

## CLINICAL CASE SEMINAR

# Hypothyroidism-Induced Macroorchidism: Use of a Gonadotropin-Releasing Hormone Agonist to Understand Its Mechanism and Augment Adult Stature\*

JAN M. BRUDER, MARY H. SAMUELS, WILLIAM J. BREMNER,  
E. CHESTER RIDGWAY, AND MARGARET E. WIERMAN

*Department of Medicine, University of Colorado Health Sciences Center (J.M.B., E.C.R., M.E.W.), and Research Service, Veterans Affairs Medical Center (J.M.B., M.E.W.), Denver, Colorado 80220; the Department of Medicine, Oregon Health Sciences University (M.H.S.), Portland, Oregon 97201; and the Department of Medicine, University of Washington (W.J.B.), Seattle, Washington 98195*

The patient was an 18-yr-old male when referred for evaluation of short stature and delayed puberty. He was born to a 36-yr-old female (5 ft, 6 in. tall). By report, he was not talking at the age of 3 yr and was placed in a special education class at age 5 yr. No early growth data were available. Failure to grow was noted at age 9 yr. He was later enrolled in a special education program through high school. After graduating, he lived in a group home. By report, his father was 175.3 cm (5 ft, 9 in. tall), and five brothers were taller than 182.9 cm (>6 ft).

At the chronological age (CA) of 18 yr, the patient was 133 cm (4 ft, 4 in.), with a height SD score of -6.6 (The height SD scores were determined using the standards of the National Center for Health Statistics, with the distance from the 50th to 15th percentile corresponding to 1.0 SD). Predicted height was 174.8 cm using the Bayley-Pinneau table for growth-delayed boys. His weight was 36.8 kg. Physical exam revealed a short male, who appeared younger than his stated age. His skin was ichthyotic, with multiple skin tags. He had puffy eyelids and decreased lateral eyebrows. The thyroid gland was approximately 25 g by palpation. Cardiovascular exam was significant for bradycardia. There was no gynecostasia. He had 2+ reflexes, with a delayed relaxation phase. Examination of the genitalia revealed adult-sized testes (normal, 12–25 mL). The right testis measured 15–18 mL, and the left 10–12 mL by comparison to the Prader orchidometer. Stretched phallus length was 3 cm. There was no pubic or axillary hair.

Laboratory evaluation revealed a hematocrit of 29% (normal, 42–54%). The creatine kinase was 1984 U/L (normal, 24–294), and cholesterol was 9.78 mmol/L (normal, <5.17). Baseline thyroid evaluation revealed a  $T_4$  level below 12

nmol/L (normal, 64–154), a  $T_3$  resin uptake of 18.9% (normal, 25–35%), and a TSH level of 950 mU/L (normal, 0.5–5). Thyroid antibodies were negative. FSH was 4.5 IU/L (normal, 1–15),  $\alpha$ -subunit was 16 pg/L (normal, 0.5–2.1), and LH was less than 1 IU/L (normal, 1–12). The mean bioactive FSH level was 4.53 IU/L (range, 2.53–5.93). The testosterone level was below 69 nmol/L (normal, 1040–3467). Dehydroepiandrosterone sulfate (DHEAS) was 43.4  $\mu$ mol/L (normal 217–1520). A PRL level was 44  $\mu$ g/L (normal, 1–10). A film of the left hand and wrist was compared to the Greulich and Pyle radiographic axis and revealed a bone age (BA) of 9 (Table 1). A lateral skull film documented a slightly enlarged sella of 13 mm. Direct molecular genetic analysis for FMR-1 mutation was negative for fragile X.

