0021-972X/85/6104-0746$02.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 61, No. 4
Printed in U.S.A.

Male Hypogonadotropic Hypogonadism: Factors Influencing Response to Human Chorionic Gonadotropin and Human Menopausal Gonadotropin, Including Prior Exogenous Androgens*

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ABSTRACT. Although testosterone (T) therapy is sufficient for maturation and maintenance of secondary sex characteristics in hypogonadal men, gonadotropins are required for stimulation of spermatogenesis. Thirteen men with hypogonadotropic hypogonadism received treatment with hCG, followed in 12 by the addition of human menopausal gonadotropin (hMG). All initially had undetectable serum LH and FSH and low T levels and were azoospermic with small testes. During therapy, all achieved normal male levels of T. Twelve of 13 had marked and continuous increase in testicular volume. Three men had sperm in the ejaculate with hCG treatment alone. All but 1 patient developed sperm in their seminal fluid during combined hCG and hMG therapy. Two men achieved three pregnancies, and 2 more had semen that produced hamster oocyte penetration assays in the fertile range during the protocol period. Four of 5 who achieved sperm densities greater than 1 million/ml while receiving combined therapy maintained or increased sperm production while receiving continued hCG therapy after hMG was withdrawn.

We examined the response to gonadotropin therapy of men who had received previous T therapy and those who had not. There were no differences in rapidity or degree of response, as assessed by rise in serum T, increase in testis volume, or maximal sperm density achieved. Multiple pituitary deficits and cryptorchidism were negative prognostic factors.

In summary, the prognosis for successful stimulation of spermatogenesis in men with hypogonadotropic hypogonadism treated with hCG/hMG is good and not adversely affected by prior androgen treatment. Despite undetectable serum FSH levels, hCG treatment was sufficient to both initiate and maintain spermatogenesis in some patients. (*J Clin Endocrinol Metab* **61:** 746, 1985)

TREATMENT of hypogonadotropic hypogonadism in men is directed at two goals. The first is the restoration of a normal androgen milieu, allowing successful virilization. The second is the induction of fertility. Adult serum testosterone (T) levels may be achieved by either exogenously administered T or stimulation of endogenous T production with hCG. The long-acting T esters have several advantages in this regard. Firstly, they are significantly less expensive than an equally effective dose of hCG. Secondly, normal virilization and potency can be maintained with biweekly or less frequent injections of T enanthate or T cypionate, whereas hCG is usually administered two or three times a week.

When fertility is desired, however, testicular stimulation with gonadotropins is necessary, and exogenous T is no longer sufficient. Several investigators have treated men with hypogonadotropic hypogonadism with gonadotropins (1–6) and LHRH (7–9). We had the opportunity to study a group of hypogonadotropic men prospectively with a standard protocol. This allowed us to assess not only the likelihood of response, but also the importance of several factors that may have prognostic significance.

Received November 21, 1984.

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* This work was supported in part by NIH Grants P-50-HD-12629 and P-32-AM-07247.

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Materials and Methods

Patients

During a 2-yr period, we treated 13 gonadotropin-deficient men, 19–42 yr of age, with exogenous gonadotropins (Table 1). This report includes all of these men. Only 7 of the men were married and immediately interested in fathering children. The other 6 were unmarried and participated hoping to obtain information of prognostic value. Eight men had hypogonadotropic eunuchoidism (HE), *i.e.* isolated gonadotropin deficiency which was present before puberty. Six of these 8 had either hyposmia or anosmia. One had associated primary adrenal failure originally appearing at age 3 yr. Two men had isolated gonadotropin deficiency (IGD) which developed after normal

