Hypophyso-Gonadal Function in Humans during the First Year of Life

I. EVIDENCE FOR TESTICULAR ACTIVITY IN EARLY INFANCY

MAGUELONE G. FOREST, PIERRE C. SIZONENKO, ANNE M. CATHIARD, and JEAN BERTRAND

From Unité de Recherches Endocriniennes et Métaboliques chez l'Enfant, Hôpital Debrousse, 69322 Lyons, France and The Department of Pediatrics and Genetics, University of Geneva Medical School, 1211 Geneva 4, Switzerland

ABSTRACT Total and unbound testosterone and Δ^4-androstenedione have been determined in 104 cord blood samples. The same sexual steroids and pituitary gonadotropins have been measured in 46 normal male infants aged 27–348 days and 34 normal female infants aged 19–332 days.

In cord blood of female neonates mean total and unbound testosterone was 29.6±7.5 and 0.89±0.4 ng/100 ml, respectively (mean±1 SD); Δ^4-androstenedione was 93±38 ng/100 ml. In male neonates mean plasma total and unbound testosterone was 38.9±10.8 and 1.12±0.4 ng/100 ml; Δ^4-androstenedione was 85±27 ng/100 ml.

In female infants testosterone concentrations remained constant during the 1st yr of life with a mean concentration of 7±3 ng/100 ml. Mean unbound testosterone and Δ^4-androstenedione concentrations were 0.05±0.03 and 16.7±8.3 ng/100 ml, respectively. Mean plasma levels of follicle-stimulating hormone and luteinizing hormone were 8.7±3.3 and 12.9±7.7 mU/ml.

In male infants mean plasma total testosterone concentration increased to 208±68 ng/100 ml from birth to 1–3 mo of age, decreasing thereafter to 95±53 ng/100 ml at 3–5 mo, 23.2±18 ng/100 ml at 5–7 mo, and reached prepubertal levels (6.6±4.6 ng/100 ml) at 7–12 mo. Mean unbound testosterone concentration plateaued from birth to 1–3 mo of age (1.3±0.2 ng/100 ml) decreasing to prepubertal values very rapidly. Mean Δ^4-androstenedione concentration, although progressively decreasing during the 1st yr of life to 11.7±4.5 ng/100 ml, was higher than in the female at 1–3 mo of life (34±11 ng/100 ml). Mean plasma level of follicle-stimulating hormone was 6.7±2.9 mU/ml, and that of luteinizing hormone was 19.7±13.5 mU/ml, significantly higher than in the female. There was no correlation between gonadotropin and age or testosterone.

The present data demonstrate that the testes are active during the first natal period. It is tempting to correlate this phenomenon to a progressive maturation of the hypothalamo-pituitary-gonadal axis. It is possible that the surge in testosterone occurring the first 3 mo could play a role in the future life pattern of the male human being.

INTRODUCTION

Until now there has been very little information on the hypophyso-gonadal function of neonates and young infants. Testosterone has been reported to be elevated in both sexes at birth although a sex difference has not been evidenced (1–6). These results have been obtained with different methods and therefore plasma values of testosterone are difficult to compare. One recent study showed that the mean testosterone concentration was much higher in male than in female newborn infants the first 2 wk of life (7). To the best of our knowledge there was no information on the concentration of physiological androgens in infancy until we were able to report preliminary data on testosterone concentration during the 1st yr of life (8). Urinary luteinizing hor-

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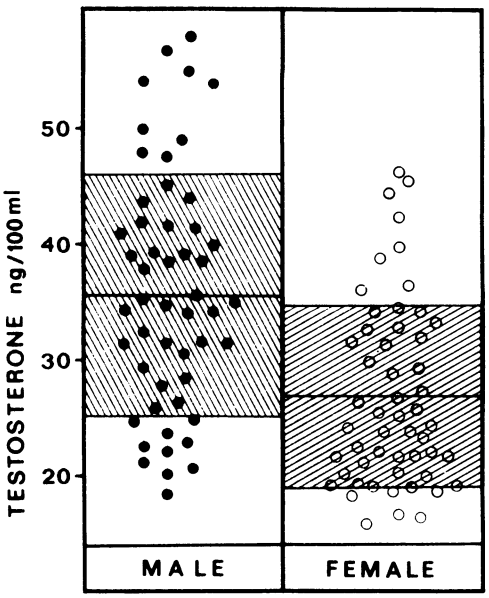

FIGURE 1 Plasma testosterone concentration in cord blood. Shaded area represents ±1 SD of the mean.

mone (LH)[1] has been reported elevated during the first 6 mo of life in males (9). FSH has ben reported to be high in cord blood (10, 11) and higher in girls than in boys during the first 2 yr of life (12).