TRH and GnRH stimulation tests and frequent nocturnal blood sampling every 15 min for 6 h between 2200–0400 h were performed and assayed for FSH,  $\alpha$ -subunit, and LH levels. TRH stimulation (200  $\mu$ g) increased TSH 2.5-fold from 950 mU/L to a peak of 2,200 mU/L (data not shown). TRH also increased FSH from 4 to 6 IU/L and  $\alpha$ -subunit levels from 15 to 19 pg/L. TRH had no effect on LH levels (Fig. 1A). TRH also increased PRL levels from 26 to 81  $\mu$ g/L. GnRH administration (100  $\mu$ g) did not change the elevated FSH levels, but increased  $\alpha$ -subunit levels from 15 to 30 pg/L and caused a small prepubertal response of LH from 0 to 1.1 IU/L (Fig. 1A). Nocturnal sampling (Fig. 1B) showed pulsatile immuno- and bioactive FSH (four pulses per 6 h) and pulsatile  $\alpha$ -subunit levels (one pulse per 6 h). There were no LH pulses.

The patient was treated with levothyroxine ( $L-T_4$ , 0.05 mg), and the dose was titrated to 0.125 mg/day to normalize his TSH level. After treatment of his hypothyroidism, the hypothalamic-pituitary-gonadal axis was activated. After 9 months of  $L-T_4$  treatment at the CA of 19 yr, his BA increased from 9 to 10 yr (Table 1). Growth velocity was 11 cm/yr, and height increased to 140 cm (-5.4 height SD). Associated with thyroid hormone-mediated acceleration of skeletal maturation, the patient's predicted height decreased by 2.8 cm, to 172 cm. The left and right testes increased to 15 and 20 mL,

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Address all correspondence and requests for reprints to: Dr. Margaret E. Wierman, Veterans Administration Medical Center, Section of Endocrinology (111H), 1055 Clermont Street, Denver, Colorado 80220.

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**Table 1.** Characteristics of subject during hypothyroid, euthyroid, prepubertal, and pubertal states

	Hypothyroid prepubertal	Euthyroid pubertal	Euthyroid prepubertal	Euthyroid pubertal
CA (yr)	18	19	21	22
BA (yr)	9	10	12	15
GV (cm/yr)	N/A	11	5.5	11
Ht (cm)	133	140	152	168
Ht SD (cm)	-6.6	-5.4	-3.7	-1.3
PR ht (cm)	174.8	172	180.3	184.6
TV (ml)	Lt 10-12, Rt 15-18	15,20	18,20	30,30
T (nmol/L)	<69	1161	<69	1872

GV, growth velocity; HT, height; PR HT, predicted height; TV, testicular volume; T, testosterone.

respectively. TSH was 2.6 mU/L, FSH was 1.14 IU/L,  $\alpha$ -subunit was 0.54 pg/L, and LH was 1.21 IU/L. The mean bioactive FSH level was 5.45 IU/L (range, 4.45–6.92). The testosterone level was pubertal at 1161 nmol/L. PRL was 13  $\mu$ g/L.

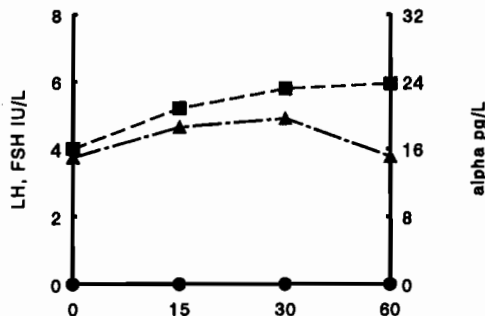
In contrast to the hypothyroid prepubertal state, in the euthyroid pubertal state, TRH administration did not in-

crease FSH levels, but caused a small increase in  $\alpha$ -subunit levels from 0.5 to 1.8 ng/mL. As before, TRH administration had no effect on LH levels (Fig. 2A). TRH also increased PRL from 4 to 26  $\mu$ g/L. GnRH testing did not affect FSH, but resulted in an increase in  $\alpha$ -subunit from 0.7 to 2.5 pg/L, and a pubertal increase in LH from 1 to 5 IU/L (Fig. 2A). Nocturnal sampling showed a pulsatile FSH