TABLE 1. Hypogonadotropic men: clinical information

Patient	Age (yr)	Diagnosis	Previous androgen therapy (months)	Serum T (ng/dl)	LH/FSH	Testis vol (ml)[a]	Other
A[b]	21	HE		70	u	<1.0	
B	27	HE	96	60	u	2.4	
C[b]	29	HE	96	62	u	2.4	
D[b]	26	HE	60	60	u	1.5	
E[b]	19	HE		20	u	2.0	
F[b]	30	HE		130	u	0.7	Previous orchiopexy for undescended testis
G[c]	28	HE	71	150	u	4.1	
H	23	HE	60	180	u	2.1	Addison's disease, L. inguinal testis, previous R. orchiopexy for undescended testis
I	34	IGD	42	80	u	5.1	Previous orchiopexy for undescended testis
J	34	IGD	2	100	u	7.9	1° hypospadius, hemochromatosis
K	28	Panhypopituitarism	96	38	u	0.6	Undescended testis, now scrotal, varicocele
L	23	Panhypopituitarism/DI	60	60	u	4.7	
M[c]	42	Hypopituitarism/DI	87	50	u	3.1	

u, Undetectable; DI, diabetes insipidus.
[a] Mean of volume of each testes.
[b] Anosmia.
[c] Eighteen-month course of hCG 8 yr previously.

puberty had occurred. The first had fathered 2 children when he was 24 and 26 yr, respectively. Subsequently, at age 27 yr, he developed decreased libido and potency. When evaluated 2 yr later, he was hypogonadal and azoospermic, but had no other abnormalities. The etiology of his deficit remains undetermined. The second patient developed symptoms of hypogonadism and a progressive decrease in ejaculate volume at age 30 yr. A diagnosis of idiopathic hemochromatosis was made, and phlebotomy therapy was begun. Other pituitary deficits were excluded by appropriate endocrine testing in all patients with HE and acquired IGD. Radiological evaluation of the sella turcica was normal in all patients, and both patients with acquired IGD had normal visual fields and head computed axial tomographic scans. Three other patients had other pituitary hormonal deficits (Table 1). Two of the 3 (K and M), had idiopathic hypopituitarism diagnosed in infancy; both had normal skull x-rays and visual fields. The third man (L) developed normally until age 12 yr, when his growth rate declined, and pubertal development ceased; he also developed diabetes insipidus. At age 27 yr, subsequent to the protocol described below, an optic glioma was identified. All 3 were receiving replacement doses of T_4. Two (K and M) required glucocorticoid replacement, and the 2 (L and M) with diabetes insipidus also were treated with arginine vasopressin and chlorpropamide. All 3 men were GH deficient, and patients K and L had received human GH therapy in the past.

Of the 13 men, 9 had been treated previously with androgens for greater than 42 months (Table 1). In addition, 3 of these men had been treated with hCG. Patients G and M had received hCG for 18 months 8 yr previously, and patient H had received 4 separate courses of 6–10 weeks of hCG between age 18 and 21 yr (total, 36 weeks). None of the remaining 10 patients had received exogenous gonadotropin therapy for any prolonged period. Four of the 13 men had had cryptorchid testes. In all but 1, both testes were scrotal before the initiation of our study. Three of the 4 had had orchopexies with simultaneous herniorrhaphies, and the fourth was treated prepubertally with a short course of hCG.

Laboratory evaluations

Serum FSH, LH, and T were measured by RIA (10). Assay sensitivity for LH was either 1.0 mIU Second International Reference Preparation (2nd IRP)/ml or 0.2 mIU First IRP (1st IRP)/ml. For FSH, the sensitivities were either 25 ng/ml LER 907/ml or 0.2 mIU 1st IRP/ml. The normal range for T was 280–1440 ng/dl. All samples for each patient were analyzed in the same assay.

Seminal fluid was collected by masturbation after at least 48 h of abstinence and sent to our laboratory through the mail. All samples were analyzed for volume, sperm concentration, and germ cell morphology. Sperm concentrations greater than 10 million/ml were analyzed with a Coulter counter (Coulter Electronics, Hialeah, FL) (11). When the concentration was lower, a hemocytometer technique was used. Before a sample was defined as azoospermic, 15–20 fields were examined in both a wet drop preparation and a centrifuged, fixed, and stained preparation.

Hamster egg sperm penetration assays were performed in four of the men (A, C, H, and I) (12). The fertile range was greater than 15% penetration.

