factor activities in both the fetal lamb and in the mother ewe. The changes were not consistent with classical disseminated intravascular coagulation. An additional stress such as hypotension is probably required to induce intravascular coagulation in the fetus. The exact mechanism responsible for the observed changes remains unclear. The changes are not related to mere exposure of fetal blood to a lowered pH. The observation that the mother ewes also experience a reduction in factor V and factor IX activity in the absence of lactic acidosis suggests the liberation of a mediator from the fetus capable of crossing the placenta. These observations support the original findings of Bishop *et al.* (3) which also suggested the liberation of a factor or factors capable of crossing the placenta and influencing coagulation activity in both fetal and maternal blood.

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PEDIATRIC RESEARCH

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Pituitary-Gonadal Function in Klinefelter Syndrome before and during Puberty

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ABSTRACT. Serum concentrations of follicle-stimulating hormone, luteinizing hormone, testosterone, and estradiol were determined at intervals before and during puberty in 40 individuals with Klinefelter syndrome (47,XXY karyotype), of whom 27 had been detected in neonatal cytogenetic screening programs. Prior to the appearance of secondary sexual changes, basal serum hormone concentrations and acute responses to stimulation with gonadotropin-releasing hormone and human chorionic gonadotropin were normal. The timing of the onset of clinical puberty was normal. Early pubertal boys showed initial testicular growth and normal serum testosterone levels, while serum follicle-stimulating hormone and estradiol concentrations were significantly elevated. By midpuberty, the Klinefelter subjects were uniformly hypergonadotropic and their testicular growth had ceased. Serum testosterone concentrations after age 15 remained in the low-normal adult range. Serum estradiol levels remained high, irrespective of the presence or absence of gynecomastia. Exaggerated responses to gonadotropin-releasing hormone are seen in pubertal subjects with elevated basal gonadotropin values. (*Pediatr Res* 19: 82–86, 1985)

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Presented in part at the Western Society for Pediatric Research, 1984.
Following the submission of this manuscript, one pubertal aneuploid subject has been found to have a low percent mosaicism with karyotype 46,XY/46,XX/47,XXY (6:13:175) in blood and fibroblasts.

Abbreviations

FSH, follicle-stimulating hormone
LH, luteinizing hormone
T, testosterone
E2, estradiol
GnRH, gonadotropin-releasing hormone
hCG, human chorionic gonadotropin

Klinefelter syndrome was first described in adult phenotypic males with gynecomastia, azoospermia, and hypergonadotropic hypogonadism, and was subsequently found to be associated with the presence of an extra X chromosome. Because the condition is rarely diagnosed until adult life, little is known about the natural history of the hypogonadism in young males with the 47,XXY karyotype.

In the past two decades, studies involving cytogenetic analysis of unselected neonates have provided an opportunity for the prospective study of boys with this karyotype. The growth, psychological development, and adolescent status of our subjects have been reported (14). The present report describes a study of pituitary-gonadal endocrine function in patients with 47,XXY before and during puberty.

MATERIALS AND METHODS

Forty subjects with a 47,XXY karyotype were available for study. In each, cultured leukocyte chromosome analysis had failed to demonstrate mosaicism. Twenty-seven subjects (age 1–16 yr) were identified during neonatal screening programs in Denver, Winnipeg and Toronto (courtesy of Dr. John Bailey, Hospital for Sick Children), and thus represent an unselected group (12). The remaining 13 boys (age 7–19 yr) were referred to these centers because of behavioral problems, gynecomastia, small testes, or micropenis, and were subsequently found to have a 47,XXY karyotype. No patient had received androgen supplementation for at least 4 months prior to being studied. A second group of 22 chromatin negative male siblings of the aneuploid subjects in the Denver Family Development Study was available as a control group for comparison with our previously published age-specific normal hormone values (16, 17).