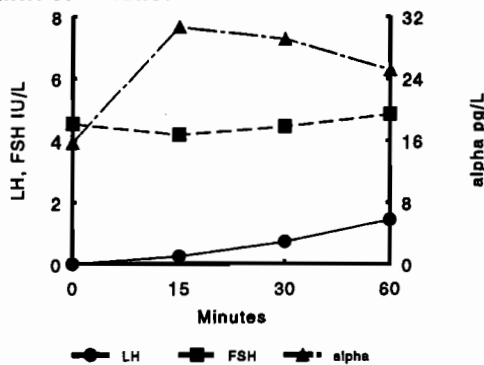
## A) HYPOTHYROID PREPUBERTAL

CA=18yrs      TV=10-12&15-18ml  
BA=9yrs      testosterone=<69nmol/L  
GV=7cm  
HT=133cm(-6.6SD)      PR.HT=174.8cm

### TRH stimulation

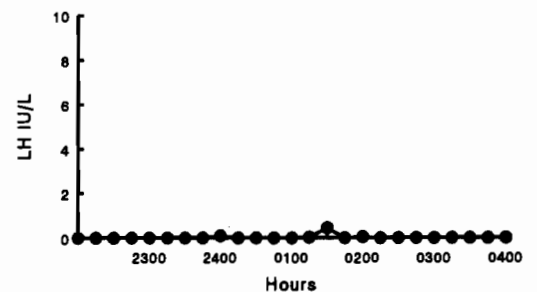
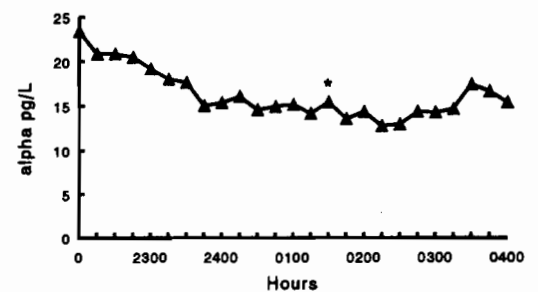
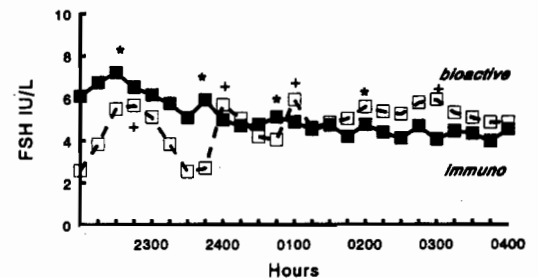


### GnRH stimulation



## B)

### Frequent blood sampling



**FIG. 1.** Hypothyroid prepubertal state. A, Clinical data include CA, BA, growth velocity (GV), height (HT), height SD score (SD), predicted height (PR.HT), testicular volume (TV), and testosterone. LH, FSH, and  $\alpha$ -subunit responses to TRH (200  $\mu$ g) and GnRH (100  $\mu$ g) stimulation. B, Pulse analysis of FSH (■, immunoactive; □, bioactive),  $\alpha$ -subunit, and LH levels measured every 15 min from 2200–0400 h. Asterisks indicate significant pulses detected by Cluster pulse analysis.