The present study was undertaken, therefore, to evaluate androgen concentrations at birth and to explore the pituitary-gonadal axis in infancy. Total and unbound testosterone and Δ^4-androstenedione (Δ^4) concentrations were measured in 104 cord blood specimens. These androgens, as well as gonadotropin levels, were determined in 80 normal infants of both sexes.

METHODS

Subjects

A group of 104 normal newborns consisting of 51 males and 53 females were studied at the time of normal vaginal delivery. Mixed arterial and venous blood was collected from the cord after its clamping. Mean birth weights were 3,332 and 3,265 g in male and female babies, respectively. The second group studied comprised 46 normal male and 34 normal female infants from 19 to 348 days of age. They were patients seen in the hospital for minor illness or surgery and free of any acute or chronic endocrine or metabolic diseases. Blood was collected at the time of sampling necessary for the control of the state of health before hospital discharge. In addition, these infants had normal genitalia, weights, and heights for their ages.

Testosterone and Δ^4-androstenedione measurement

1–2 ml of plasma were extracted by ethyl ether (3× with 2 vol). Extracts were chromatographed on Celite columns. Testosterone (T) and Δ^4-androstenedione (Δ^4) were eluted separately (7).

T was measured by a sensitive radioimmunoassay (RIA) technique as previously reported (7). The antiserum was obtained in rabbit after injection of T-3-carboxy-oxime-bovine serum albumin conjugate. Its affinity constant was 6×10^{10} M^{-1} at 4°C. Cross-reaction with dihydrotestosterone and Δ^4 was 36% and <1%, respectively. Dilution of the antiserum was 1:140,000. Mean T recovery in 245 determinations was 76.2±6.4%.

Δ^4 was reduced to T by the addition of 0.2 ml of 6 mg sodium borohydrate in 20 ml of methanol. After 10 min at 4°C, the reaction was stopped with one drop of glacial acetic acid. After evaporation to dryness, Δ^4 reduced to T was purified by a second Celite chromatography. Mean recovery of reduction and purification of reduced Δ^4 was 55.2%. T obtained in such a way was then measured by the same RIA system. Total recovery for 120 determinations of Δ^4 was 35.5±5.3%.

The percentage of testosterone bound to proteins was measured by equilibrium dialysis at 37°C on 1:5 diluted plasma as described (13). The results of percentage binding of T are given uncorrected for dilution in the Results section and in Fig. 2.

Unbound testosterone concentration was calculated as percentage of unbound T corrected for plasma dilution times total T concentration, as previously reported (14).

LH and FSH were determined by the double antibody RIA method described elsewhere (15, 16). Results are expressed in mU/ml of Medical Research Council (MRC) LH standard 68/40 and FSH standard 68/39.[2] The sensitivity of the method was 0.7 mU/ml for LH and 0.5 mU/ml for FSH. The coefficient of variation for duplicate determinations was 8% for LH and 4.7% for FSH. Interassay reproducibility was within 17 and 13% for LH and FSH, respectively.

Statistical analysis was made with Student's *t* test and the least squares method.

RESULTS

Plasma testosterone concentration. Individual values, means±1 SD, obtained in the cord blood of 104 newborns are given on Fig. 1. Although the range is rather wide in both sexes and male and female values overlap, the mean concentration (35.7±10.5 ng/100 ml) observed in the 51 males is significantly ($P < 0.0025$) higher than the one obtained in the 53 female neonates (26.8±8.0 ng/100 ml). This slight but significant sex difference was also evidenced in 42 of these cord plasmas

[1] *Abbreviations and trivial names used in this paper:* Δ^4-androstenedione (Δ^4), androst-4-ene-3,17 dione; dihydrotestosterone, 17β-hydroxy-5α-androstan-3 one; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MCRT, metabolic clearance rate of testosterone; MRC, Medical Research Council; RIA, radioimmunoassay; TeBg, testosterone-estradiol binding globulin; testosterone (T), 17β-hydroxy-androst-4-en-3 one.

[2] These standards were kindly supplied by the National Institute of Medical Research, London. FSH MRC 68/39 is equivalent to 32.8 U/ampoule by the Steelman-Pohley assay; LH MRC 68/40 pituitary standard to 39.8 U/ampoule by the Parlow ovarian ascorbic acid depletion method in terms of the 2nd International Reference Preparation of human menopausal gonadotropins.

randomly chosen for further studies and for which individual values are given in Table I.

