Data on Virilization and Erotosexual Behavior in Male Hypogonadotropic Hypopituitarism During Gonadotropin and Androgen Treatment

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The goal of this investigation was to assess whether or not gonadotropin therapy enhanced the degree of virilization and psychosexual behavior of men with hypogonadotropic hypopituitarism. Pre- and post-gonadotropin assessments of virilization in four men indicated that gonadotropin therapy was associated with dramatic improvements in the degree of virilization that each man previously obtained on androgen only. Retrospective interview data on erotosexual behavior indicated improved erotosexual function on gonadotropin as compared to the prior androgen treatment. These data suggest that complete virilization in these men was partially gonadotropin dependent. Whether or not the behavioral benefits reported by these men represented a direct or synergistic effect of gonadotropin in the expression of erotosexual behavior or an indirect effect of improved virilization can not be answered by these data.

Key words: Gonadotropin, hCG, hMG, virilization, beard growth, sexual behavior, hypogonadotropism, hypopituitarism.

Men with congenital or childhood onset hypogonadotropic hypogonadism report dissatisfaction with their degree of virilization after treatment with exogeneous testosterone (Clopper, unpublished dissertation data). Many of these patients also lack GH and some have deficiencies of ACTH and TSH as well. For these hypogonadotropic hypopituitary individuals, the primary emphasis of treatment during adolescent years is to maximize height with GH therapy. As a result, testosterone treatment frequently is initiated late in adolescence. However, years of testosterone replacement leave these men with persisting concerns about their lack of beard growth, scant axillary and body hair, and a misleading boyish appearance (Money and Clopper, 1975; Money et al, 1980; Clopper et al 1981; MacGillivray et al, 1981).

Behavioral studies of hypogonadotropic hypopituitary males (Money and Clopper, 1975; Lundberg and Wide, 1978; Money et al, 1980) suggest that these men experience delayed onset of adult sexual and erotic behavior and may also exhibit low frequencies of sexual behavior that persist into the third and fourth decade of life despite years of testosterone replacement. In contrast, men with hypergonadotropic hypogonadism virilize well on testosterone therapy and achieve apparently normal adult levels of sexual interest and behavior when testosterone administration is introduced (Money and Alexander, 1967). These observations suggest that the effectiveness of testosterone treatment in androgen deficient males may be partially gonadotropin dependent.

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The goals of this research were to determine whether gonadotropin treatment would enhance the degree of virilization and improve the psychosexual status of men with hypogonadotropic hypopituitarism. This report presents the physician-observed and patient-perceived advantages of gonadotropin over androgen therapy in four of these patients.

Materials and Methods

Subjects

Four males, two with idiopathic and two with post-surgical hypopituitarism volunteered for gonadotropin treatment. Their age range was 15 to 30 years. Three had received six to ten years of intramuscular testosterone enanthate (200 mg) every two to three weeks. Gonadotropin treatment was started in the youngest participant at 15 years of age because of dramatic benefits documented in the older patients. He had received Halotestin® 5 to 10 mg per day for the two previous years.

A summary of the endocrine status of the four participants is given in Table 1. All were deficient in GH, ACTH, TSH, FSH and LH. The two men with craniopharyngiomas were also vasopressin (ADH) deficient. PRL concentrations were normal in all males. Table 2 contains data pertaining to the treatment schedule with GH, androgen, human menopausal gonadotropin (hMG), and hCG, thyroid, cortisone, and ADH for each man.

Treatment

Gonadotropin therapy was begun one to two months after cessation of androgen treatment. The regimen consisted of 2,000u hCG (in 0.2 ml diluent) and one vial hMG (in 1.0 ml diluent) given as a single intramuscular injection three times weekly. Therapy with L-thyroxine (3μg/kg/day), hydrocortisone (10 mg/m^2/day), and arginine vasopressin (50 μl bid intranasally) were continued throughout the period of gonadotropin treatment.