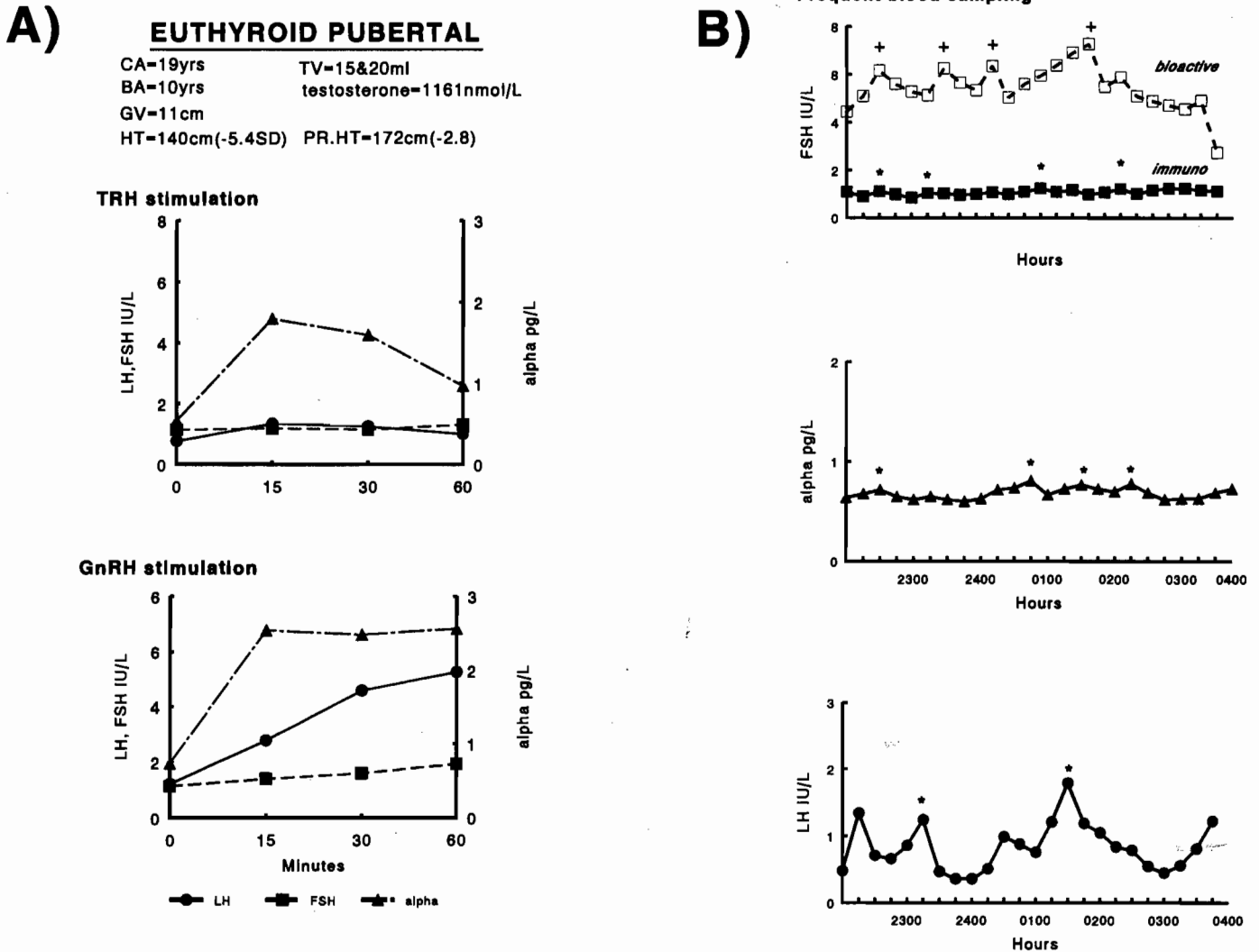


FIG. 2. Euthyroid pubertal state. A, Clinical data (see Fig. 1). LH, FSH, and  $\alpha$ -subunit responses to TRH (200  $\mu$ g) and GnRH (100  $\mu$ g) stimulation. B, Pulse analysis of FSH ( $\blacksquare$ , immunoactive;  $\square$ , bioactive),  $\alpha$ -subunit, and LH levels measured every 15 min from 2200–0400 h. Asterisks indicate significant pulses detected by Cluster pulse analysis.

(four pulses per 6 h),  $\alpha$ -subunit (four pulses per 6 h), and LH levels (two pulses per 6 h; Fig. 2B).

To attempt to augment his adult stature and determine whether the enlargement of the testes was GnRH dependent, the patient was treated with a GnRH analog, Lupron (7.5 mg, im, every month). At the age of 21 yr, after 2 yr of GnRH analog administration, he was restudied. His bone age increased from 10 to 12 yr (Table 1). Linear growth continued at 5.5 cm/yr. His height increased to 152 cm (-3.7 height sd), and predicted height improved by 5.5 cm, to 180.3 cm. During GnRH analog treatment, the TSH level was 2.2 mU/L; FSH, LH, and testosterone levels were undetectable; and  $\alpha$ -subunit was 0.69 pg/L. The mean bioactive FSH level was 2.69 IU/L (range, 2.19–3.99). During GnRH analog therapy, testicular size did not regress, but remained stable at 18–20 mL. DHEAS was 157.4  $\mu$ mol/L. The PRL level was 9  $\mu$ g/L.