80 normal infants 1–12 mo of age of both sexes were also studied. Results obtained in 46 male infants are listed according to age in Table II. There was obvious variation of testosterone levels with age in this group. Therefore results have been grouped for each 2-mo interval for statistical analysis (Table IV). There is a bimodal pattern in total testosterone levels of male infants during the 1st yr of life. From birth to about the 2nd mo a gradual increase of testosterone level occurs. In the 1–3-mo group the mean±1 SD testosterone concentration is significantly higher ($P < 0.001$) than the one we previously obtained in the first 2-wk of life using the same method (Table IV). Mean testosterone level in this later age is significantly higher than in cord blood ($P < 0.0001$). After 1–3 mo of age there is a gradual decrease until the 7th mo of life. Mean testosterone concentration in the 3–5-mo group was significantly different ($P < 0.001$) from the 5–7 mo group. From 7 to 12 mo of age testosterone levels were similar to those we observed in prepubertal children of both sexes (Table IV).

In the female infants the pattern of total testosterone concentration during the 1st yr of life was very different from the one we observed in the male. Individual values are given in Table III. The mean testosterone concentration found in the 1–3 mo group although slightly lower, was not significantly different from that observed in the first 2 wk of life and in addition there was no difference in mean values found in the subsequent 2-mo groups (Table IV). Furthermore, the mean testosterone concentration in female infants between 1 and 12 mo is similar to that we observed in prepubertal girls. Although elevated at birth, circulating testosterone levels decrease rapidly during the first weeks of life in female neonates and then remain unchanged until puberty.

Plasma androstenedione concentration. The results of the plasma Δ^4 determinations in the cord of 42 newborns are listed in Table I. This androgen was also markedly elevated at birth in both sexes, without sex difference. Individual plasma Δ^4 concentrations in male and female infants are given in Tables II and III, respectively. In male infants the pattern observed for Δ^4 was not parallel to that of testosterone. There was a significant ($P < 0.0001$) decrease from birth to 1–3 mo of

TABLE I

Total Testosterone (T), Percent Unbound T and Absolute Unbound T, Δ^4- Androstenedione (Δ^4), and Ratio Δ^4/T in Cord Blood

Male					Female				
Testosterone					Testosterone				
Total	Unbound		Δ^4	Δ^4/T	Total	Unbound		Δ^4	Δ^4/T
ng/100 ml	*% total**	*ng/100 ml*	*ng/100 ml*		*ng/100 ml*	*% total**	*ng/100 ml*	*ng/100 ml*	
39	2.8	1.1	122	3.1	26	2.7	0.7	57	2.2
44	3.8	1.7	85	1.9	22	2.7	0.6	59	2.7
35	2.9	1.0	63	1.8	33	3.3	1.1	103	3.1
26	3.3	0.9	107	4.2	35	3.0	1.0	108	3.1
34	3.0	1.0	88	2.6	38	2.4	0.9	97	2.5
55	2.9	1.6	146	2.7	19	2.4	0.5	78	4.1
42	2.6	1.1	113	2.7	27	3.2	0.9	98	3.7
50	4.4	2.2	68	1.4	45	3.5	1.6	175	4.0
34	2.6	0.9	59	1.7	34	3.9	1.3	142	4.2
21	3.1	0.7	60	2.9	16	3.5	0.6	69	4.3
42	3.3	1.4	79	1.9	22	3.3	0.7	62	2.9
54	2.6	1.4	87	1.6	24	2.9	0.7	63	2.6
22	3.2	0.7	55	2.5	33	3.0	1.0	78	2.4
44	3.7	1.6	93	2.1	32	3.6	1.1	75	2.4
58	2.0	1.2	78	1.3	36	2.3	0.9	102	2.8
23	2.3	0.5	52	2.2	33	3.7	1.2	58	1.8
35	2.4	0.9	63	1.8	20	2.0	0.4	61	3.0
32	2.5	0.8	55	1.7	27	2.5	0.7	98	3.6
35	2.0	0.7	64	1.8	34	2.8	1.0	191	5.6
54	2.3	1.3	128	2.4	36	2.8	1.0	79	2.2
39	2.6	1.0	110	2.8					
40	2.8	1.1	102	2.6					

* Corrected for plasma dilution.

