Correlation of Serum Follicular Stimulating Hormone (FSH) and Luteinizing Hormone (LH) as Measured by Radioimmunoassay in Disorders of Sexual Development

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ABSTRACT Serum FSH and LH levels in 104 patients with disorders of sexual development were determined by radioimmunoassay and compared with serum FSH and LH levels in 164 normal individuals.

32 of 35 gonadal dysgenesis patients (ages 4.8–18.9 yr) had serum FSH levels which were elevated above the range of normal for chronological age, and 19 had serum LH levels similarly elevated. All patients with elevated serum LH levels were 11 yr of age or older. However, 8 of 10 gonadal dysgenesis patients, ages 4.8–10.9 yr, had serum FSH levels elevated above the normal range. In accord with these observations was the finding that in normal girls, serum FSH levels may increase at an earlier age than do serum LH levels (FSH, 5–8 yr of age; LH, 9–10 yr of age). These data indicate that serum FSH determinations may be helpful in diagnosing gonadal dysgenesis during childhood.

Serum gonadotropin levels within the range of normal for chronological age were found in 2 of 18 girls with idiopathic isosexual precocity. The other 16 had serum FSH levels elevated above the range of normal for chronological age, and 8 also had serum LH levels similarly elevated. In all instances serum FSH and LH levels were in the range expected for the stage of sexual development.

In 35 boys, ages 13.1–17.8 yr, with delayed adolescence, serum gonadotropin levels correlated with stage of sexual development and, therefore, were often less than those expected for age.

8 patients with premature pubarche, 5 patients with premature thelarche, and 3 patients with adolescent gynecomastia had serum gonadotropin levels within the range of normal for chronological age.

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INTRODUCTION

Insight frequently is gained in understanding normal physiologic mechanisms by studying developmental aberrations occurring in nature. This principle prompted us to correlate serum concentrations of FSH and LH with the clinical state in patients with various disorders of sexual development and to compare these values with those found in normal individuals at various ages and stages of sexual development.

MATERIALS AND METHODS

Serums from 104 patients with anomalous sexual development were obtained at the time of referral (1964–69) and stored at −20°C. Serums were also obtained from 93 normal females (ages 2–31 yr), 71 normal males (ages 5–18 yr), and 12 hypopituitary patients (ages 13–25 yr). The LH concentrations in some of these individuals were reported previously (1), as were the radioimmunoassay techniques for determining FSH and LH (2–9). Results are reported as milli International Units (mIU) of the second international reference preparation of human menopausal gonadotropin (2nd IRP-HMG). The standard deviation (SD) for FSH in multiple assays is ±1.1 mIU/ml at a level of 7.1 mIU and ±3.4 mIU at 83.4 mIU/ml. The SD for LH in multiple assays is ±1.2 mIU at a level of 8 mIU/ml and ±3.2 mIU at 35 mIU/ml.

Bone ages were evaluated using the Greulich and Pyle standards (10). Height ages were determined from Wilkins' textbook (11). Staging of sexual development in males was according to the system of Tanner (12). Boys in stage I were completely prepubertal; those in stage II had enlargement of the scrotum and testis; those in stage III had enlargement of the penis; those in stage IV had further enlargement of the penis and scrotum and growth of the prostate; and those in stage V had genitalia adult in size. In females stage I was defined as completely prepubertal, stage II as the presence of glandular breast tissue only, stage III as the presence of both breast tissue and sexual hair, and stage IV as the presence of breast tissue, sexual hair, and menarche.