Each subject had venous blood drawn at the initial assessment and at up to six subsequent visits, for determination of serum concentrations of FSH, LH, T, and E2. In 15 47,XXY individuals, ages 6–14 yr, more detailed testing of pituitary-gonadal function was carried out with sequential GnRH and hCG stimulation tests. An intravenous bolus of 200 μg GnRH (gonadorelin, Factrel, Ayerst) was administered, and samples obtained at −30, 0, 15, 30, 45, 60, 120, and 180 min for assay of serum FSH and LH. Each subject also received 2000 units hCG (Pregnyl, Organon) intramuscularly on 3 consecutive days, followed by determination of serum T and E2 24h after the last injection (20). All samples were assayed in the same laboratory using previously described radioimmunoassays for FSH (4), LH (5), T (19), and E2 (19). The interassay coefficient of variance for each assay was less than ±12% over the period of the study. The significance of differences between groups was evaluated by the nonparametric Mann-Whitney test because the data were not normally distributed. Informed consent was obtained from the parents.

RESULTS

The development of the 27 boys identified by newborn cytogenetic survey has been reported (14). All pubertal subjects have developed satisfactory secondary sexual characteristics. None showed any genital ambiguity. Prior to the first appearance of pubic hair, which usually occurred between ages 11–14 yr, most were growing at or above the 50th percentile for height and had a normal penile size. One boy, who was referred because of apparent micropenis (2.6 cm at age 11 yr), later entered puberty spontaneously and showed normal penile growth. At age 10, the median testicular volume, using the Prader orchidometer, was 1 ml (range 0.5–2 ml). With the appearance of pubic hair (Tanner stage PH_2) median testicular volume increased to 4 ml (range 2–10 ml). Six boys were followed with annual examinations through puberty. Of these, five showed an initial increase and then a subsequent decrease in testicular size, whereas in the sixth, testicular volume remained at 2.5–3 ml. Therefore, at stage PH_{4-5} median testicular volume was only 3 ml (range 2–7 ml). Of the seven patients referred after the age of 10 yr, gynecomastia was present initially or developed subsequently in five. One of six unselected pubertal boys (age 13 yr) has slight rounding of the aureola with no palpable glandular tissue.

The basal serum concentrations of FSH and LH in 47,XXY subjects are shown in Figure 1. It can be seen that virtually all FSH and most LH values were normal before age 12, but by age 14 the values for both were uniformly elevated. Figure 2 shows that the magnitude and timing of the initial adolescent rise in serum T were relatively normal. However, T levels plateaued after age 14, and individual values subsequently failed to rise above the middle of the normal range. Serum FSH, LH, and T values for the control siblings fell within the normal range. Six of the 47,XXY boys showed slight elevations of E2 (up to 2 ng/dl) before the clinical onset of puberty and before any rise in T. A similar unexplained slight elevation was observed in one of the siblings, although E2 concentrations at this age (8–10 yr) were not significantly different between the two groups.

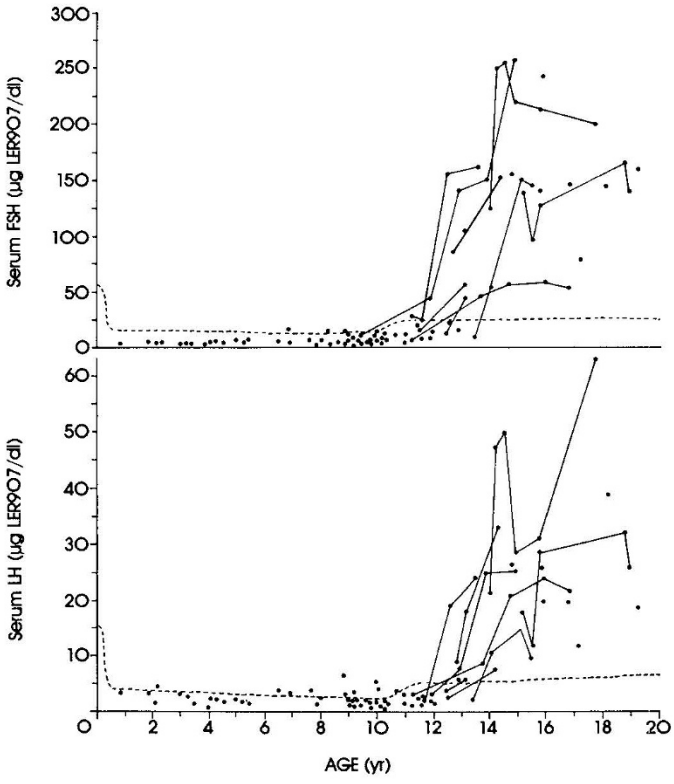

Fig. 1. Basal serum FSH and LH concentrations in boys with 47,XXY before and during puberty. The *dotted lines* show the upper limit of the normal range in males (16). Successive values from the same subject are connected from the time they exceed the normal range. The FSH and LH, which are expressed in μg LER907/dl, may be converted to IU/liter by multiplying the FSH value by 0.5 and the LH value by 4.5.