TABLE II

Total Testosterone (T), Percent Unbound T and Absolute Unbound T, Δ⁴-Androstenedione (Δ⁴), ratio Δ⁴/T, LH and FSH in Plasma of Normal Male Infants

Age	Testosterone			Δ⁴	Δ⁴/T	FSH	LH
	Total	Unbound					
days	*ng/100 ml*	*% total**	*ng/100 ml*	*ng/100 ml*		*mU/ml*	*mU/ml*
27	124	0.8	0.99	21	0.17	6.2	13.0
28	232	0.6	1.46	38	0.17	4.3	8.5
45	312	0.5	1.69	39	0.12	4.6	11.5
53	233	0.8	1.82	47	0.20	10.2	16.0
57	257	0.7	1.83	28	0.11	11.2	19.0
60	245	0.6	1.42	31	0.13	5.8	12.5
63	255	0.6	1.48	—	—	3.6	26.2
65	107	0.8	0.80	13	0.13	5.8	12.5
66	137	0.8	1.12	—	—	2.0	47.5
73	126	0.7	0.86	—	—	—	—
73	256	0.4	1.10	47	0.18	8.0	21.5
76	152	0.6	0.97	35	0.22	12.2	46.0
84	261	0.4	1.15	39	0.15	8.2	33.5
94	55	0.6	0.33	10	0.18	2.9	5.5
94	105	0.6	0.64	24	0.23	8.2	13.5
99	115	0.7	0.82	20	0.18	3.6	4.5
108	165	0.7	1.12	12	0.07	2.9	3.0
117	155	0.9	1.36	61	0.40	6.0	17.5
117	40	0.9	0.37	8	0.21	7.4	13.5
118	26	0.8	0.21	19	0.74	4.8	14.5
118	117	0.6	0.70	11	0.09	3.3	11.7
120	125	0.9	1.07	25	0.20	6.1	11.5
121	57	0.5	0.27	35	0.62	11.0	19.0
121	59	0.6	0.37	—	—	—	—
129	25	0.8	0.20	42	1.66	8.2	11.0
129	91	0.5	0.47	17	0.19	8.0	50.0
136	192	0.4	0.75	26	0.14	9.0	26.5
161	7	1.1	0.07	34	5.20	4.5	16.0
166	14	0.8	0.11	16	0.14	12.7	27.5
167	53	0.9	0.48	17	0.32	8.9	12.0
168	21	0.7	0.14	14	0.65	—	—
182	18	0.6	0.11	14	0.76	5.6	7.5
184	20	1.0	0.20	11	0.57	—	—
186	5	0.8	0.04	9	1.74	—	—
210	49	0.4	0.18	8	0.17	9.2	22.5
222	6	0.9	0.05	12	2.24	8.2	44.5
235	5	0.6	0.03	13	2.68	5.8	13.0
236	7	0.7	0.05	14	2.04	2.3	3.2
245	2	0.8	0.02	6	2.80	2.5	2.9
260	18	0.7	0.13	—	—	9.6	8.0
275	7	0.6	0.04	11	1.61	8.3	—
279	4	0.9	0.04	12	2.88	8.0	50.0
294	4	1.1	0.05	—	—	4.0	—
297	2	0.4	0.01	7	2.96	10.9	40.5
323	10	0.9	0.09	21	2.13	7.1	21.5
348	8	0.7	0.06	9	1.18	1.7	11.0

* Corrected for plasma dilution.

life. Thereafter mean Δ^4 concentrations (Table IV) decreased more slowly than during the first 2 mo of life ($P < 0.005$ for group 1–3 mo vs. 3–5 mo; $P = 0.05$ for group 3–5 mo vs. 5–7 mo).

In contrast, in the female infants the pattern of Δ^4 was somewhat similar to that observed for testosterone. The high levels observed in cord blood dropped very rapidly between birth and 1–3 mo of age ($P < 0.0001$). None of the mean values of each subsequent 2-mo groups are significantly different from each other (Table IV); however, the small difference in mean levels of Δ^4 between the 1–3-mo and 7–12-mo group is significant ($P = 0.005$).

During infancy mean plasma Δ^4 level was similar in both sexes, except for the 1–3-mo group in which mean concentration was higher in the male ($P < 0.005$) than in the female. The reverse was observed in adults (Table IV).

Androstenedione/testosterone ratio (Δ^4/T). Individual values obtained in cord, male and female infants are given in Tables I, II, and III, respectively. At birth the ratio is significantly ($P < 0.0025$) higher in female

TABLE III

Total Testosterone (T), Percent Unbound T and Absolute Unbound T, Δ^4-Androstenedione (Δ^4), Ratio Δ^4/T, LH and FSH in Plasma of Normal Female Infants

