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Serum Leptin Levels in Normal Children: Relationship to Age, Gender, Body Mass Index, Pituitary-Gonadal Hormones, and Pubertal Stage*

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ABSTRACT

It is commonly accepted that at least in girls puberty starts when a minimum level of body mass or a certain amount of body fat are present. However the precise signal by which adipose stores inform the hypothalamus of the degree of energetic reserves is unknown. Leptin is a hormone produced by the adipocytes to regulate food intake and energy expenditure at the hypothalamic level. To understand whether leptin is the adipose tissue signal that allows puberty, 789 normal children of both sexes, age 5–15 yr, were transversally studied. Leptin levels, as well as gonadal and gonadotropins levels, were analyzed in addition to the determination of auxological parameters.

In an age-related analysis, leptin levels in girls rose from 5–15 yr (from 4.3 ± 0.4 to 8.5 ± 0.9 μg/L) in parallel with body weight. Boys always had lower leptin levels than girls (3.3 ± 0.3 μg/L at 5 yr), but they rose in parallel with weight until 10 yr (5.3 ± 0.7 μg/L), when a striking decrease was observed until 15 yr (3.0 ± 0.3 μg/L). In girls, leptin was the first hormone to rise followed by FSH and later by LH and estradiol. A similar pattern occurred in boys, despite the fact that leptin dropped after 10 yr when testosterone rises. Divided into three pubertal stages, *i.e.* P1 = prepuberty, P2 = early puberty, and P3 = overt puberty, in girls the four hormones rose progressively from P1 to P3, but from P2 to P3 the percent increment was greater for LH and estradiol. In boys, leptin decreased from P1 to P3, whereas FSH, LH, and testosterone rose. The age-related changes were not caused by adiposity variations, because data did not change when subtracting values of children over 97% of standard deviation score of body mass index.

In conclusion: 1) leptin appears to increase in both boys and girls before the appearance of other reproductive hormones related to puberty; 2) leptin levels in boys are always lower than in girls, although they increase with age until the age 10 yr; 3) leptin in boys declines about the time testosterone increases. Leptin may well be a permissive factor for the initiation of pubertal events. (*J Clin Endocrinol Metab* **82:** 2849–2855, 1997)

ONE OF the most fascinating aspects of human development is the complex series of events of puberty (1). Although the lay concept of puberty is clear-cut, the scientific definition and staging is strikingly difficult, and the step-by-step hormonal events that lead to the acquisition of reproductive maturity is still being debated (2). It is known that puberty onset is triggered at a hypothalamic level through the increased release of GnRH (3). However, why this process occurs at any particular age and not before or after is unknown. It is widely accepted that a minimum level of body mass or a certain amount of body fat is necessary before female puberty may start (4, 5). In infant rats, a controlled food restriction blocks body growth, impeding the start of puberty, and later on when *ad libitum* food is provided, rapid body growth ensues with an immediate starting of the pubertal process (6, 7). Interestingly enough, the effects of food restriction or low body weight on the male reproductive function are scarce, if any (6). Epidemiological studies in humans based on auxological information led to similar conclusions (8).

Assuming that women need to attain a fixed amount of body fat before the pubertal process starts, the question is how the hypothalamus becomes aware of the fact that a safe dotation of adipose tissue has been built. A logical candidate to convey such information from the adipose tissue to the hypothalamus is the newly discovered hormone leptin (9). Leptin is produced by the adipocytes to regulate food intake at hypothalamic level, and its circulating levels directly correlate with the amount of body fat and body mass index (BMI) (10, 11). Furthermore, leptin plays a role in the gonadal axis, because it is able to correct reproductive dysfunction in some experimental animal models (12, 13).

In the present work, the levels of circulating serum leptin and their relationship with age or pubertal development have been assessed in a large group of healthy children of both sexes. The aim of this work has been to understand the relationship between leptin and the pubertal process in humans.

Subjects and Methods

A cross-sectional study was made up of healthy children from three basic educational schools in the province of Pontevedra, North-West

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Spain. The schools were randomly selected from all the State schools of the province, and in each of them the participating children were selected by a random process to assure on an epidemiological basis that the population studied was representative of the Spanish child population. Of the 1069 eligible children, 789 were included; 343 girls with a mean age of 10.11 ± 0.14 yr, ranging from 5–15 yr, and 446 boys with a mean age of 10.00 ± 0.13 yr, ranging from 5–15 yr. The study was approved by the General Hospital Ethical Committee, and informed consent was previously obtained from all the childrens' parents.