Protocol

Patients were initially treated with im hCG (Profasi, Serono, Braintree, MA). Twelve received 1500–2000 IU, and 1 (E) received 4000 IU three times a week for 3–24 months. In 12 of the men, human menopausal gonadotropin (hMG; Pergonal, Serono), containing 75 IU FSH and 75 IU LH, then was added to the hCG, and both preparations were given 3 times weekly for an additional 4.5–11 months. At the end of the first course of hCG/hMG, 7 men continued to receive hCG alone for 5–36 months; 4 men then received a second course of hMG plus hCG. The dose of hMG was reduced by 50% during this period in 3 of these men (A, D, and F). All injections were self-administered by the patients at home.

At least three serum samples for LH, FSH, and T determinations were collected at 20-min intervals or on separate days either before therapy was begun or after an interval of no therapy of at least 1 month. Serum T was also measured 1 and 3 months after beginning hCG therapy and again after 3 months of hMG/hCG therapy. Single samples were drawn 4–48 h after the last dose of gonadotropins. Seminal fluid was examined at frequent intervals in all men during a baseline period and throughout therapy.

Testicular dimensions were measured with calipers before treatment and at each clinic visit during therapy. Testicular volume was estimated by the following formula: $V = 4/3\ \pi \left(\frac{a}{2}\right)^2\left(\frac{b}{2}\right)$, where a equals the short testicular axis, and b equals the long testicular axis (in centimeters). Volumes are expressed as the average of the 2 testicles. In 87 normal men, testicular volume calculated in this manner was 17.5 ± 0.7 (±SEM) ml (range, 8.5–47.8 ml) (Ley, S. B., C. A. Paulsen, G. Mozaffarian, M. Higley, and J. M. Leonard, in preparation).

Results

Pretreatment

Serum LH and FSH concentrations were undetectable in all patients. Baseline serum T concentrations (mean of at least three samples) and testicular volume are shown in Table 1. All patients had azoospermia on the first 3–24 seminal fluid specimens obtained, and only 1 man had less than 6 azoospermic samples before the appearance of sperm in his ejaculate.

Four men had testicular biopsies. Two HE patients and one patient with multiple deficits (patient K; Fig. 1) had immature seminiferous tubules and no Leydig cells. The single patient with acquired IGD had very few Leydig cells and only immature germinal elements.

Response to therapy

All 13 men responded to hCG with an increase in serum T into or above the normal range. After 3–5 months of hCG treatment, their serum T values ranged from 530–2490 ng/dl (mean, 866 ng/dl). The addition of hMG to hCG for 3 months further increased serum T in most men, with values ranging from 310–2580 ng/dl (mean, 1156). The values in previously cryptorchid men did not differ, ranging from 930–2580 ng/dl.

Twelve of the 13 men treated with hCG had an increase in testicular volume, as shown in Table 2, before the addition of hMG. The volume increased further in 11 of the 12 men during combined hCG and hMG therapy.

Serial testicular biopsies were obtained from one patient (K) with multiple pituitary deficits before treatment and after therapy with hCG and hMG (Fig. 1). There was both an increase in both seminiferous tubular diameter and the number and maturity of germinal cells.

Of the 13 men, 12 had sperm in their ejaculate after a variable period of therapy (Table 2). In 3 men, all with HE, sperm first appeared after treatment with hCG alone for 5–24 months; the maximal sperm concentrations during hCG therapy were 1.1, 13, and 6.5 million/ml. After hMG was added in 2 of these 3 men, sperm concentrations rose to 16.9 and 80 million/ml, respectively. The other 9 men remained azoospermic until after they had received combined hCG and hMG therapy for 0.5–9 months (mean, 5.0 months). Their maximal counts ranged from 1.0–107 million/ml, with those with multiple pituitary defects having the poorest seminal fluid response to treatment.