Age	Testosterone			Δ^4	Δ^4/T	FSH	LH
	Total	Unbound					
days	*ng/100 ml*	*% total**	*ng/100 ml*	*ng/100 ml*		*MU/ml*	*mU/ml*
19	12	—	—	—	—	—	—
21	13	0.6	0.078	—	—	14.4	13.5
28	7	1.0	0.066	22	3.3	9.9	10.0
30	14	0.9	0.126	18	1.3	8.0	—
44	3	0.7	0.021	13	4.2	10.2	24.5
57	9	0.6	0.057	—	—	—	—
72	1	1.1	0.011	—	—	8.5	8.5
82	9	0.7	0.065	25	2.7	14.2	30.5
84	10	0.6	0.061	18	1.9	6.0	3.7
90	4	0.4	0.019	11	2.4	11.2	22.5
91	6	0.8	0.047	15	2.5	14.2	21.0
95	5	0.5	0.026	16	3.1	8.2	19.0
97	7	0.6	0.044	18	2.5	4.1	4.5
99	8	0.6	0.046	23	3.0	—	—
104	13	0.6	0.070	32	2.5	—	—
110	4	0.8	0.031	18	4.5	—	8.2
117	7	0.7	0.046	7	1.1	6.9	4.5
125	7	0.5	0.033	12	1.6	8.0	12.5
152	7	0.7	0.048	18	2.7	10.4	9.0
154	6	0.7	0.041	—	—	—	—
155	12	1.0	0.119	17	1.4	2.5	3.5
179	3	0.8	0.023	—	—	10.3	18.5
184	4	0.5	0.018	9	2.6	7.8	12.0
185	8	0.8	0.062	16	2.0	12.4	24.0
190	5	0.6	0.031	—	—	—	—
194	9	0.5	0.045	6	0.7	—	—
210	3	0.7	0.020	—	—	7.5	15.5
223	4	0.7	0.026	12	3.4	12.8	10.0
243	7	0.8	0.053	10	1.4	3.4	1.8
247	8	0.6	0.044	—	—	9.9	10.0
264	3	0.8	0.025	11	3.5	6.1	17.0
286	11	0.3	0.037	—	—	5.6	8.0
293	4	0.7	0.030	12	2.9	9.9	19.0
332	5	0.6	0.028	—	—	4.3	3.5
Mean	7	0.7	0.045	17	2.6	8.7	13.2
±1 SD	±3	±0.2	±0.025	±8	±0.9	±3.3	±7.6

* Corrected for plasma dilution

TABLE IV

Changes with Age in Plasma Concentration (Mean±1 SD) of Total and Unbound Testosterone (T), Δ^4 Androstenedione (Δ^4), Ratio Δ^4/T, LH, and FSH of Male and Female Normal Subjects from Birth to Adulthood

Age	No.	Testosterone			Δ^4	Δ^4/T	LH	FSH
		Total	Unbound					
		ng/100 ml	*% total**	*ng/100 ml*	*ng/100 ml*		*mU/ml*	*mU/ml*
Male								
cord	22	39±11‡	2.9±0.6	1.1±0.4‡	85±27	2.3±0.7‡	—	—
1–15 days§	14	68±60‡	1.3±0.2	0.8±0.8‡	—	—	—	—
1–3 mo	13	208±68‡	0.6±0.1	1.3±0.4‡	34±11‡	0.2±0.04‡	22.3±13.4	6.8±3.2
3–5 mo	14	95±53‡	0.7±0.2	0.6±0.4‡	24±15	0.4±0.4‡	15.5±11.8	6.3±2.6
5–7 mo	8	23±18‡	0.8±0.2	0.2±0.1	15±8	1.2±1.7	17.1±8.0	8.2±3.2
7–12 mo	11	6.6±4.6	0.8±0.2	0.05±0.03	12±5	2.3±0.6	24.0±18.3	6.6±3.1
Prepubertal children	35	6.6±2.5§	0.7±0.2§	0.04±0.01§	—	—	3.9±2.1	1.5±0.7
Adult	17	572±135‡	1.4±0.3‡	7.9±2.3‡	107±25‡	0.2±0.05‡	—	—
Female								
cord	20	30±7	3.0±0.5	0.89±0.29	93±38	3.2±0.9	—	—
1–15 days§	15	12±6	1.2±0.2	0.14±0.06	—	—	—	—
1–3 mo	9	9±4	0.8±0.2	0.06±0.03	19±4	2.7±1.1	17.4±9.6	10.2±3.1
3–5 mo	9	6.7±2.7	0.6±0.1	0.04±0.02	17±7	2.6±1.0	13.2±7.6	8.8±3.5
5–7 mo	8	6.8±3.1	0.7±0.2	0.05±0.03	14±5	2.2±0.6	13.4±8.0	8.5±4.2
7–12 mo	8	5.5±2.8	0.7±0.2	0.03±0.01	11±1	2.8±1.0	10.6±6.2	7.4±3.2
Prepubertal children	27	6.6±2.5§	0.7±0.1§	0.04±0.01§	—	—	3.4±1.3	1.4±0.6
Adult	15	37±10	0.9±0.2	0.31±0.07	151±38	4.4±1.5	—	—

* Corrected for plasma dilution.

‡ Values statistically different in male vs. female of the same age group.