Standing height was measured using a portable direct reading Harpenden stadiometer. Weight was determined for the children without shoes or coats using a calibrated electronic scale. To study the effect of stature, height was expressed in meters, and to evaluate the influence of nutritional status, weight was expressed as a percentage of median weight for height age (WFHA), using the Spanish standards (14). The mean BMI, defined as weight in kilograms divided by the square of height in meters (kg/m^2) (15) was calculated, as well as a corrected BMI for children based on the formula $weight/height^{2.88}$ ($kg/m^{2.88}$) (16). Blood samples were obtained in the morning (0900–1100 h) by standard venipuncture technique, and after clotting at 4 C, the serum was separated by centrifugation and stored at −20 C until assay.

To assess the effect of age on the parameters measured, the children were grouped according to their chronological age. Because of the relatively low number of subjects, in both girls and boys the groups of 5- and 6-yr-olds were collapsed into a single cell. A similar approach was undertaken for the groups of 14- and 15-yr-olds. To assess the effect of pubertal development on the hormonal parameters studied, the children were grouped according to their stage of pubertal development. Puberty stages were established based on testosterone levels in the boys and estradiol levels in the girls as previously described (17–19), and three groups of children (P1 = prepuberty, P2 = early puberty, and P3 = overt puberty) were studied. The cut-off for prepubertal and pubertal stages for either testosterone and estradiol had been previously determined in a sample of 186 children (90 girls and 90 boys) from our normal pediatric population. The P1 group consisted of 188 girls with estradiol levels <36.57 pmol/L and 327 boys with testosterone levels <1.74 nmol/L. The P2 group consisted of 49 girls with estradiol levels ranging from 36.68–91.69 pmol/L and 34 boys with testosterone levels ranging from 1.74–5.21 nmol/L. Finally, the P3 group consisted of 106 girls with estradiol levels >91.69 pmol/L and 85 boys with testosterone levels >5.21 nmol/L (Table 1). In pubertal girls, the date of the last menses was not registered, thus hormonal values were obtained at an unsynchronized menstrual stage.

Hormone assays

Total testosterone levels were measured by solid-phase RIA (Coat-A-Count, Diagnostic Products Corp., Los Angeles, CA). The sensitivity was 0.138 pmol/L (0.04 ng/mL), the maximal interassay coefficient of variation (CV) was 7.9%, and the maximal intraassay CV was 4.9%. Estradiol in serum was determined by solid-phase RIA (Coat-A-Count, Diagnostic Products Corp.). The sensitivity was 18,355 pmol/L (5 pg/mL), the maximal interassay CV was 5.5%, and the maximal intraassay CV was 2.8%. Serum LH and FSH concentrations were measured in duplicate by two-site monoclonal immunoradiometric assays (IRMA, Nichols Laboratories, San Juan de Capistrano, CA) using the first and second International Reference Preparations as standards, respectively. The assays had a sensitivity of 0.1 IU/L for LH and 0.2 IU/L for FSH. Their maximal interassay CV was 5.4% (LH) and 3.8% (FSH), and their maximal intraassay CV was 2.6% (LH) and 2.3% (FSH). Values less than assay sensitivity were assigned the value of assay sensitivity.

Serum leptin levels were measured in duplicate by RIA for leptin (11) using commercial kits (Human Leptin RIA, Linco Research Inc., St. Charles, MO). The limit of sensitivity was 0.5 $\mu g/L$, the intraassay CV was 8.3%, and the interassay CV was 6.2%.

Statistical analyses

Results are presented as mean ± SEM of absolute values; the data was analyzed on a Macintosh Centrix 650 using Statview 4.02 (Abacus Concepts Inc., Berkeley, CA). The effect of gender and pubertal stage on leptin and other hormonal parameters and the differences between the experimental groups were evaluated by two-way ANOVA with repeated measures followed by Scheffe's test. When appropriate, a log transformation of data was carried out for leptin, estradiol, FSH, and LH. The effect of age, weight, height, BMI, and sex hormone and gonadotropin levels on leptin values and their relationships was assessed by simple linear correlation (Pearson's test), multivariate regression analysis, and stepwise correlation analysis. Values of $P < 0.05$ were considered significant.

Results

To clarify the age-related changes in serum leptin levels as related to the auxological parameters, the 789 children studied (Table 1), were subdivided into nine subgroups of each sex (Fig. 1). As expected, in both the girls and boys, height and weight steadily increased from age 5 until 15 yr with significant ($P < 0.05$) differences *vs*. the 5- to 6-yr-old group. The BMI, calculated as kg/m^2, progressively increased with age, being significantly different compared with the 5- to 6-yr-old group ($P < 0.05$), but no differences in BMI were observed between boys and girls (Fig. 1). As an indication that the population studied was normal with <13% of children considered in the low or high weight range (see below), the BMI values, as well as the standard deviation score of body mass index (SDS-BMI), were within the normal range in any age group. Furthermore, the BMI calculated as $kg/m^{2.88}$ (16), were within the normal range with no differences between the girls and the boys and with no increase with respect to the 5- to 6-yr-old group (Fig. 1).