Physical examinations and biochemical measurements (testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone sulfate, 17 hydroxyprogesterone) were performed prior to, and every two to three months during, gonadotropin treatment. Plasma steroids were assayed by the methods described by Peterson et al (1977). Semen specimens from the three older patients were analyzed. Self-report data of erotosexual behavior during androgen and gonadotropin therapy were retrospectively obtained using a standard personal interview protocal towards the end of the gonadotropin treatment period.

Results

Physical Findings

Table 3 is a summary of the physician ratings of the degree of virilization observed in each man at the end of his initial treatment with androgen (A) and following the period of gonadotropin therapy (Gn). The main benefits of androgen treatment were pubic hair growth, voice deepening, and phallic enlargement. Facial, body, and extremity hair was scant or absent in all patients. Testicular volumes were pre-pubertal prior to and throughout androgen therapy.

Within six to 12 months of starting gonadotropin therapy, marked improvements were observed in the growth of beard, as well as axillary, gential, perigenital, body, and extremity hair. All men had a more mature masculine appearance. Figures 1–4, respectively, illustrate the changes in axillary hair, perigenital hair, body hair, and beard growth which occurred on gonadotropin treatment. Testis volume increased significantly in all patients (Table 3). Some variability in the degree of virilization among the participants was observed during both the gonadotropin and the androgen treatment periods.

Mild gynecomastia (≤3cm) developed in three of the men during gonadotropin treatment. However, it resolved following a 50 percent reduction of the hCH dose.

Plasma steroids

During testosterone enanthate treatment, the three older patients had normal plasma levels of

TABLE 1. Description of Sample: Pituitary Hormone Status, Etiology of Endocrine Deficits and Age at the Initiation of Gonadotropin

Case	Age	Etiology	GH	TSH	ACTH	FSH	LH	PRL	ADH*
1	15	congenital	●	●	◇	●	●	N	N
2	23	congenital	●	◇	◇	●	●	N	N
3	23	organic (tumor)	●	●	●	●	●	N	◇
4	30	organic (tumor)	●	●	●	●	●	N	●

* Antidiuretic hormone

● = complete deficit, treated. ◇ = slight deficit, variably treated. N = normal, not treated.

TABLE 2. History of Endocrine Treatment at Last Follow-up
AGES OF HORMONE TREATMENT

Case	Growth Hormone	Androgen*	Gonadotropin†	Thyroid	Cortisone	Antidiuretic Hormone
1	5–16	14–15	15–17	9–17	None	None
2	7–18	16–23	23–25	18–25	None	None
3	10–17	17–23	23–25	9–25	11–25	11–22
4	17–20	20–30	30–32	17–32	17–32	23–32

* Cases 2–4 received testosterone enanthate 200 mg/every two to three weeks while case 1 received Halotestin® 5–10 mg/day.
† Gonadotropin treatment in all cases consisted of combined treatment with hCG (2000 μ) and hMG (1 vial containing 75 IU of LH and 75 IU of FSH) 3×/week.

testosterone (T;574–800 ng/dl) and dihydrotestosterone (DHT; 55–99 ng/dl). Their concentrations of androstenedione (Δ4), dehydroepiandrosterone sulfate (DHEAS) and 17 hydroxyprogesterone (17-OHP) were in the pre-pubertal range.

Table 4 provides data on the concentrations of T, DHT, Δ4, DHEAS, and 17-OHP during the baseline (B) period and the gonadotropin (Gn) treatment period. The baseline levels of these steroids were obtained one to two months after cessation of androgen administration. At that time, all steroid concentrations were in the pre-pubertal range. Following gonadotropin therapy, the plasma concentrations of T, DHT, Δ4, DHEAS, and 17-OHP increased significantly. In fact, all post-gonadotropin concentration of these steroids, except for DHEAS, were in the normal adult range.