§ From previous work (7).

than in male neonates, but in both sexes significantly ($P < 0.001$) lower than in adult females (Table IV).

In male infants 1–3 mo of age the mean ratio Δ^4/T is comparable to that of adult males (Table IV). This ratio increases progressively from 1 to 7 mo of age to a value which is not different to the one found in female infants throughout the 1st year of life (Table IV).

Percentage binding of testosterone. The percentage of testosterone bound to plasma proteins in cord blood was low in both sexes (85.65±3% and 85.26±2.4% in male and female, respectively). Values in this group are similar to those previously reported (14).

Individual values found in infants of both sexes are given in Fig. 2. There was no difference according to age from 1 to 12 mo. In addition there was no sex difference in T binding at this period, the mean±1 SD values being 96.42±0.99% and 96.67±0.94 in male and female infants respectively. These values are not different from what we obtained in prepubertal children of both sexes (97.04±0.74% [7]).

Therefore there is a rapid increase in the binding of T from birth to about the 1st mo of life. From then on this percentage binding, significantly higher in both sexes than in adults, remains rather constant until puberty.

Unbound testosterone concentration. In cord unbound testosterone levels are higher in male than in female newborns ($P < 0.025$) (Table IV).

Individual values obtained in male infants are given in Table II and those of female infants in Table III. In male infants the changes with age in total testosterone and unbound testosterone concentrations were not parallel. As a result of increased binding of T at the time of increased total T concentration, the unbound T levels at 1–3 mo of age are of the same range as the ones observed at birth. Furthermore the mean value of unbound T found the first 2 wk of life, although slightly lower, is not significantly different from that of the cord or that of the 1–3-mo-old infants (Table IV). Circulating unbound testosterone levels are of the same range from birth to about the 3rd month of life. After this age there is a progressive and significant decrease in unbound T plasma concentrations, mean values obtained in each 2-mo interval being different from each other (Table IV). Finally, from 7 to 12 mo of age, values are similar to that of prepubertal children.

In female infants the high unbound T levels observed at birth drop very rapidly. From 1 to 12 mo of age the levels observed in female infants are not different and are comparable to those of 7–12 mo male infants and prepubertal children (Tables III and IV).

Plasma LH. Individual values found in male infants are given in Table II and those of female infants in Table III. In the two groups there were high plasma LH concentrations with no significant difference according to age. The mean values from 1 to 12 mo of age were 19.7±13.5 and 12.9±7.7 mU/ml in male and female, respectively. Although there is a wide range of values, the sex difference is significant ($P < 0.025$). However, in both sexes LH levels in infants are very significantly ($P < 0.0001$) higher than in prepubertal children where no sex difference was observed (3.9±2.1 and 3.4±1.3 mU/ml in boys and girls, respectively). When we studied the correlation between LH values and age there was no correlation in male ($r = -0.009$), or female infants ($r = -0.215$). Finally the statistical analysis showed a total lack of correlation between testosterone and LH levels in both male and female infants.

Plasma FSH. The concentrations of FSH in male and female infants are listed in Tables II and III. During the 1st yr of life mean FSH was significantly ($P < 0.01$) higher in female (8.7±3.3 mU/ml) than in male infants (6.7±2.9 mU/ml). Again in the two groups FSH levels were significantly ($P < 0.0001$) higher than in prepubertal children (1.5±0.7 and 1.4± 0.6 mU/ml in boys and girls, respectively). A correlation ($r = -0.352$) between FSH values and age was not found in female or in male infants ($r = 0.09$). There was also no correlation between testosterone and FSH concentration in either sex.