Table 1 compares median serum hormone levels in the 47,XXY boys and the control siblings between ages 8 and 14 yr. At age 8–10 yr there were no significant differences. At 11–12 yr, T and E2 levels were higher in the 47,XXY boys, a possible indication that they had entered puberty slightly earlier than the control siblings. By age 13–14 yr their sex steroid concentrations were within the normal range, but the 47,XXY subjects were clearly hypergonadotropic.

Because testicular size is not a valid index of pubertal development in Klinefelter syndrome, the subjects were assigned pubertal stages solely on the basis of pubic hair development. Table 2 summarizes the relationship of serum hormone concentrations to these pubertal stages. Increased serum concentrations of FSH and E2 were apparent by stage PH_2. By midpuberty (stage PH_{3-5}), the 47,XXY boys were significantly hypergonadotropic, even though at this stage their T and E2 concentrations were not abnormal. Serum T and E2 levels in six boys at the time of diagnosis of gynecomastia were not significantly different from those in age-matched 47,XXY subjects without gynecomastia.

Stimulation tests with GnRH and hCG were carried out in late childhood and early puberty in an effort to uncover more subtle abnormalities of pituitary-gonadal function. In response to 3 days of hCG stimulation (Fig. 3), all 14 47,XXY patients increased their serum T level. In all but two, the peak T value was at least as high as in normal boys at the same level of development (20), even though several patients already had elevated basal FSH and/or LH concentrations. The median post-hCG peak serum E2 concentration was 1.8 ng/dl (range 1.0–3.4 ng/dl) in the prepubertal subjects and 2.7 ng/dl (range 1.0–6.9 ng/dl) in the early pubertal subjects, both of which are within the normal range (20). Similarly, hCG administration did not induce any significant abnormality in the E2/T ratio at this stage of puberty.

The peak FSH and LH responses to a single intravenous dose of GnRH are shown in Figure 4. Exaggerated responses were observed in 47,XXY boys who already had elevated basal serum gonadotropin values. However, acute GnRH stimulation did not evoke abnormal responses in subjects with normal basal FSH and LH levels.

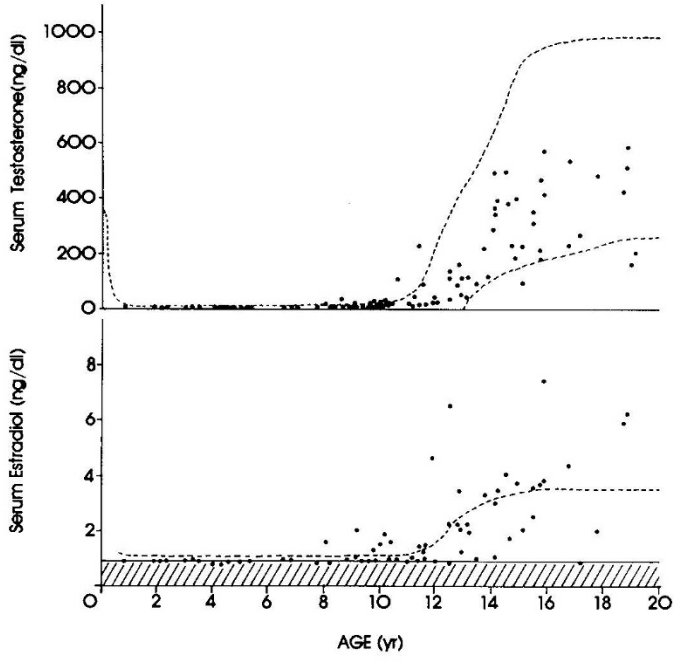

Fig. 2. Basal serum concentrations of T and E2 in boys with 47,XXY before and during puberty. The *dotted lines* show the normal range for T and the upper normal limit for E2 (16). The *shaded area* shows the lower limit of sensitivity of the E2 radioimmunoassay.