Semen Analysis

Sperm counts were performed on three patients during gonadotropin treatment. The results of the

TABLE 3. Physician Ratings of Virilization for Four Men With Hypogonadotropic Hypopituitarism Treated With Gonadotropin (Gn)* After Androgen (A)† Treatment

Characteristic	Case 1	2	3	4
Beard Growth				
Post A	P	P	P	+
Post Gn	+ + +	+ + +	+ + + +	+ + + +
Pubic Hair				
Post A	T_2	T_4	T_5	T_4
Post Gn	T_5	T_5	T_{5+}	T_5
Axillary Hair				
Post A	P	P	P	P
Post Gn	T_5	T_5	T_5	T_5
Chest Hair				
Post A	P	P	P	P
Post Gn	+ + + +	+ + +	+ + +	+ + + +
Perianal and Inner Thigh Hair				
Post A	P	P	P	P
Post Gn	+ + + +	+ + +	+ + +	+ + +
Hair on Extremities				
Post A	+	+	+	P
Post Gn	+ + +	+ + +	+ + +	+ + +
Testicular Volume‡				
Post A	1;1	3;3	3;3	4;4
Post Gn	8;15	10;12	25;25	20;20

* Combined hCG (2000 u) and hMG (75 IU each of LH and FSH) 3×/week.
† Cases 2–4 had 200 mg TE every two to three weeks; case 1 had 5–10 mg Halotestin®/day.
P = Prepubertal.
+ = Ordinal rating of increase over prepubertal state.
T_x = Tanner stage X.
‡ Estimated testicular volumes according to Prader (right;left testis).

Fig. 1. Axillary hair growth in a man with hypogonadotropic hypopituitarism (case 1) after 17 months of Halotestin® therapy (5–10 mg/day) (A, left axilla) followed by 15 months of therapy with combined hCG (2000u) and hMG (1 vial containing 75 IU each of LH and FSH) 3×/week (B, right axilla).

semen analyses are given in Table 5. Each sample was analyzed within 1 hour of semen collection. The period of abstinence is unknown in all cases.

Self Report Data

All men reported that androgen therapy provided increased density of pubic hair, phallic enlargement, and voice deepening, but that it did not stimulate hair growth in the facial, axillary, chest, abdomen, and perianal areas. Their observations were in agreement with physician assessments.

Table 6 summarizes the perceived benefits of gonadotropin therapy reported by the patients. All men noted improved growth of beard and body hair and increased testicular volumes. Patient and physican assessments of these characteristics were in agreement. Three men also perceived an increased penis size which was not confirmed by physician measurement. The increase in testicular volume was considered by all patients to be an important benefit of gonadotropin therapy.

All four men also self-rated their libido and self-confidence in social, as well as sexual situations, as significantly increased during gonadotropin treatment over and above what is was during the androgen treatment period (Table 6). Furthermore, the cyclic waxing and waning of their interest in sex, which the three testosterone treated men had noted during their androgen treatment, no longer occurred after beginning gonadotropin. This, too, was cited as a benefit of the gonadotropin regimen.

The reported increase in libido after gonadotropin treatment is consistent with self-report data given by each man on the average weekly frequency of ten types of erotosexual behavior during the two treatment periods (Table 7) and with data