TRH and GnRH testing demonstrated undetectable FSH and LH levels. There was a small increase in  $\alpha$ -subunit in response to the TRH stimulation test (0.69 to 1.67 pg/L), but

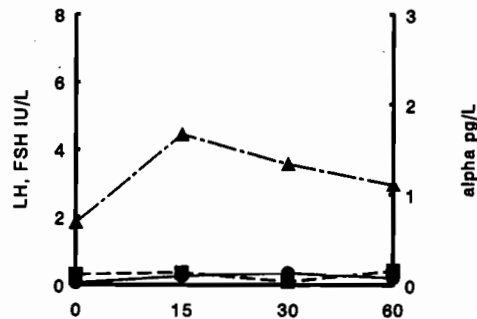
no response to GnRH administration (0.8 to 1.0 pg/L; Fig. 3A). Pulse studies revealed undetectable immunoactive FSH and LH levels, but detectable  $\alpha$ -subunit levels, with three  $\alpha$ -subunit pulses per 6 h and low, but detectable, bioactive FSH pulses (four per 6 h; Fig. 3B).

At the age of 22 yr, 1 yr after release from GnRH analog suppression of gonadarche, the patient returned for re-evaluation (Table 1). Skeletal maturation was rapid; his bone age increased from 12 to 15 yr. A growth spurt occurred, with a growth velocity of 11 cm/yr. His height was 168 cm (-1.3 height sd), and predicted height improved by 9.8 cm over baseline, to 184.6 cm. Testicular size increased to 30 mL bilaterally. TSH was 0.6 mU/L, FSH was 4.3 IU/L,  $\alpha$ -subunit was 0.3 pg/L, LH was 1.41 IU/L, and testosterone was 1872 nmol/L. DHEAS was 244.3  $\mu$ mol/L. The PRL level was 6  $\mu$ g/L.

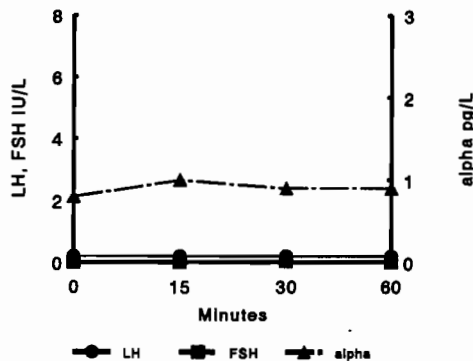
TRH administration did not stimulate FSH, LH, or  $\alpha$ -subunit levels. GnRH testing revealed increases in FSH from 4 to 7 IU/L, and in LH from 1 to 8 IU/L, consistent with his

**A) EUTHYROID PREPUBERTAL**  
 CA=21yrs TV=18&20ml  
 BA=12yrs testosterone=<69nmol/L  
 GV=5.5cm  
 HT=152cm(-3.7SD) PR.HT=180.3cm(+5.5)