DISCUSSION

Klinefelter syndrome is the most common form of male hypogonadism, but the definitive clinical picture of micro-orchidism, gynecomastia, and eunuchoidism does not appear until after midpuberty and may never be fully expressed. Children with the 47,XXY karyotype demonstrate relatively few clinical findings, although there may be some who show reduced testicular size or penile length. Their testes contain a reduced number of spermatogonia, but tubular fibrosis and hyalinization of seminiferous tubules are not observed until after the onset of puberty (6). The testes of adult patients reveal extensive fibrosis and hyalinization, while Leydig cell volume may be preserved (1). Clinical findings in the adult Klinefelter patient include absent or markedly reduced spermatogenesis, and hypergonadotropic hypogonadism with low-normal or frankly reduced levels of serum T and high-normal or elevated levels of serum E2 (7). Even in elderly patients, as testicular function declines further, this increased E2/T ratio is maintained (8).

The present study confirms that during childhood, and even into early puberty, pituitary-gonadal function is relatively normal in 47,XXY subjects (15). In contrast to the elevated serum FSH values characteristic of completely agonadal individuals (18), all of our subjects had normal FSH levels before puberty. The few occurrences in late childhood of slightly increased serum LH levels for age, even though they were not accompanied by testicular enlargement or increased T values, may have been a sign of impending puberty. A slight increase in E2 was observed in six 47,XXY subjects before puberty, but the group's values were not significantly different from normal, and this finding does not appear to be characteristic of prepubertal patients with the karyotype.

The onset of puberty was determined as the first appearance of pubic hair because of the difficulty using testicular growth in

Table 1. *Age-related serum gonadotropin and gonadal steroid concentrations in boys with a 47,XXY karyotype compared to control siblings*

Age (yr)	Subjects	*n*	FSH (μg/dl)	LH (μg/dl)	T (ng/dl)	E2 (ng/dl)
8–10	47,XXY	17	8.1 (3.8–15.0)	2.6 (1.3–6.7)	14 (<10–110)	1.4 (<1.0–4.6)
	Controls	5	7.0 (4.1–11.0)	2.5 (1.5–3.6)	10 (<10–14)	2.0 (<1.0–2.0)
11–12	47,XXY	10	15.8 (6.3–85.0)	2.5 (1.9–8.7)	50 (14–227)*	1.4 (<1.0–6.5)*
	Controls	13	10.0 (7.5–30.0)	2.5 (2.1–5.5)	14 (<10–145)	1.0 (<1.0–2.2)
13–14	47,XXY	9	125.0 (41.0–150)**	17.6 (5.8–33.0)***	216 (92–498)	2.1 (<1.0–3.3)
	Controls	6	13.0 (6.1–35.0)	3.6 (2.1–6.4)	45 (15–304)	2.0 (1.1–3.2)

Values are median with the range in parentheses. To reduce sampling frequency bias, each subject contributed no more than one specimen to each age interval. Differences between 47,XXY subjects and control siblings were calculated with a two-tailed Mann-Whitney test and are significant where indicated with * $p < 0.05$, ** $p = 0.001$, and *** $p = 0.002$.

Table 2. *Pubertal stage-related serum gonadotropin and gonadal steroid concentrations in boys with a 47,XXY karyotype compared to control siblings*

Pubertal stage	Subjects	*n*	FSH (μg/dl)	LH (μg/dl)	T (ng/dl)	E2 (ng/dl)
PH_1	47,XXY	40	8.0 (3.6–23.0)	2.5 (1.3–6.7)	14 (<10–135)	1.0 (<1.0–6.5)
	Controls	14	9.2 (2.7–30.0)	2.5 (1.5–5.1)	11 (<10–145)	1.0 (<1.0–2.0)
PH_2	47,XXY	6	42.5 (15.0–150)*	5.4 (1.1–19.0)	69 (<10–115)	2.2 (<1.0–4.6)**
	Controls	9	11.0 (6.1–16.0)	2.5 (2.1–4.8)	15 (<10–110)	1.0 (<1.0–2.2)
PH_{3-5}	47,XXY	18	150 (44.5–264)***	24.0 (7.0–63.0)***	367 (92–566)	3.2 (<1.0–7.4)
	Controls	8	22.5 (10.0–35.0)	5.7 (2.5–8.4)	316 (31–462)	3.0 (1.9–5.6)