Of the 13 men, 7 were married and seeking fertility. Four of the 7 men who desired fertility achieved sperm concentrations greater than one million/ml. Of these, 2 fathered a total of 3 children. In spite of normal sperm penetration tests (24%, 21%, and 35% penetration), a third man (C) has not successfully impregnated his apparently normal wife. The fourth man, who had a maximal sperm count of 3.6 million/ml also was unable to achieve a pregnancy, but his sperm count was above one million/ml for only 4 months before completion of the protocol. Withdrawal of hMG led to a rapid return to azoospermia.

hCG, second course

Five men (A, C, G, I, and J) who achieved sperm counts greater than one million/ml during the therapy described continued to receive hCG alone for 5–31 months. During this period, 4 of the 5 had further significant increase in sperm density. One of these men (J) fathered his second child 28 months after stopping hMG during continued hCG therapy. Patient A, who did not maintain sperm in his ejaculate after hMG was discontinued, was 1 of the 3 men with HE who had originally responded to hCG alone. Regression of spermatogenesis may have been due to poor compliance, as he admitted missing one third to one half of his hCG injections during this latter period.

Two additional men did not have more than one mil-

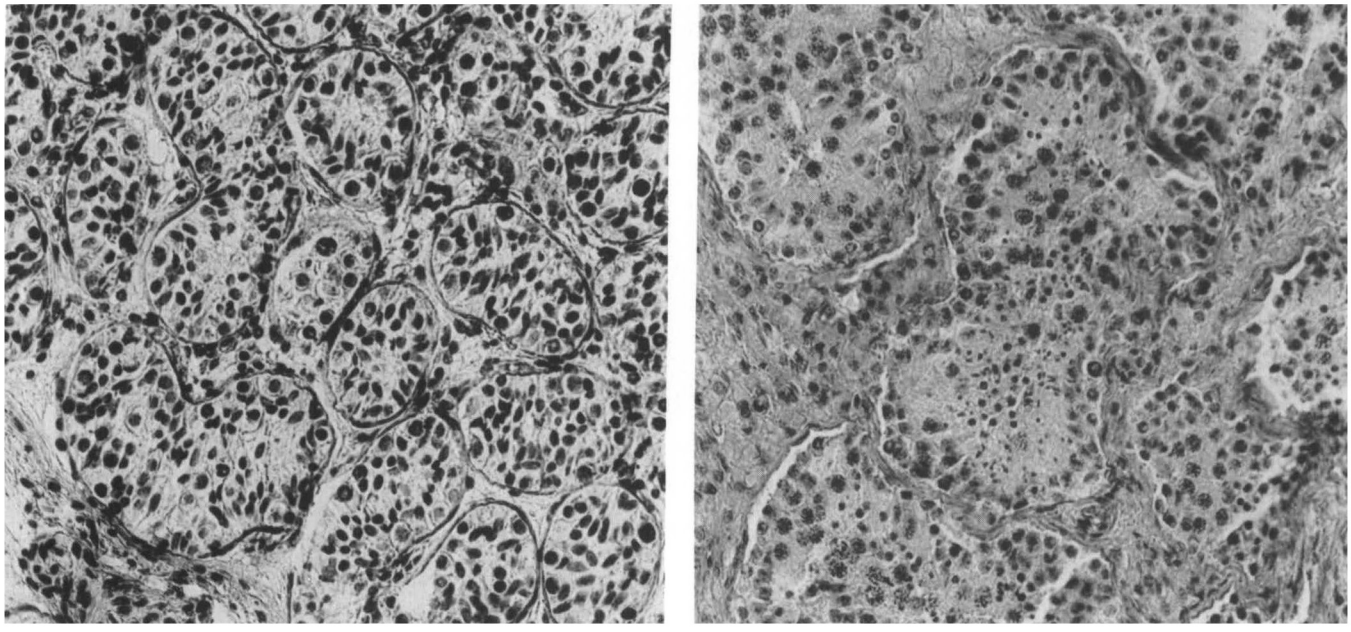

FIG. 1. Testicular biopsies (×64) before (*left*) and during (*right*) treatment with hCG and hMG (patient K). Note the marked increase in the seminiferous tubular diameter, the number and maturity of germinal cells, and interstitial cellularity in response to therapy.