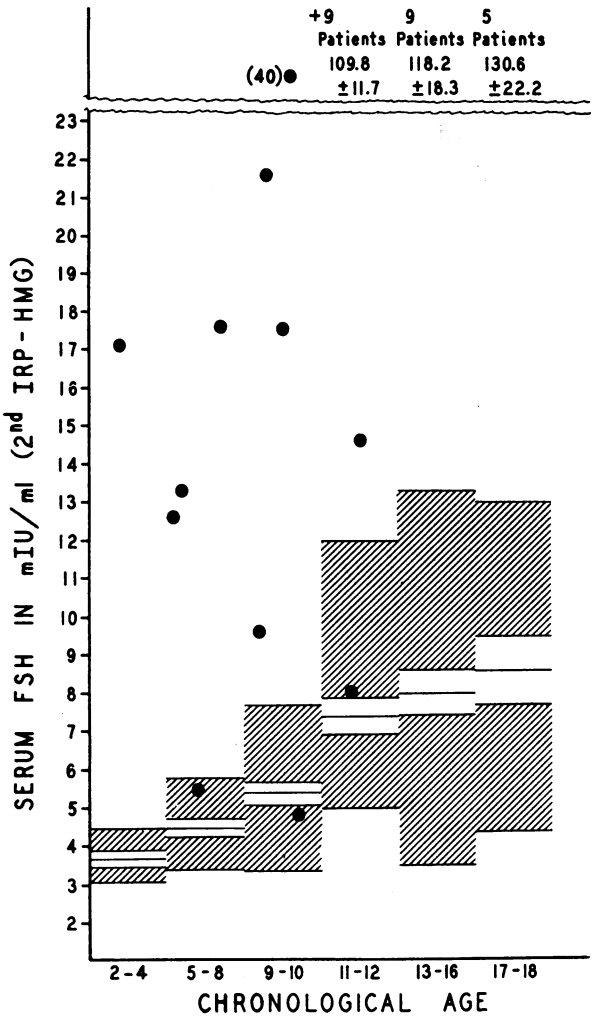

FIGURE 1 Serum FSH levels (mIU/ml of 2nd IRP-HMG) in 35 gonadal dysgenesis patients (black dots) shown with the range (hatched area), mean, and SE (clear area) for normal females of comparable age groups.

RESULTS

Gonadal dysgenesis. Gonadotropin determinations were obtained in 35 girls, ages 4.8–18.9 yr, with gonadal dysgenesis. 11 were XO by karyotype; 8 had a mosaic karyotype; 4 had an X isochromosome; and 12, who had not been karyotyped, were sex chromatin negative. No correlation between gonadotropin levels and karoytype was found. 8 of 10 girls, ages 4.8–10.6 yr, had FSH values above the range of normal. None had LH values above the range of normal. None had LH values above the range of normal (Figs. 1 and 2), although the mean for the younger age group was greater than that for normal females (Table I). FSH values above the range of normal were found in 10 of 11 girls, ages 11.1–12.8 yr, and in 8 of these the LH values were similarly elevated.

In agreement with these findings is the observation that in the normal girls tested, serum FSH levels increased before serum LH levels (Table II). Mean FSH determinations for the 2–4- and 5–8-yr age groups of girls were significantly different from each other ($P < 0.01$). A significant difference between means by age groups for LH in these girls first occurred for the 9–10 yr age group, which differed significantly from the 5–8 yr group

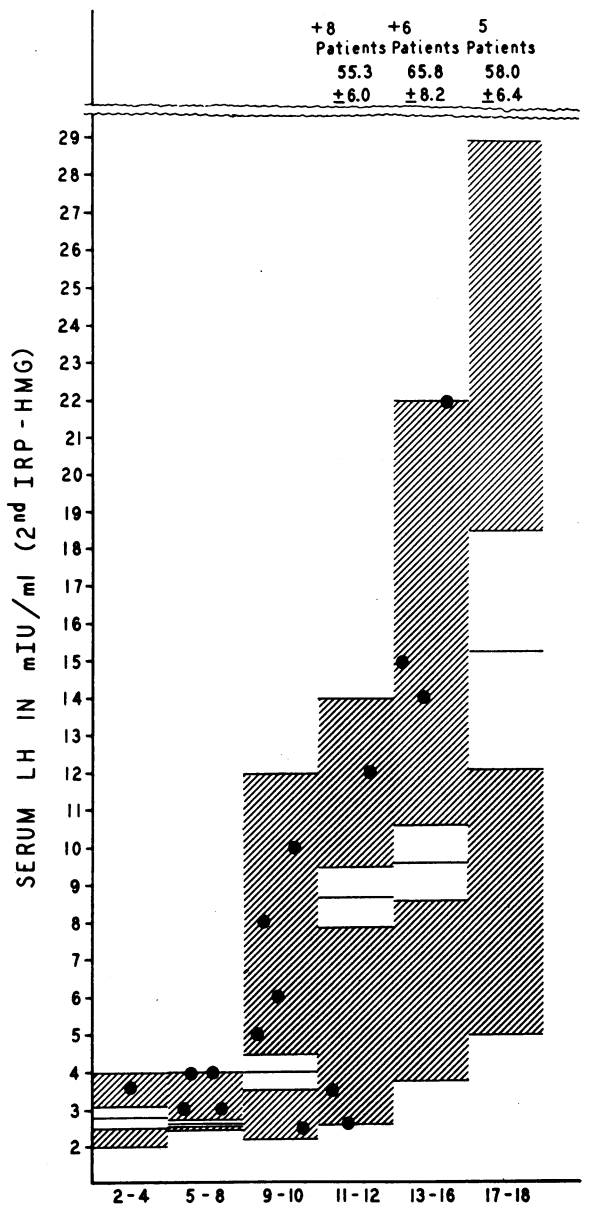

FIGURE 2 Serum LH levels mIU/ml of 2nd IRP-HMG) in 35 gonadal dysgenesis patients (black dots) shown with the range (hatched area), mean, and SE (clear area) for normal females of comparable age groups.