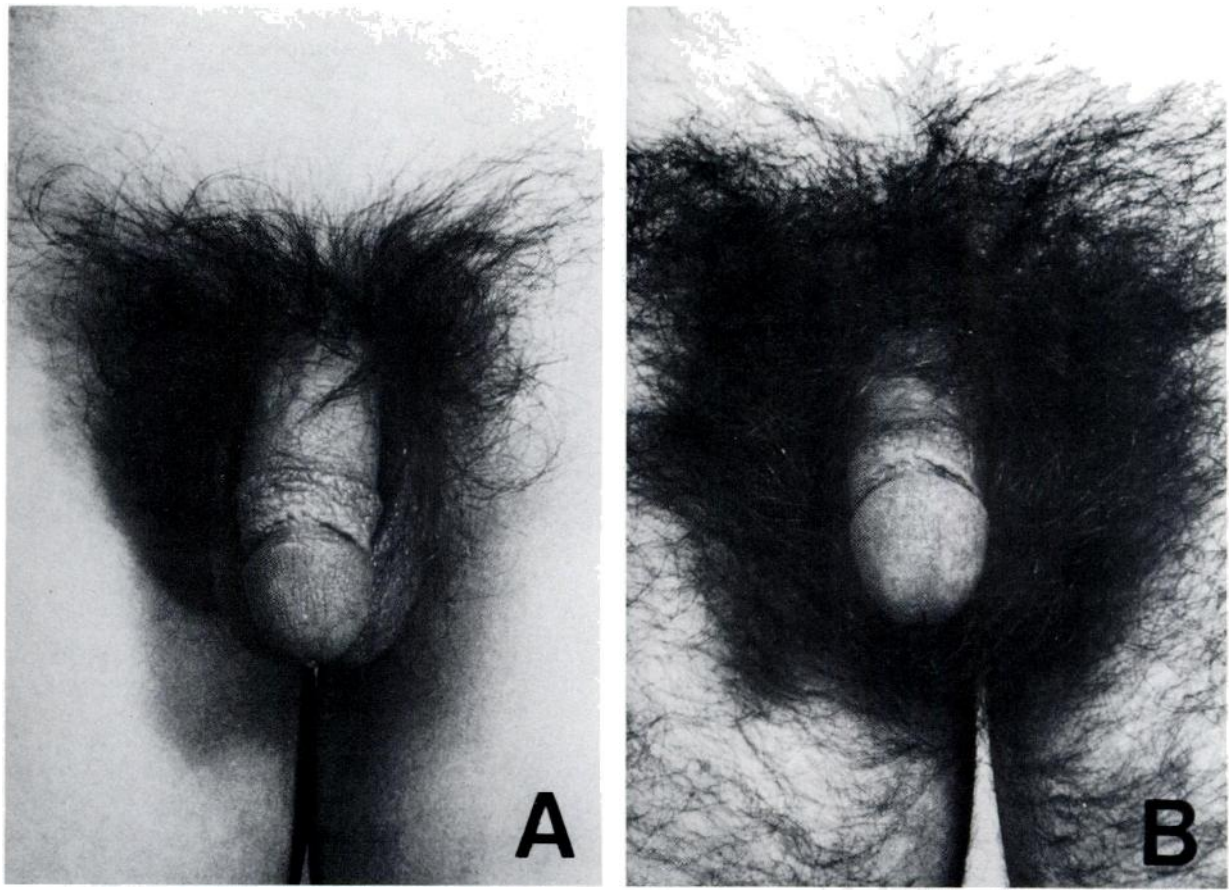

Fig. 2. Perigenital hair growth in a man with hypogonadotropic hypopituitarism (case 3) after six years of testosterone therapy 200 mg TE/once every two to three weeks (A), and after 15 months of therapy with combined hCG (2000u) and hMG (1 vial containing 75 IU each of LH and FSH) 3×/week (B).

on the onset of these behaviors. While each man reported the onset of several types of erotosexual behavior other than erection during androgen treatment, each man also reported the onset of additional types of erotosexual behavior after beginning gonadotropin. For all men, the reported onset of erection was in childhood prior to treatment with either androgen or gonadotropin. Table 7 gives each man's estimate of his average weekly frequency of 10 types of erotosexual behavior during the two treatment periods. The last two columns in this table summarize the number of cases with any experience of each behavior and the number of experienced cases reporting their highest average weekly frequency estimate for the gonadotropin treatment period. For each behavior, the majority of experienced men reported a higher frequency estimate for the gonadotropin treatment period than for the androgen treatment period.

All patients expressed a preference for the gonadotropin regimen over the androgen protocol. This was true in spite of the fact that the gonadotropin regimen required injections three times per week compared to an injection of androgen every two to three weeks. Two men (cases 2 & 3) who were changed back to testosterone injections after two years of gonadotropin administration have recently requested resumption of gonadotropin treatment.