TABLE 2. Hypogonadotropic men: results of treatment

Patient	Therapy (months)			Testis volume			First Spermato-zoa (months)	Max. count ($\times 10^6$/ml)
	hCG	hCG + hMG	Total	Baseline	After hCG	After hCG + hMG		
A[a]	32	4	36	1.0	2.7	3.6	24	16.9
B	13		13	2.4	5.3[b]		5	13.0
C[a]	11	7	18	2.4	7.2	7.7	8	59.0 (123)[c]
D	6	10	16	1.5	4.0	8.4	13	0.2 (2.4)
E	16	11	27	2.0	2.0	2.0	20	5.2
F	7	9	16	0.7	2.3	3.7	13	0.1 (0.1)
G	6	10	16	4.1	4.7	9.0	11	1.3 (3.6)
H	6	9	15	2.1	2.0	3.4		0
I[a,d]	5	9	14	5.1	7.6	9.5	6	7.4 (10.0)
J[d]	3	9	12	7.9	10.4	12.5	4	64.0 (107.0)
K	8	10	18	0.6	2.6	4.9	12	1.0 (0.3)
L	7	10	17	4.7	5.6	6.9	8	1.0
M	6	8	14	3.1	7.0	7.3	12	1.0

[a] Positive sperm penetration assay.
[b] Volume after 1 yr of hCG.
[c] Values in parentheses are the subsequent maximal count obtained with further therapy (see text).
[d] Pregnancy.

lion sperm/ml during the first courses of hCG and hCG/hMG. After discontinuing hMG, they were treated with hCG alone for 5 months. Neither of these men had any further increase in the number of ejaculated sperm.

Finally, patient B, who was not treated with hMG, continued to have sperm densities between 7 and 13 million/ml for 53 months.

hCG and hMG, second course

Four men (A, D, F, and I) were treated with a second course of hCG and hMG. Patient I had a further increase in sperm density, and 5 months after restarting hMG, he impregnated his wife. His maximum sperm count was 10.0 million/ml. Several months later, while treated with hCG alone, he had a positive sperm penetration assay (21% penetration) and a simultaneous density of 7.0 million sperm/ml. A second patient (D) also increased his sperm density during the second course of hMG, and after 8 months, it was 2.4 million/ml. This was a marked increase compared to that during his first course of therapy, but a sperm penetration assay performed at this point was negative. A third patient (A) was described

above. During the second course, he returned to his original level of sperm production, and at a sperm density of 2.5 million/ml, had a clearly positive sperm penetration assay (37% penetration). The fourth man (F) did have an increase in sperm production during the second course of hMG.

Prognostic factors

Previous androgen therapy. We analyzed the response of seven of the eight men with HE (Table 1) to determine the effect of previous androgen therapy on subsequent response to exogenous gonadotropins. The eighth man was excluded because he had bilateral undescended testes and idiopathic Addison's disease. Three of the men had not received any previous therapy and were prepubertal or peripubertal when first examined at 19, 21, and 31 yr of age, respectively. Their initial hormonal therapy was, therefore, the hCG administered in this protocol.

Four of the men had been treated with androgens (T enanthate or T cypionate, 200 mg every 2 weeks) for 60–96 months before beginning treatment with hCG. One of these men had also received hCG for 18 months 8 yr previously, but had since been treated only with T enanthate. These four men were sexually mature, except for small testes, at the time of our study. Comparing Leydig cell response, as measured by serum T levels, after 1 and 3 months of hCG treatment, there was no difference between these two groups (Fig. 2).

Previous androgen therapy also had no negative effect on seminiferous tubular response, as determined by the

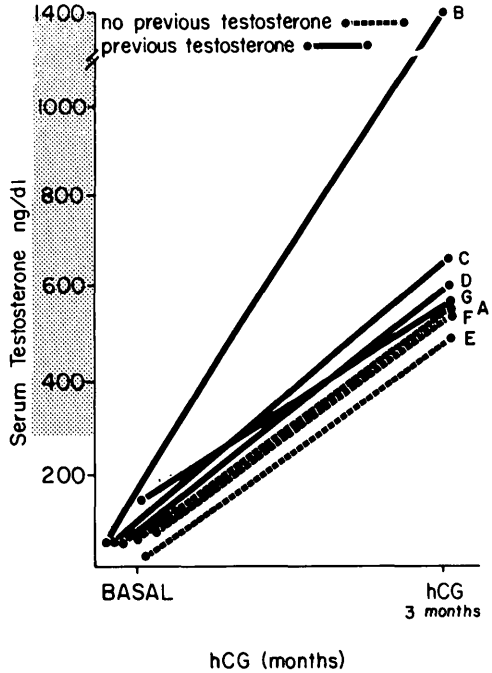

FIG. 2. Serum T responses to hCG in hypogonadotropic hypogonadal men who had (patients B, C, D, and G) and had not (patients A, E, and F) received previous T treatment.