TABLE I

Gonadal Dysgenesis

Age	Number of patients	FSH			LH		
		Range	Mean	SE	Range	Mean	SE
			mIU/ml			*mIU/ml*	
2–4	1	—	17.1	—	—	3.6	—
5–8	4	5.5–17.6	12.3*	2.5	3.0–4.0	3.5‡	0.3
9–10	5	4.8–40.0	18.7*	6.1	2.5–10.0	6.3‡	1.3
11–12	11	8.0–162.5	91.9*	15.4	2.5–83.0	41.3*	7.8
13–16	9	30.0–195.0	118.2*	18.3	14.0–90.0	40.6*	8.4
17–18	5	82.0–195.0	130.6*	22.2	40.0–77.0	58.0*	6.4

* $P < 0.005$ for difference between mean of normal females in Table II.
‡ $P < 0.05$ for difference between mean of normal females in Table II.

($P < 0.01$). By the age of 16, LH levels in gonadal dysgenesis patients were consistently above the normal range, although FSH levels were always greater than LH levels.

Idiopathic isosexual precocity. The onset of sexual development in 18 girls ranged from birth to 8 yr of age. Their ages at the time serums were obtained ranged from 2.0 to 10.0 yr (Table II). FSH and LH determinations were consistent with the range of values for the stage of sexual development in 17 of the 18 girls. The mean

TABLE II

Normal Females and Hypopituitary Subjects

Stage	Age	Number of patients	FSH			LH		
			Range	Mean	SE	Range	Mean	SE
				mIU/ml			*mIU/ml*	
	Hypopit							
	all ages	12	2.2–3.2	2.8	0.1	1.0–2.0	1.4	0.1
	2–4	10	3.1–4.5	3.7*	0.2	2.0–4.0	2.8*	0.3
	5–8	11	3.4–5.8	4.5*	0.2	2.5–4.0	2.6	0.1
	9–10	18	3.4–7.7	5.4*	0.3	2.2–12.0	4.0*	0.5
	11–12	20	5.0–12.0	7.5*	0.5	2.4–14.0	8.7*	0.8
	13–16	23	3.5–13.3	8.0	0.6	3.8–22.0	9.6	1.0
	17–18	7	4.4–13.0	8.6	0.9	5.0–29.0	15.3‡	3.2
I	2–12	27	3.1–5.7	4.2	0.2	2.0–7.5	2.9	0.4
II	8–12	13	4.6–7.1	5.5*	0.2	2.5–11.5	3.9*	0.8
III	9–14	23	5.0–12.0	8.0*	0.4	2.5–14.0	8.4*	0.6
IV	12–18	26	3.5–13.0	8.0	0.5	3.0–29.0	11.3‡	1.3
Adults§								
Follicular			4.0–17.2	8.3	0.3	5.0–57.0	12.8	1.0
Midcycle peak			13.7–22.5	19.3	2.0	76.0–90.0	83.5	3.7
Luteal			4.0–15.0	6.9¶	0.4	3.0–41.0	11.6¶	1.3
				Idiopathic Isosexual Precocity				
	2–4	3	5.5–13.3	9.3‖	1.9	4.5–9.5	6.4‖	1.3
	5–8	11	3.6–16.0	9.6‖	1.3	2.5–22.0	6.1‖	1.6
	9–10	4	9.6–22.6	14.5‖	2.5	6.0–18.0	11.3	2.2
III	2–9	11	3.6–14.0	8.4	0.9	2.5–12.0	4.8‖	0.8
IV	2–10	7	9.0–22.6	14.2‖	1.8	4.5–22.0	11.4	2.2

* P of <0.01 for difference from mean of preceding group.
‡ P of <0.03 for difference from mean of preceding group.
§ Menstrual cycles of 4 normal adult females with regular menses.
¶ P of <0.005 for difference from mean of follicular phase.
‖ P of <0.01 for difference from mean of normal females.

values for FSH and LH by age groups were significantly different ($P < 0.01$) from the mean values of normal girls of the same age (Table II). FSH values in 16 of the 18 girls were greater than the range of normal for chronological age. 8 of the 18 girls had LH values elevated above the range of normal for chronological age. FSH and LH levels within the range of normal for chronological age were found in 2 of the 18 girls.