Discussion

Our data suggest that gonadotropin therapy is more effective than testosterone treatment for virilizing young men with childhood onset hypogonadotropic hypopituitarism. Despite three to ten years of intramuscular testosterone administration, our three older patients remained under-

Fig. 3. Abdominal hair growth in a man with hypogonadotropic hypopituitarism (case 1) after 17 months of Halotestin® therapy (5–10 mg/day) (A) and after 21 months of therapy with combined hCG (2000u) and hMG (1 vial containing 75 IU each of LH and FSH) 3×/week (B).

masculinized. Within six to 12 months of starting gonadotropin treatment, dramatic improvement in all aspects of virilization was achieved. The benefits occurred even though these patients were 23 to 30 years old at the onset of gonadotropin therapy. Additional advantages of gonadotropin treatment included testicular enlargement and sperm production. The youngest patient exhibited an equally excellent response to gonadotropin administration and was fully virilized by the age of 17 years. Consequently, we recommend that consideration be given to starting gonadotropin therapy in the mid to late adolescent years in similar patients in order that age-appropriate sexual maturation can result. The height status of each GH deficient patient will be an important factor in this decision.

The androgen therapy received previously by our patients was probably not a significant factor in influencing the efficacy of gonadotropin therapy since normal puberty is characterized by increasing levels of gonadotropin production followed by appropriate increments in testosterone secretion. This question, however, deserves further investigation.

Studies in the rat have shown that prior FSH exposure enhances the testosterone response to LH (Odell and Swerdloff, 1976). This sequence of therapy was not a prerequisite for complete virilization in our patients since they were given hCG and hMG simultaneously. In fact, the pace of virilization was equal to or more rapid than that seen in normal puberty. It is possible that similar degrees of virilization would have occurred with

Fig. 4. Beard growth in a man with hypogonadotropic hypopituitarism (case 3) after 65 months of testosterone therapy 200 mg TE every two to three weeks (A), and after five months of therapy with combined hCG (2000u) and hMG (1 vial containing 75 IU each of LH and FSH) 3×/week (B).

hCG alone albeit without improvement in testis volume or sperm production. If this is the case, the cost of treatment would be markedly reduced.

The data regarding behavioral changes in our patients during gonadotropin treatment are as impressive as the data on physical changes. Androgen, principally testosterone, is considered a major activator of sexual behavior in men and

TABLE 4. Plasma Levels and Normal Values (ng/dl) for Five Steroids After Discontinuing Androgen (B*) and While on Gondadotropin Treatment (Gn)†

	T		DHT		Δ4		DHEAS		17-OHP	
Case	B	Gn	B	Gn	B	Gn	B	Gn	B	Gn
1	1	446	1	80	21	125	2	48	12	90
2	14	340	7	106	13	200	14	134	12	410
3	5	338	1	146	‡	79	47	61	10	150
4	14	360	‡	92	23	95	5	40	26	190
Normal	300–1000		30–80		50–150		100–350		100–200	

* B = baseline.
† Gn = after GH treatment.
‡ Missing data.

TABLE 5. Semen Analysis Data for Three Men during Gonadotropin Treatment

	Case		
	2	3	4
pH	7.5	7.5	8.5
Volume	3 ml	.3 ml	3 ml
Count	24×10^6	24.4×10^6	7.6×10^6
% Motility	90	58	82
% Abnormal Forms	13	7	9

TABLE 6. Perceived Benefits of Gonadotropin* Treatment Over and Above the Benefits of Androgen† Treatment

Reported Benefit	Number of Cases Reporting Improvement on Gonadotropin (N = 4)
↑ Beard growth	4
↑ Axillary hair	4
↑ Body hair	4
↑ Perianal hair	4
↑ Testis size	4
↑ Penis size	3
↑ Libido	4
↑ Self-confidence	4

* Gonadotropin treatment consisted of combined treatment with hCG (2000u) and hMG (1 vial containing 75 IU each of LH and FSH) 3×/week.

† Three cases received testosterone enanthate (200 mg every two to three weeks) while one case received Halotestin® (five–ten mg/day).