**TRH stimulation**



**GnRH stimulation**



**B)**

**Frequent blood sampling**

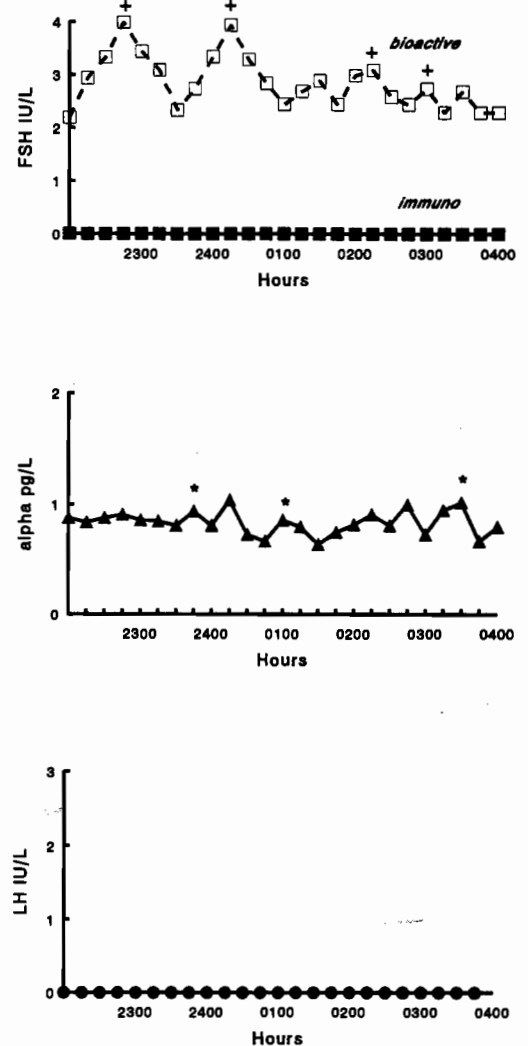


FIG. 3. Euthyroid prepubertal state. A, Clinical data (see Fig. 1). LH, FSH, and  $\alpha$ -subunit responses to TRH (200  $\mu$ g) and GnRH (100  $\mu$ g) stimulation. B, Pulse analysis of FSH (■, immunoactive; □, bioactive),  $\alpha$ -subunit, and LH levels measured every 15 min from 2200–0400 h. Asterisks indicate significant pulses detected by Cluster pulse analysis.

pubertal state (Fig. 4A).  $\alpha$ -Subunit increased minimally from 0.35 to 0.71 pg/L. TRH also increased PRL from 4 to 17  $\mu$ g/mL. Frequent sampling studies revealed pulsatile gonadotropin levels consistent with normal puberty (five FSH pulses and two LH pulses per 6 h). There were two  $\alpha$ -subunit pulses (Fig. 4B).

**Literature Review**

Children with hypothyroidism often present with short stature and delayed puberty. Rarely, signs of precocious sexual maturation, such as testicular or ovarian enlargement or menstrual bleeding, may be present (1–5). Sixty-nine cases have been reported, 40 females and 29 males (1–5). This disorder is characterized by various degrees of virilization, but delayed, rather than accelerated, BA and slowing of the growth velocity. Girls can exhibit evidence of estrogenization, including breast development, galactorrhea, and menses. In boys, macroorchidism without virilization has been

observed. In both sexes, there is reversal of the precocity with treatment of the hypothyroidism.

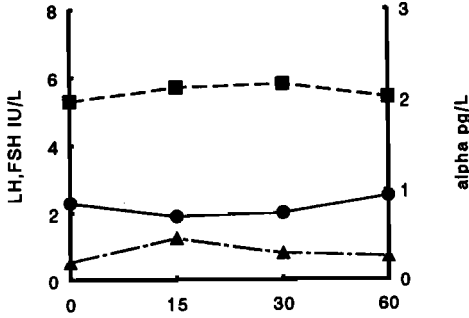
The growth deficit in childhood hypothyroidism may be modest or severe. Treatment of juvenile hypothyroidism results in a rapid growth spurt, but even more rapid skeletal maturation. Thus, with treatment, the child exhibits some catch-up growth, but often a significant deficit in adult stature may occur (6). GnRH analogs have previously been used in children with central precocious puberty to decrease gonadotropin secretion to prepubertal levels and allow linear growth to augment ultimate adult stature (7). In addition, GnRH agonist treatment of boys with central precocious puberty results in a decrease in testicular size of approximately 50% (7). Based on the unusual presentation of precocity in boys with childhood hypothyroidism, we wished to investigate further the relationship between hypothyroidism and macroorchidism.