Values are median with the range in parentheses. To reduce sampling frequency bias, no more than one specimen was included from each subject per year. Pubertal stage was assigned according to pubic hair development. Differences between 47,XXY subjects and control siblings were calculated with a two-tailed Mann-Whitney test and are significant where indicated with * $p = 0.003$, ** $p < 0.05$, and *** $p < 0.001$.

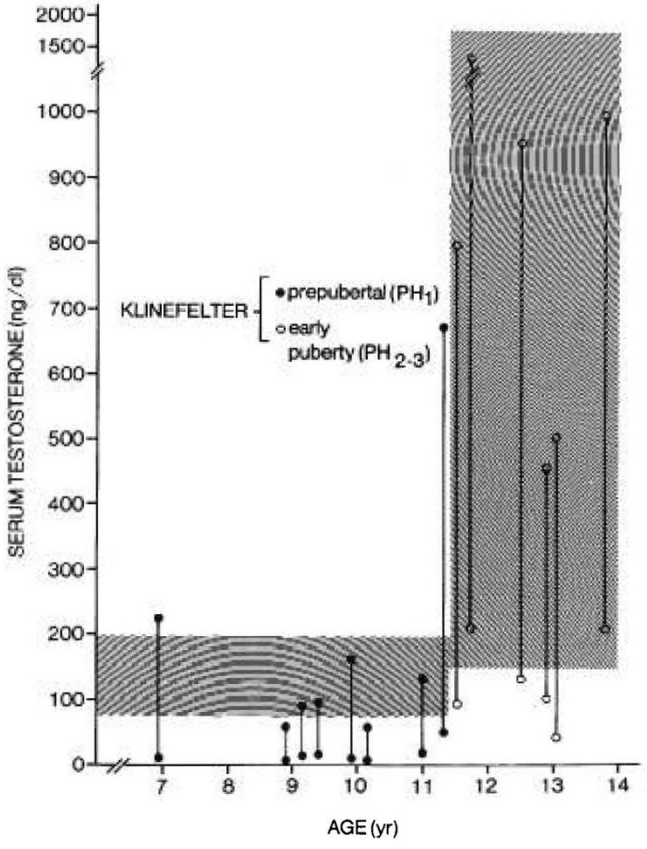

Fig. 3. The serum T response to 3 daily 2000 U doses of hCG in boys with a 47,XXY karyotype before puberty (●) and after the appearance of pubic hair (○). The basal and peak poststimulation values for each subject are connected. The *shaded area* indicates the normal range for peak values observed in healthy prepubertal and early pubertal boys (20).