Interestingly, the values of plasma leptin showed two differentiated patterns depending on gender. In the girls, leptin

TABLE 1. Clinical and hormonal characteristics of groups studied. Values are mean ± SEM.

Characteristic	Prepubertal (P1)		Early puberty (P2)		Overt puberty (P3)	
	Girls (n = 188)	Boys (n = 327)	Girls (n = 49)	Boys (n = 34)	Girls (n = 106)	Boys (n = 85)
Age (yr)	8.37 ± 0.14	8.85 ± 0.12	11.22 ± 0.22	12.65 ± 0.19	12.69 ± 0.13	13.38 ± 0.12
Height (m)	1.33 ± 0.01	1.35 ± 0.01	1.50 ± 0.02	1.56 ± 0.01	1.57 ± 0.01	1.64 ± 0.01
Weight (kg)	31.09 ± 0.65	33.39 ± 0.58	44.86 ± 1.91	47.77 ± 1.49	52.09 ± 0.99	55.37 ± 1.00
% WFHA	107.9 ± 1.4	111.3 ± 1.2	114.2 ± 3.8	109.7 ± 3.3	114.7 ± 2.1	114.7 ± 1.8
BMI (kg/m^2)	17.39 ± 0.21	17.5 ± 0.17	19.82 ± 0.64	19.42 ± 0.44	20.93 ± 0.34	20.60 ± 0.29
SDS-BMI	0.131 ± 0.09	0.439 ± 0.08	0.575 ± 0.23	0.355 ± 0.18	0.631 ± 0.12	0.602 ± 0.10
BMI ($kg/m^{2.88}$)	13.56 ± 0.15	13.81 ± 0.12	13.97 ± 0.43	13.12 ± 0.29	14.08 ± 0.24	13.42 ± 0.20
Leptin ($\mu g/L$)	5.47 ± 0.28	4.38 ± 0.22	7.10 ± 0.71	4.06 ± 0.46	8.11 ± 0.55	2.71 ± 0.19
Testosterone (nmol/L)		0.3 ± 0.01		3.16 ± 0.2		11.9 ± 0.5
Estradiol (pmol/L)	19.8 ± 0.2		64.5 ± 2.5		274.7 ± 25.1	
FSH (IU/L)	1.6 ± 0.09	1.06 ± 0.04	4.4 ± 0.4	2.13 ± 0.1	4.7 ± 0.2	3.3 ± 0.1
LH (IU/L)	0.1 ± 0.03	0.1 ± 0.00	1.1 ± 0.2	0.3 ± 0.06	2.9 ± 0.4	0.8 ± 0.07