Long-standing severe primary thyroid failure was seen in this case of hypothyroidism-induced macroorchidism. A

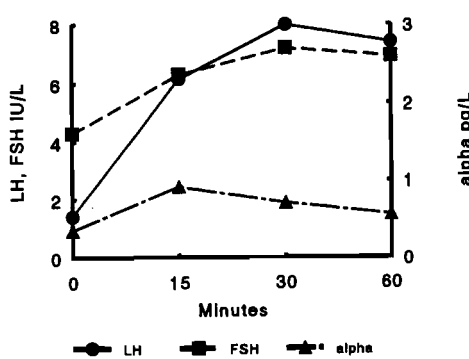
**A) EUTHYROID PUBERTAL**

CA=22yrs TV=30ml  
 BA=15yrs testosterone=1872nmol/L  
 GV=11cm  
 HT=168cm(-1.3SD) PR.HT=184.6cm(+9.8)

**TRH stimulation**



**GnRH stimulation**



**B)**

**Frequent blood sampling**

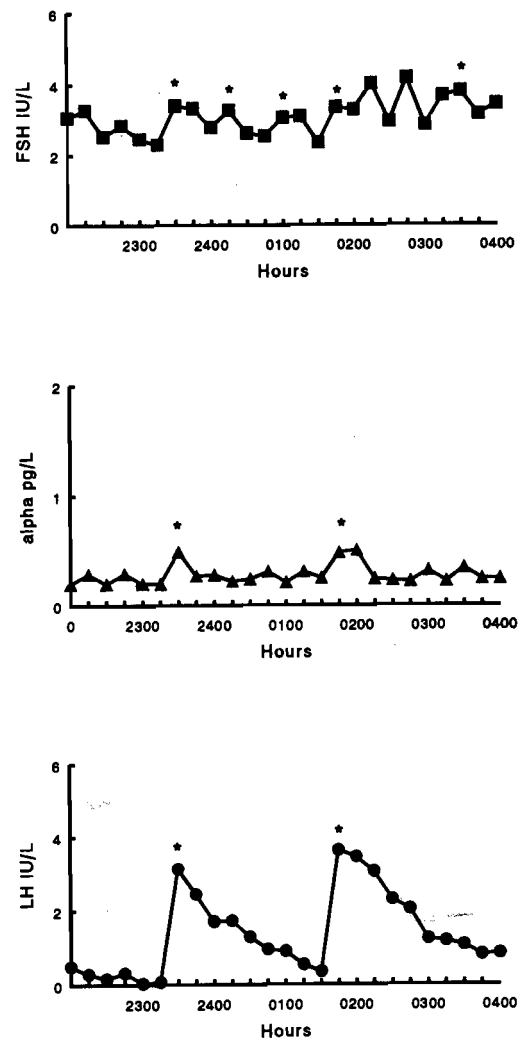


FIG. 4. Euthyroid pubertal. A, Clinical data (see Fig. 1). LH, FSH, and  $\alpha$ -subunit responses to TRH (200  $\mu$ g) and GnRH (100  $\mu$ g). B, Pulse analysis of FSH,  $\alpha$ -subunit, and LH levels measured every 15 min from 2200–0400 h. Asterisks indicate significant pulses detected by Cluster pulse analysis.

markedly elevated TSH level was associated with elevations in FSH,  $\alpha$ -subunit, and PRL levels. Increases in  $\alpha$ -subunit and PRL levels are seen in hypothyroid patients with and without signs of precocious puberty. However, an elevation of FSH levels usually is not observed in hypothyroid individuals, but is commonly seen in true precocious puberty. FSH has previously been reported to be elevated in hypothyroidism-induced precocious puberty (3, 4, 7). There are several reports of elevations in LH levels in hypothyroid precocity, but the RIAs for LH in those early studies had significant cross-reaction with free  $\alpha$ -subunit (3, 4, 7). In our patient, LH levels were prepubertal.