Constitutional delayed adolescence. Patients with possible or proven hypopituitarism were excluded. The 35 males ranged in age from 13.1 to 17.8 yr (Table III). They either had not attained stage III of sexual development by age 13 yr or stage IV by age 14 yr. Height age was delayed and ranged from 1.5 to 5.8 yr with a mean of 3.5 ±SE of 0.1 yr. In the 26 males who had bone age determinations, there was a mean retardation of 3.4 ±SE of 0.09 yr (range 1.5–5.5 yr). 5 boys were in stage I, 17 in stage II, and 13 in stage III of sexual development. The FSH values were all within the range expected for the stage of sexual development rather than for age. Similarly this was so for the LH values in 21 (5 of 5 in stage I, 10 of 17 in stage II, and 6 of 13 in stage III) of the boys. The 14 remaining boys had LH values which were less than that expected for stage of sexual development. 18 of 35 FSH determinations and 22 of 35 LH determinations were below the range of normal for chronological age.

Premature pubarche. 8 patients, 7 girls and 1 boy, were referred because of isolated development of pubic hair. They ranged in age from 1.2 to 8.8 yr. Their serum values for FSH ranged from 4.0 to 5.3 (mean = 4.5 ±SE of 0.2 mIU/ml) and for LH, from 2.0 to 3.8 (mean = 2.7 ±SE of 0.1 mIU/ml), and are those expected for stage I of sexual development.

Premature thelarche. The serum FSH levels of 4.0–4.5 (mean = 4.3 ±SE 0.03 mIU/ml) and LH levels of 2.0–3.4 (mean = 2.7 SE 0.3 mIU/ml) were consistent with stage I of sexual development in 5 girls. These girls, ages 1.5–3.9 yr, were referred for breast enlargement without evidence of other secondary sex characteristics.

Adolescent glynecomastia. 3 males with adolescent development (13.1–14.1 yr of age) were referred because of gynecomastia. All were sex chromatin negative and were diagnosed as having adolescent gynecomastia. The FSH levels (6.3 ±SE 1.0 mIU/ml) and LH levels (5.5 ±SE 0.4 mIU/ml) were consistent with the stage of sexual development in each instance.

DISCUSSION

The mean serum LH values, as determined in our laboratory (9), for normal males increase approximately threefold from childhood to adulthood (3.4–10.9 mIU/ml), while serum FSH values increase only 1.7-fold (4.2–7.4 mIU/ml) (5). Mean serum LH values for normal females increase similarly (2.8–12.8 mIU/ml), as do the serum FSH values (3.7–8.3 mIU/ml) which are reported in the current manuscript. Previously we reported that

TABLE III
Normal Males

Stage	Age	Number of patients	FSH			LH		
			Range	Mean	SE	Range	Mean	SE
			mIU/ml			*mIU/ml*		
	13–14	18	5.0–14.0	8.1	0.6	5.0–14.0	9.4	0.6
	15–16	18	5.0–23.0	8.7	1.0	4.0–13.0	9.0	0.5
	17–18	10	4.0–14.0	9.2	1.2	7.5–19.0	14.1*	1.2
I	5–11	25	2.5–7.0	4.5	0.2	2.5–5.8	3.9	0.2
II	10–13	17	3.0–9.0	5.9*	0.3	4.0–12.0	6.8*	0.5
III	12–14	11	2.5–14.0	8.1*	0.9	6.0–11.0	8.5‡	0.5
IV	12–17	18	3.5–15.0	8.5	0.8	4.0–15.5	9.5	0.7
			Constitutionally Delayed Adolescent Development (Males)					
	13–14	23	3.8–16.3	6.6§	0.8	2.5–9.0	4.4§	0.4
	15–16	10	2.0–8.0	4.8§	0.5	2.5–6.5	4.1§	0.4
	17–18	2	4.7–4.8	4.8	—	5.5–6.0	5.8	—
I	14–15	5	3.8–5.3	4.4	0.2	2.5–3.5	2.9¶	0.2
II	13–17	17	3.8–7.0	4.7¶	0.3	2.0–5.5	3.9§	0.3
III	14–17	13	2.5–16.3	8.2	1.3	3.0–7.5	5.5§	0.5

* P of <0.01 for difference from mean of preceding group.
‡ P of <0.03 for difference from mean of preceding group.
§ P of <0.01 for difference from mean of normal males.
¶ P of <0.03 for difference from mean of normal males.