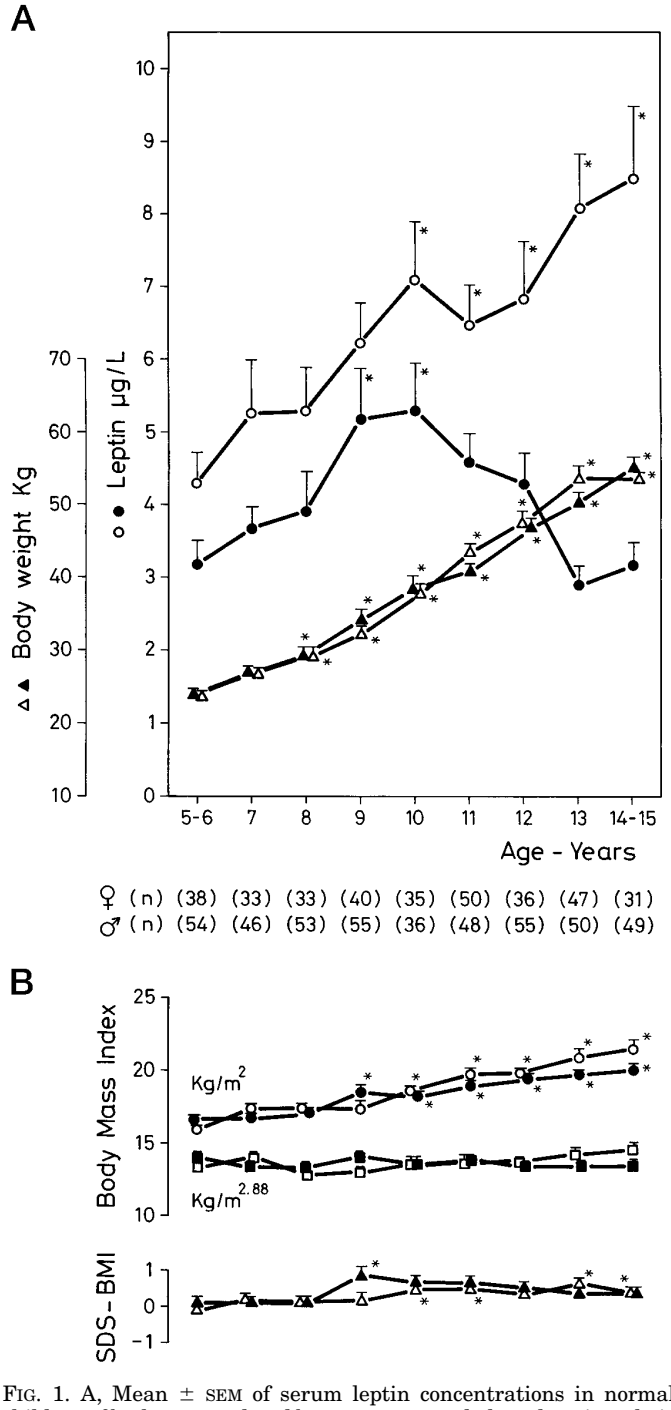

FIG. 1. A, Mean ± SEM of serum leptin concentrations in normal children of both sexes ordered by age groups and plotted against their respective body weight. B, Mean ± SEM of BMI calculated as Kg/m^2 (19) or corrected as $Kg/m^{2.88}$ (20), as well as SDS-BMI. Boys, *filled symbols*; girls, *open symbols*; (n) number of children in each age group. *, $P < 0.05$ *vs.* respective value in 5- to 6-yr-old group.

values evolved parallel with body weight and independently of BMI, increasing from the 5- to 6-yr-old group value (4.3 ± 0.4 µg/L) to 8.5 ± 0.9 µg/L in the 14-to 15-yr-old group. From the 10 yr-old group to the 14–15-yr-old group the increase in leptin was significant ($P < 0.05$ *vs.* the 5–6 yr-old group) (Fig. 1). In contrast, leptin levels in the boys were lower than in the girls from the initial period of observation at 5–6 yr (3.3 ± 0.3 µg/L), despite the absence of differences in body weight. Leptin values in the boys also showed an increase in parallel with body weight up to the 10-yr-old period (5.3 ± 0.7 µg/L, $P < 0.05$ *vs.* the 5- to 6-yr-old group). Afterwards, a clear inversion in the pattern was evident, with a progressive decrease in leptin levels, 3.0 ± 0.3 µg/L at 14–15 yr, lower although not significantly, than at 5–6 yr. It is obvious that the progressive leptin decrease was not related to any change in the auxological parameters measured. To understand the relationship of the observed plasma leptin values with the other biological parameters, a simple linear regression analysis was undertaken. A positive correlation ($P < 0.0005$), was observed in both sexes only between leptin and weight and leptin and BMI.

To observe whether these leptin changes were related to the hormonal changes associated with pubertal development, leptin values were plotted against FSH, LH, and gonadal hormone levels. In the girls (Fig. 2), between 5–6 yr and 10 yr the first hormone to increase was leptin, followed by FSH from 1.0 ± 0.1 IU/L at 7 yr to 2.3 ± 0.3 IU/L at 10 yr ($P < 0.001$). LH and estradiol experienced no significant changes between the 5- to 6-yr-old and the 10-yr-old group (0.1 ± 0.05 to 0.3 ± 0.1 IU/L and 19.0 ± 0.4 to 49.7 ± 9.0 pmol/L, respectively). From age 10 yr, leptin levels increased steadily, whereas FSH values plateaued from age 12 yr. In contrast, the first significant increase *vs.* the 5- to 6-yr-old group in estradiol was observed at 11 yr (87.2 ± 15.6 pmol/L,