Several hypotheses have been proposed to explain this disorder. These include 1) TRH action on the gonadotropes in addition to thyrotropes, 2) TSH action on the gonad via the gonadotropin FSH receptor due to structural similarities among the glycoprotein hormone receptors, 3) elevated PRL levels, 4) pituitary tumor formation, 5) alterations in gonadal steroid metabolism, and 6) increased sensitivity of the hy-

pothyroid gonad to gonadotropin stimulation. Our data support the role of TRH in the process. Specifically, the patient's FSH level rose in response to TRH, but not GnRH. TRH normally does not stimulate FSH. Past studies in normal controls showed that a FSH response to TRH may have been confounded by cross-reactivity with  $\alpha$ -subunit in the RIA assays. Recent studies in adults suggested that FSH levels may increase after continuous TRH administration (8). In addition, patients with gonadotropin-secreting pituitary tumors demonstrate a response of FSH or LH to TRH administration (9). These data suggest that the increase in FSH levels seen in our patient may be related to the overlap in TRH responses at the level of the pituitary, as postulated by Van Wyk and Grumbach (2).

Our studies suggest that this process is independent of GnRH. Support for the GnRH independence of this disorder is the blunted response of the gonadotropins to GnRH, as seen in this case and reported by others (4). The prepubertal testosterone level and low DHEAS levels, which suggest

absent adrenarche, explain the lack of peripheral androgenic effects that is characteristic of this syndrome. As enlarged testes may be the only manifestation of this type of precocity in boys, unless testicular size is adequately evaluated, this entity may go unrecognized. The fragile X syndrome, another etiology for macroorchidism, must be excluded.

Stimulation of FSH as well as TSH levels by continuous high levels of TRH may explain the macroorchidism, independent of virilization, in boys with this disorder. If the prepubertal testes is exposed to FSH stimulation without testosterone, the Sertoli cells theoretically could continue to proliferate and result in macroorchidism. The fact that our patient's testes did not decrease during GnRHa treatment supports the hypothesis that the macroorchidism is independent of GnRH-mediated effects on FSH production.

In addition to the effect of TRH to stimulate FSH, another potential contributor to the macroorchidism in these patients is the effect of TSH on FSH receptors at the level of the testis to augment FSH action. The fact that most patients with primary hypothyroidism with high TSH levels do not have macroorchidism suggests that this is not the primary defect in the syndrome.

During GnRH agonist therapy, the serum bioactive FSH, but not immunoreactive FSH, levels remained detectable, albeit lower than the pretreatment levels. In previous studies on the effects of GnRH agonist on bioactive FSH in adult male controls, the levels decreased, increased, or were unchanged (reviewed in Ref. 10). There has been no previous study that addresses the pulsatility of bioactive FSH. Interestingly, the bioactive FSH levels remained pulsatile in this patient during GnRHa treatment. The  $\alpha$ -subunit levels were also detectable and pulsatile. Previous investigators reported that  $\alpha$ -subunit levels are elevated after GnRH analog administration, in contrast to the uniform repression of LH and FSH levels (11). These results are consistent with a constitutive non-GnRH-dependent component to bioactive FSH and  $\alpha$ -subunit secretion.

Treatment of this young man with a GnRH agonist for 2 yr significantly reduced his height deficit and increased his predicted adult stature. Previously, it was thought that catch-up growth after treatment of hypothyroidism in childhood was complete. Recent studies, however, suggest that a modest to moderate deficit in adult stature may persist (6). We initiated a further delay in gonadarche to augment linear growth before epiphyseal fusion. The calculated changes underrepresent the ultimate gain, because without intervention with GnRH analog, the skeletal maturation during  $L-T_4$  treatment would exceed the rate of linear growth, prompting early epiphyseal fusion. Thus, the Bailey-Pinneau charts for delayed boys overestimate the predicted ultimate adult height without intervention. This case demonstrates the usefulness of administration of a GnRH analog to delay

gonadarche, allow linear growth, and improve adult predicted height.

In conclusion, careful analysis and longitudinal investigation of a child with hypothyroidism-induced macroorchidism suggests that FSH and  $\alpha$ -subunit activity driven by TRH, independent of GnRH, trigger testicular enlargement, which is not reversible with removal of the FSH signal. Further studies are needed to examine the potential direct effects of TSH acting on the FSH receptor in the gonad to contribute to the syndrome. In addition, our data suggest that GnRH agonist administration can be useful to augment predicted height in this disorder.

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