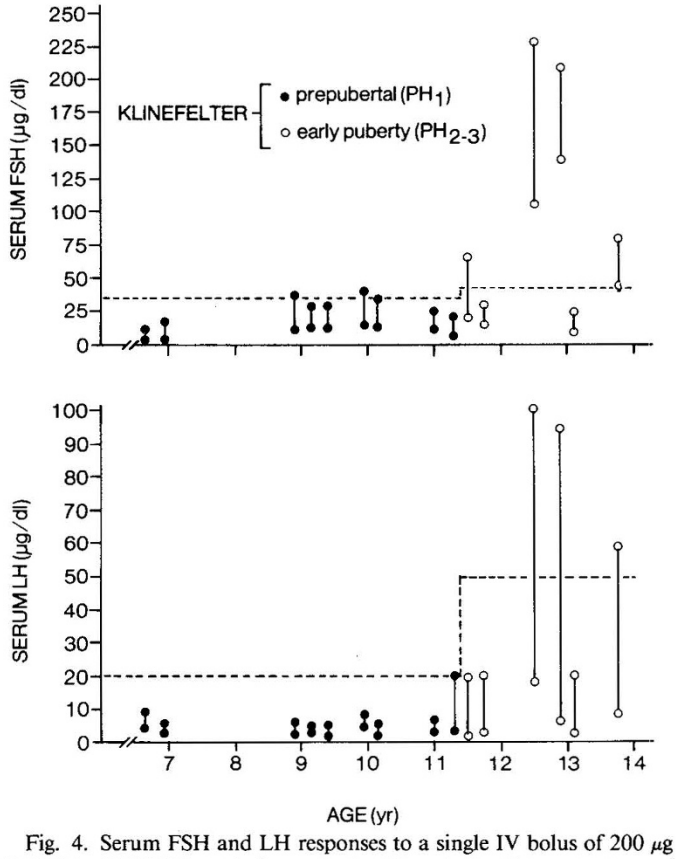

Fig. 4. Serum FSH and LH responses to a single IV bolus of 200 μg GnRH in 47,XXY boys before puberty (●) and after the appearance of pubic hair (○). The basal and peak poststimulation gonadotropin values for each subject are connected. The *dotted line* indicates the upper limit of peak post-GnRH values observed in healthy prepubertal and early pubertal boys.

Klinefelter patients. Its occurrence was at least as early as in the control siblings and was accompanied by a normal initial rise in serum T level. The observed testicular volumes for the 47,XXY patients at puberty stage PH_2 were only slightly smaller than those (mean 5 ml, range 3–10 ml) observed in the normal population. However, after an initial increase in size, continued testicular growth did not occur, and no patient even approached the normal adult mean volume of 15 ml (range 12–25 ml).

Even though their T concentrations during early puberty were similar or greater than the controls, and within the normal range for age or pubertal stage (16), many Klinefelter subjects showed abnormal serum FSH values soon after clinical puberty was apparent, and by midpuberty they were clearly hypergonadotropic (present study and Ref. 11). High E2 concentrations were found throughout puberty. Particularly in early puberty, many patients showed a high E2/T ratio, which presumably accounts for the frequent occurrence of gynecomastia (3, 9). High E2 levels might also be expected to induce relatively high levels of sex hormone-binding globulin, thus further reducing serum free T (2). In Klinefelter syndrome, high E2 levels appear to reflect increased testicular estrogen secretion rather than enhanced peripheral aromatization (13), a phenomenon which likely results from excessive FSH stimulation (10). It is of interest that the administration of hCG in our study, which is an LH-like stimulus, does not further increase the E2/T ratio in these hypergonadotropic individuals (7).

The basic endocrine defect in Klinefelter syndrome appears to be gonadal. The relative roles of the testicular structure and function observed at puberty and elevated gonadotropin secretion is not presently understood. We found that during childhood, serum gonadotropin levels are normal even following GnRH stimulation. By midpuberty, Klinefelter subjects are hypergonadotropic, even though their basal T levels are not markedly reduced and T secretion can be increased further either by the administration of hCG or infusion of sufficient GnRH to raise endogenous LH even further. It would appear that high circulating gonadotropin levels may exacerbate the primary testicular lesion and cause the progressive hyalinization and fibrosis. Eventually, testicular damage or a local effect of intratesticular estrogen leads to diminished T reserve. It remains to be seen to what extent early aggressive T therapy might influence the course of this adolescent endocrine dysfunction.

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PEDIATRIC RESEARCH

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Studies on Requirements for Amino Acids in Infants with Disorders of Amino Acid Metabolism. I. Effect of Alanine

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ABSTRACT. Two infants with disorders of propionate metabolism were studied at 7 months of age to determine optimum levels of intake of protein and calories to meet the requirements for essential amino acid for growth in infancy, and at the same time minimize the accumulation of toxic intermediates. An effect of alanine was found that permitted growth at otherwise limiting levels of protein intake. This was not simply an effect of nonessential nitrogen as neither glycine nor glutamic acid could substitute for alanine in this protein-sparing effect. This appears to represent further evidence of the relationship between alanine and the branched-chain amino acids and of the importance of the alanine-glucose cycle in human physiology. (*Pediatr Res* 19: 86–91, 1985)

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Abbreviation

BA, baseline period