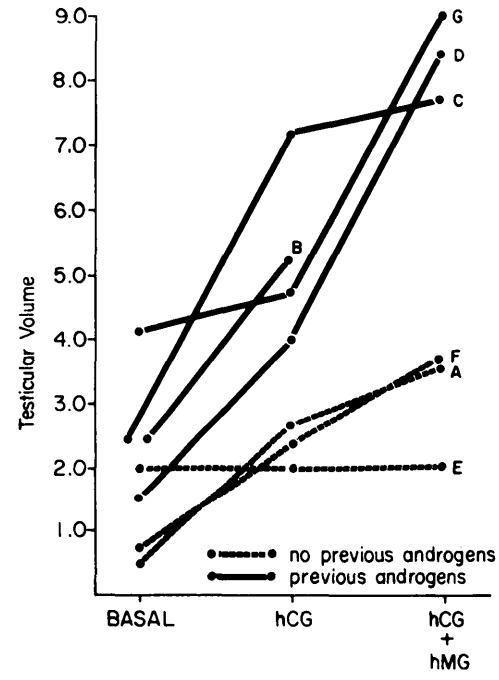

FIG. 3. Changes in testicular volume (milliliters) after therapy with hCG and then hCG and hMG in hypogonadotropic hypogonadal men who had and had not received previous T treatment.

change in testicular volume, the time to appearance of first sperm in the ejaculate, and the maximal sperm count achieved. The changes in testicular volume during therapy are displayed in Fig. 3. The time to appearance of first ejaculated sperm and the maximal count obtained are detailed in Table 2.

Fertility was a goal for only one of the androgen-pretreated men, patient C. He achieved a sperm density greater than 5×10^6/ml. He has so far not had a child, but as stated above, both he and a second androgen-pretreated patient had fertile sperm penetration tests.

Other factors. Men with multiple pituitary defects or cryptorchidism had the least response to treatment (Table 2). Those with postpubertally acquired isolated gonadotropin deficiency had the best response in terms of both sperm density and proven fertility. No other factor, including initial serum T level, initial testis volume, age, or the presence or absence of anosmia, correlated with the likelihood of response.

Toxicity. There were no adverse reactions during the course of drug therapy with either hCG and/or hMG, except for moderate acne in two patients.

Discussion

Patients with hypogonadotropic hypogonadism have been treated with exogenous gonadotropins (1–6) and pulsatile LHRH (7–9). The potential for testicular response to these therapies appears to be good (13). Our

results with 13 consecutive prospectively treated patients confirm these impressions and provide further information on prognostic factors, including prior androgen therapy, which might alter the response to therapy.

Of the 13 hypogonadotropic hypogonadal men treated, administration of hCG normalized serum T in all. After initial treatment with hCG, subsequent addition of hMG led to a further increase in serum T, an effect also found by Sherins *et al.* (6) in 9 HE men. In animals, FSH augments hCG-stimulated T production in hypophysectomized rats (14) and in *in vitro* preparations of rabbit testes (15), an effect perhaps mediated through an increase in Leydig cell LH receptors (16). We found no decrease in T responses in the men with cryptorchidism. Although cryptorchid patients may have compromised testicular steroid synthetic capacity, this difference disappears during prolonged hCG treatment (17).

All but one of our patients had an increase in testes volume during treatment, although testicular volume was not a good predictor of outcome or course of therapy. Final testicular size was low compared to that in normal men (Ley, S. B., C. A. Paulsen, G. Mozaffarian, M. Higley, and J. M. Leonard, in preparation), but 11 of the 13 patients continued to have testicular growth during the study period. All men were initially azoospermic. The only patient who did not develop sperm in his ejaculate during therapy had undescended testes.