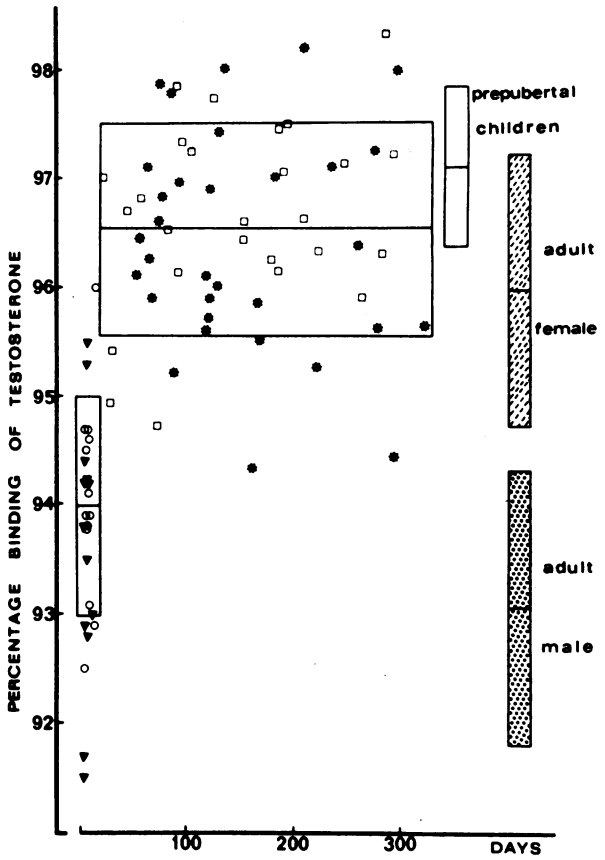

FIGURE 2 Individual values, mean±1 SD of the percentage binding of testosterone during the 1st yr of life. Mean±1 SD values observed in prepubertal children and adults are given for comparison. ▲ male, ○ female: the first 2 wk of life. ★ male, □ female: 1–12 mo of age.

DISCUSSION

The values of T concentration found in cord blood in the present study are in the same range as those previously reported when either a double isotope method (1, 2) (except in one report [4]) or a competitive protein binding technique (3, 5) was used. They are lower than values determined by the RIA method without prior chromatography (6). In none of the previous studies were sex differences in T levels demonstrated, contrary to the present findings. The considerably greater number of subjects and the high sensitivity of the RIA method used could explain this discrepancy. Our values for Δ^4 are within the range of those previously published (1, 2). In the latter studies mean male values were slightly (1) or significantly (2) higher in the male than in the female. Conversely in our series the reverse was observed. The Δ^4/T ratios found in our male subjects are in excellent agreement with those reported earlier (2). At the same time a similar pattern of T and Δ^4 has been shown in the cord blood of Rhesus monkeys (17). Our results strongly suggest that testicular activity is present at birth.

Apparently this is the first report of both plasma T and Δ^4 levels during infancy. The most striking finding was the high plasma T concentrations found in male infants the first 3 mo of life. The possibility of measuring an unknown steroid present at this age, which would have the same polarity as T and an important cross-reactivity in the immunoassay for T is quite unlikely.

Elevated urinary LH excretion has been reported in normal infants by Buckler and Clayton (9). Plasma LH concentrations obtained in the present report are in agreement with the urine data. Faiman and Winter (12) reported similar plasma concentrations of LH and FSH both in male infants and in prepubertal boys. In the male infants presently studied the range of plasma gonadotropins was much higher than in male prepubertal subjects. This discrepancy might be related to the younger age of our series. Similar to our findings these authors reported higher plasma FSH levels in girls

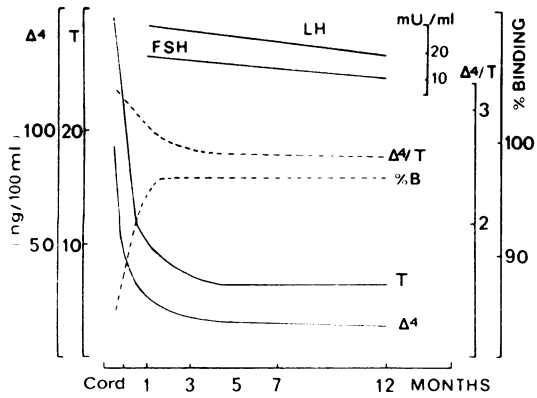

FIGURE 3 Pattern of the percentage binding of testosterone (%B), plasma testosterone (T), Δ^4-androstenedione (Δ^4), LH, and FSH levels in the female infant during the 1st yr of life.

0–2 yr than in boys. This sex difference in FSH levels seems to be a constant finding both in the human during fetal life (11, 18–20), at birth (10), and during infancy (12), and in primates (21).

The origin of testosterone has not been clearly identified in infants of either sex. It is known that at birth and during the 1st wk of life the cortisol secretion rate is higher than later in life (22). The similar pattern in T and Δ^4 concentrations (Fig. 3) observed in female infants is somewhat parallel to that of cortisol secretion and would support the view that in female infants, as in prepubertal children, T is primarily of adrenal origin. The higher T levels in male compared to female infants during the first 3 mo of life suggest that most of the T produced at this period in male infants is of testicular origin.

The increase in plasma T concentration from birth to the 3rd mo of life might not in fact represent an increase in T production. If during this period T production remains unchanged, increasing plasma levels of T could reflect a progressive decrease in the metabolic clearance rate (MCRT). It has been shown that changes in MCRT are inversely correlated with changes in the binding capacity of testosterone-estradiol binding globulin (TeBg) (23). It appears from our data (Figs. 3 and 4) that the similar increase in the percentage of T bound to plasma proteins coinciding with opposite changes in plasma T concentrations in the male and the female infants during the first 3 mo of life would rule out such a hypothesis. Furthermore in the male infants after the 3rd mo of life, the decrease in T levels with constant protein binding would not favor a change in MCRT.