↑ = increase over improvement perceived on androgen.

women (Rubin et al, 1981). While the men in this study reported some increase in libido and sexual behavior on the androgen regimen, additional improvements in erotosexual behavior occurred for all men after beginning gonadotropin. This enhancement of erotosexual behavior during gonadotropin treatment remains unexplained. It is possible that the improvement in virilization in our men led to improved self-esteem, self-confidence, and mood, which, in turn, enhanced the expression of their erotosexual behavior. Perhaps their improved virilization enhanced their acceptability to others as potential sexual partners, thereby creating more opportunities for erotosexual activity. Alternately, the gonadotropin treatment might have had some direct neuroendocrine effect which enhanced the erotosexual behavior of these men. The present data are insufficient to evaluate these alternatives. More objective data on changes in the sexual responsiveness of these men, such as

TABLE 7. Self-report Data on the Average Weekly Frequency* of Ten Types of Erotosexual Behavior During Androgen (A)† and Gonadotropin (Gn)‡ Treatment

	Case								Number of Cases	
	1		2		3		4			
Type of Treatment	A	Gn	A	Gn	A	Gn	A	Gn	With Any Experience Ever	With Highest Frequency on Gn
Average Weekly Frequency										
Erection§	1	7	2.5	10.5	2.5	5.5	10.5	20	4	4
Ejaculation	NE	1	2	5.5	2.5	2.5	3.5	5	4	3
Masturbation	NE	1	1	7	.04‖	.02‖	3.5	5	4‖	3
Dating	NE	1	.04	2.5	?	7	NE	.04	4	3¶
Necking	NE	.5	.02	.05	2	3.5	NE	.04	4	4
Petting	NE	NE	NE	.04	1	2.3	NE	NE	2	2
Intercourse	NE	NE	NE	NE	.04	.25	NE	NE	1	1
Erotic Wet Dreams	NE	NE	.25	.5	NE	.38	?	7	3	2¶
Erotic Dry Dreams	NE	NE	2.5	4.5	NE	.63	NE	7	3	3
Erotic Day Dreams	NE	NE	7	12	NE	NE	?	3.5	2	1¶

NE = no experience reported.

? = missing data.

* Weekly frequency = reported number of times per time period ÷ by number of weeks in time period, e.g. once a month = 1 ÷ 4 = .25.

† Subject 1 had 5–10 mg/day Halotestin; subjects 2–4 had 200 mg TE every two to three weeks.

‡ Gonadotropin treatment combined hCG (2000 u) and hMG (1 vial containing 75 IU LH and 75 IU FSH) 3×/week.

§ Erection was the only behavior reported to begin in childhood (N = 4) prior to both androgen and gonadotropin treatment.

‖ Includes one man who masturbated only for sperm counts, no regular history.

¶ Incomplete data on one additional case.

data on spontaneous rates of nocturnal penile tumescence, would be helpful.

Information concerning the precise mechanisms responsible for the phenomenon of virilization in normal adolescent males is limited. Several investigators have suggested that GH and androgen act synergistically to produce enhancement of linear growth (MacGillivray et al, 1974) and virilization (Zachmann and Prader, 1970). In our gonadotropin treated hypopituitary patients, virilization proceeded without concurrent GH therapy. All men were deficient in adrenal androgens throughout both treatment protocols. Gonadotropin administration led to increased plasma concentrations of Δ4 and DHEAS. The rise of DHEAS after gonadotropin has been attributed to testicular secretion of this steroid (Laatikainen et al, 1971; DePeretti and Forest, 1978). The role of these steroids in the virilization process is unclear. Also, very little is known about testosterone kinetics after hCG, compared to testosterone injections. Testosterone concentrations may have been more consistently elevated with hCG than with testosterone therapy. The report of cyclical variation in libido while on testosterone, but not during gonadotropin treatment, appears to support this notion.

We are left with the observation that young men with severe gonadotropin deficiency beginning in childhood will not become fully virilized if testosterone is the only form of treatment. The dramatic benefits seen during gonadotropin therapy in our patients suggest that the process of complete virilization is gonadotropin dependent. Whether the gonadotropin directly or indirectly enhances the biological efficacy of the sex steroids or whether other mechanisms are involved in the process of male virilization needs further evaluation.

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