serum LH increases first at the age of 9–10 yr in both boys and girls (9), and that serum FSH rises simultaneously with LH in boys (5). In the current study, we have demonstrated that serum FSH in girls may increase before LH, i.e., the mean value (4.5 ±0.2 mIU/ml) for the 5–8 age group of females in this study is significantly different ($P < 0.01$) from the mean value of the 2–4 yr age group (3.7 ±0.2 mIU/ml). Unfortunately, Raiti, Johanson, Light, Migeon, and Blizzard (5) did not test male children younger than 5, and it is undetermined if boys 5–8 yr of age have a significantly higher mean value for FSH than boys 2–4 yr of age.

Utilizing observations referred to in the preceding paragraph and the data presented in this manuscript concerning serum FSH and LH values in various disorders of sexual development, certain pertinent comments can be made. The rise in serum FSH, but not LH, at an early age in patients with gonadal dysgenesis is in accord with the observation in normal girls that FSH may progressively rise in females during early childhood, while LH does not. The data obtained in the patients with gonadal dysgenesis are indicative that serum FSH determinations may be helpful in clinically assessing the gonadal structure during childhood. The occasional reports of positive bioassays for gonadotropins in very young patients with gonadal dysgenesis (13, 14) may be explained by the observation that increased FSH levels occur early (as compared with normal female children) in this group of patients. The marked rise of of serum FSH, but not LH, early in the life of the patient with gonadal dysgenesis and the markedly disproportionate elevation of serum FSH, as compared with serum LH, in the older patients with this syndrome may be indicative of different suppressive agents for the inhibition of FSH and LH release. An alternative explanation is that the maturation of the physiological regulatory mechanism for FSH occurs at an earlier chronological age than that for LH. Further studies to elucidate these possibilites are needed.

The current data reported for patients with sexual precocity are in accord with those previously reported by Guyda, Johanson, Migeon, and Blizzard (1) and Root, Moshang, Bongiovanni, and Eberlein (15) for LH and Kenny et al. (16) for LH and FSH. These investigators also found values compatible with the stage of sex development rather than age. Bioassay data on urinary extracts from patients with idiopathic isosexual precocity are in accord with the data presented in the current report, as excretion of gonadotropins in excess of those found in early childhood have been reported (17–19). The data suggest that idiopathic isosexual precocity results from premature activation of the hypothalamic-pituitary-gonadal axis, which is normally activated at, and responsible for, normal adolescent development (11, 20). Data regarding the autonomy of the hypothalamic-pituitary-gonadal axis and, therefore, the suppressibility of the gonadotropins in such individuals have not been reported. Such studies based on comparing suppressibility of gonadotropins in normal individuals will have to be pursued before one can unequivocally state that the hypothalamic-pituitary-gonadal axis is completely normal except for precocious maturation in these individuals.

Serum FSH and LH concentrations in patients with constitutional delayed adolescence are more compatible with the stage of sexual development than with the age.[1] Guyda et al. (1) previously reported similar findings for LH, but this is the first report where FSH has been studied in this group of patients. These data are consistent with the concept that this disorder merely represents a deviation from the average time and pattern of development (11). The delay in bone age found in patients with this disorder also is in support of this general concept, since osseous development is an indicator of general body tissue maturation (23).

The serum FSH and LH levels in patients with premature pubarche, premature thelarche, and adolescent gynecomastia, which are normal for age, are consistent with the current concepts regarding the development of each entity. The former is attributed to the elaboration of adrenal androgens prior to the elaboration of gonadotropins by the pituitary (11, 23). Premature thelarche is believed, though not specifically documented, to result from increased end organ sensitivity to very small amounts of estrogen (11, 23), and adolescent gynecomastia is believed to result from a greater than usual conversion of androgens to estrogens (11). Our data for patients with premature thelarche, however, differs from that of Kenny et al. (16), since these authors found slightly increased levels of FSH and LH in this disorder. Further studies will permit clarification of the role of gonadotropins as a possible causative factor in this entity.

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[1] This laboratory and Yen have analyzed (data to be published) the variance between the previously published data of the two laboratories on serum LH in normal males (9, 21). It was concluded that the differences were attributable to interlaboratory variation with respect to absolute values and to population variation with respect to trends. Similar trends were obtained when both laboratories assayed the same serums. It is not unreasonable to assume that this may be true for the variance between the FSH serum data of the two laboratories (5, 22) in as much as the serums are the same as those reported in their respective LH papers (9, 21).

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