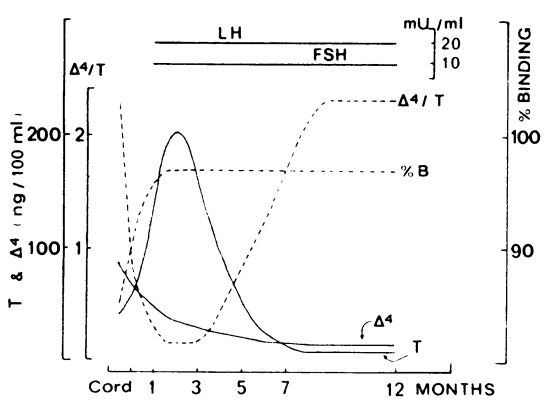

FIGURE 4 Pattern of the percentage binding of testosterone (%B), plasma testosterone (T), Δ^4-androstenedione (Δ^4), LH, and FSH levels in the male infant during the 1st yr of life.

The increase in total T concentration occurring during the first mo of life could be due to the increase in protein binding. Factors responsible for the postnatal TeBg increase are totally unknown. However, the well known action of estrogens on TeBg production (1) is not likely to play a part at this age as estrogens have been demonstrated to drop drastically in a few hours after birth (24).

Although it is difficult to prove from the present state of our knowledge, the increase in plasma testosterone levels in the postnatal period is likely to reflect an increase in testicular production. Supportive evidence is given by the low Δ^4/T ratio observed during this period; at 1–3 mo of age, the Δ^4/T ratio is similar to that of adult males. After 3 mo of life, the Δ^4/T ratio increases progressively to values observed in female infants (Figs. 3 and 4).

In contrast to the high levels of unbound and total T found in male infants during the first 3 mo of life, no clinical sign of androgenicity is usually observed, suggesting a relative insensitivity of the end organ receptors.

The decrease of both total and unbound T levels in male infants after the 3rd mo of life could represent a period of decreasing testicular activity independent of the levels of pituitary gonadotropins. Decreased secretion of T may be the result of a diminished sensitivity of the testis to endogenous gonadotropins.

Plasma immunoassayable LH was not measured in infants less than 19 days old in order to eliminate the contribution of human chorionic gonadotropin which might occur in early neonatal period. High levels of LH and FSH were found in infants from 1 to 12 mo of age (Fig. 4). These levels did not correlate with the T concentration in plasma. Although it has been recently demonstrated that in adult men there is a fluctuating pattern of serum LH and FSH (25) the range of gonadotropins levels found in infancy is considerably higher than that observed in childhood. These high

levels of gonadotropins might represent an increased pituitary production or be the result of decreased metabolic clearance. It is possible that the systems responsible for metabolizing and excreting LH and FSH do not mature until after 12 mo of life. The other possibility is that the elevated immunoassayable gonadotropin represents circulating α-subunit which is biologically inactive.

One of these factors, alone or associated, may explain the apparent absence of parallelism in the pattern observed in testosterone and LH or FSH during the 1st yr of life. In addition maturational changes of the gonadostat in the neonatal hypothalamus are likely to occur. Evidence for maturation of the hypothalamus during the first months of life has already been suggested. Pituitary growth hormone level is high during the first 2 mo (26). Paradoxical response to stimuli like glucose or glucagon have been shown (27, 28). Sleep-induced growth hormone peaks do not appear before 2 mo of life (29) and are contemporary with changes of the synchronous hemispheric activity (30). A circadian pattern of ACTH secretion becomes apparent between 1 and 3 yr of age (31). Such a maturing process may affect the sensitivity of the hypothalamus to stimulation or suppression by circulating gonadal hormones.

Plasma testosterone increase in male infants during the first months of life probably reflects testicular activity and might have an important physiological role on the sexual hypothalamic differentiation. The postnatal action of androgens in imprinting hypothalamic nervous centers at a critical period of neural differentiation has been clearly established in rodents (32, 33). However, demonstration that an estrogen induced surge of LH can be obtained in both gonadectomized adult male and female Rhesus monkeys (34) strongly suggests that the control of secretion of gonadotropins in rodents cannot be applicable to primates. A possible role of this postnatal rise of testosterone on the male behaviour throughout childhood, adolescence and adulthood remains to be demonstrated.

The present data demonstrate that testes are active during the postnatal period. It is tempting to correlate this phenomenon to a progressive maturation of the hypothalamo-pituitary-gonadal axis. It is possible that the surge of testosterone during the first 3 mo of life plays a role in the future life pattern of the male human being.

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