levels of testosterone. When normal levels of testosterone are produced, examinations should be conducted monthly to determine whether any testicular growth has occurred. Sperm counts should also be assessed monthly during a 1-year period. Because of the high cost of human menopausal gonadotropin (or FSH) preparations, hCG should be the initial therapy of choice for at least 6 to 12 months. Use of hCG, in the absence of exogenous FSH, can often complete spermiogenesis in men with partial gonadotropin deficiency (68). In general, the response to hCG can be predicted on the basis of the initial testicular volume—the greater the initial testicular volume, the greater the chance of responding to hCG only (69). In one study, however, investigators demonstrated that most patients will respond to hCG alone regardless of initial testicular volume (70). Studies have shown that combining purified FSH and testosterone without LH or hCG does not stimulate spermatogenesis in truly hypogonadotropic men (71).

If spermatogenesis has not been initiated by the end of 6 to 12 months of therapy with hCG or LH, administration of an FSH-containing preparation is initiated in a dosage of 75 IU intramuscularly three times a week along with the hCG injections. After 6 months, if sperm are not present or are present in very low numbers (<100,000/mL), the human menopausal gonadotropin (or FSH) dosage can be increased to 150 IU intramuscularly three times a week for another 6 months. If pregnancy occurs, the patient’s regimen can be switched to only hCG to allow continued spermatogenesis for subsequent potential pregnancies. After delivery, if no further pregnancies are desired, the patient can be switched to testosterone therapy if desired, or long-term hCG therapy can be continued in conjunction with appropriate contraceptive measures, if needed. Rarely, antibodies against hCG may arise and prevent any response to therapy; in such a case, human LH may be effective (72). Recombinant LH has recently become available and may be of use in selected patients.

GnRH Therapy

In patients with an otherwise intact pituitary gland and hypogonadotropic hypogonadism, synthetic GnRH can be given in a pulsatile fashion subcutaneously through a pump every 2 hours. GnRH therapy is monitored by measuring LH, FSH, and testosterone levels every 2 weeks until levels are in the normal range, at which point monitoring can be adjusted to every 2 months. GnRH can be used to initiate pubertal development, maintain virilization and sexual function, and initiate and maintain spermatogenesis. In most patients, these effects may take from 3 to 15 months to achieve sperm production (73). As with gonadotropin therapy, fertility can be achieved with very low sperm counts—often in the range of 1 million/mL. GnRH may be more effective than gonadotropin stimulation in increasing testicular size and initiating spermatogenesis in many patients with hypogonadotropic hypogonadism (74).

Other Treatment Considerations

Antiestrogen Therapy in Oligospermia

Long-term use of low-dose clomiphene citrate at 25 mg daily to increase pituitary stimulation of testicular function has often been attempted in men with oligospermia (75). Tamoxifen has been used in countries other than the United States. The results are unpredictable, and