Two of the seven married men seeking fertility fathered normal infants. Four unmarried patients also were probably fertile. Two had normal sperm penetration assays, which are highly correlated with male fertility (12), and two more achieved sperm densities of 13 and 5.2 million/ml. It is important to stress that accepted norms for seminal fluid sperm concentration may not be relevant in evaluating fertility in these patients (4). Patient I initiated a pregnancy while sperm concentrations ranged between 6.5 and 10.0 million sperm/ml. He and two other patients also had positive sperm penetration assays when their sperm densities were 7.0, 2.5, and 11.0 million sperm/ml.

Three patients developed sperm during hCG treatment alone, and 2 additional patients had sperm in their ejaculates within 1 month after addition of hMG therapy. In a previous series (6), 11 of 13 men with HE developed mature sperm in the ejaculate within 1 yr of starting hCG as the only therapy; other researchers (18) reported similar patients. hCG alone was also able to sustain spermatogenesis in our patients and in several others reported previously (3, 4, 6, 19). Because the FSH activity of hCG is probably insignificant (<0.001 IU/IU hCG) (20), this response implies that endogenous FSH was present, but in concentrations below current detection limits. This hypothesis is supported by data from Kulin *et al.* (21), who reported a wide variation of urinary gonadotropin values in hypogonadal patients whose serum gonadotropin levels were undetectable. Specifically, in patients with undetectable serum FSH, urinary gonadotropin values were detectable over a 20-fold range. In another report, Boyar *et al.* (22) described 2 patients who had measurable serum LH only during nocturnal spikes. All of our patients had undetectable serum FSH on multiple samples analyzed by RIA. Since those patients who developed sperm in their ejaculate during hCG treatment alone also achieved the highest sperm concentrations, the response to hCG may have prognostic significance.

Our study design allowed us to assess the commonly held impression that prepubertal androgen therapy causes irreversible testicular damage in hypogonadotropic patients. We found no evidence to support this. Initial testis volumes were generally higher in the androgen-pretreated patients. All three men who developed sperm in their ejaculate after hCG therapy alone had previously received T for 2–96 months. Leydig cell potential, as measured by acute and chronic T responses to hCG/hMG, and germ cell responses, as reflected by changes in testicular volume, time to appearance of sperm in the seminal fluid, and maximal sperm concentrations, were not decreased by previous androgen therapy. The lack of effect of androgen pretreatment is supported by other reports in hypogonadal men (3, 23), by the use of Testosterone rebound as a therapy for infertility (24, 25), and by the use of T enanthate as a reversible form of male contraception (26, 27).

Cost and convenience factors favor the T esters, and they are the preferable mode of therapy in hypogonadotropic men until fertility becomes a goal. The major use for either hCG/hMG or pulsatile LHRH is the induction of fertility. Although both therapies are effective, their relative efficacies have not been directly compared. A recent report suggests that response rates are similar (9). LHRH treatment requires that patients wear an infusion pump throughout the day. Because hCG/hMG therapy requires only three or fewer injections a week, gonadotropin therapy is likely to be preferred by many patients. As it is probable that even lower doses of hCG (28, 29) and hMG (6) may be effective, further studies designed to optimize dose and injection schedules may further increase this advantage.

In summary, hypogonadotropic men can be treated effectively and safely with T esters until they desire fertility. We then recommend hCG alone; an early response to this medication probably has prognostic value. From our results and those of others, it seems prudent to treat with hCG alone for 1 yr, or until testicular volume reaches a plateau. Then hMG should be added. Cryptorchidism and prepubertally acquired multiple pituitary defects were negative prognostic factors, whereas

patients with gonadotropin deficiency acquired postpubertally responded quickly and dramatically. Androgen pretreatment did not have a negative effect on outcome. As long as testicular volume continues to increase, therapy should be continued. In some patients, induction of fertility may occur in a matter of months. In others, increased sperm counts may not be obtained for 1–2 yr or longer.

Acknowledgment

Serono Laboratories, Inc. (Braintree, MA), generously donated the hMG used in this study.

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