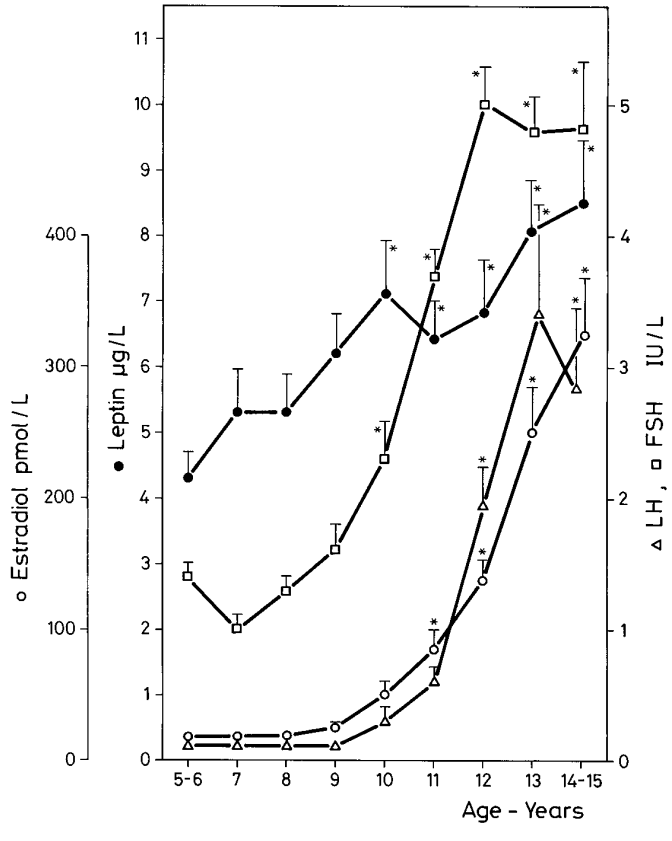

FIG. 2. Mean ± SEM serum concentrations of leptin (●), FSH (□), LH (△), and estradiol (○) in normal girls studied, ordered by age groups. *, $P < 0.05$ *vs.* respective hormone values in group age 5–6 yr.

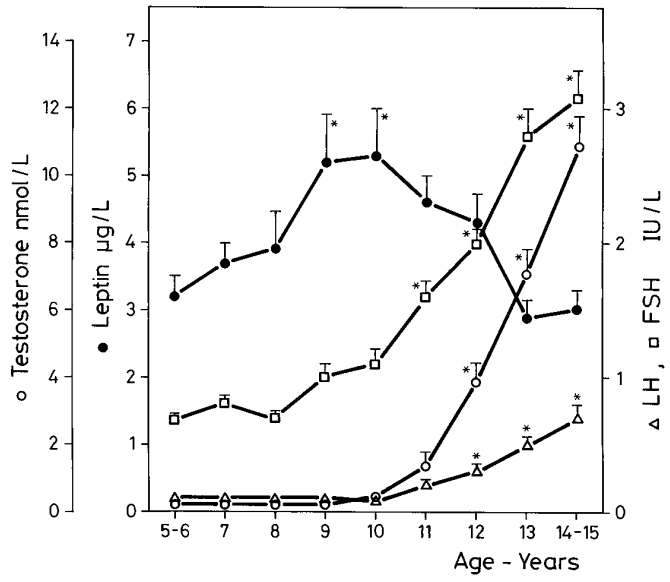

FIG. 3. Mean ± SEM serum concentrations of leptin (●), FSH (□), LH (△), and testosterone (○) in normal boys studied, ordered by age groups. *, $P < 0.05$ *vs.* respective value in group age 5–6 yr.

$P < 0.05$), whereas the first significant increase in LH values was observed at 12 yr (1.9 ± 0.3 IU/L, $P < 0.005$), with these two values increasing thereafter (Fig. 2). In the girls, a positive correlation ($P < 0.005$), was observed between leptin and either estradiol, FSH, and LH.

In the boys (Fig. 3), a leptin increase was observed in the 9- and 10-yr-old group, whereas FSH, LH, and testosterone did not change from age 5–6 yr to age 10 yr. The progressive rise observed from the age 8-yr period in FSH values became significantly ($P < 0.001$) higher *vs.* the low age group at age 11 yr (0.7 ± 0.07 and 1.6 ± 0.1 IU/L at 5–6 yr and 11 yr, respectively), and was higher ($P < 0.005$) at all age periods thereafter. The third increase in hormonal values was observed for LH and testosterone at 12 yr (LH, 0.1 ± 0.02 IU/L at 5–6 yr and 0.3 ± 0.05 IU/L at 12 yr, $P < 0.001$; testosterone 0.1 ± 0.01 and 3.9 ± 0.6 nmol/L at 5–6 yr and 12 yr, respectively, $P < 0.001$). Coincidentally with the increase in FSH, LH, and testosterone values, an inversion in the leptin values was observed, which decreased from the age 10-yr period thereafter. In the boys, leptin was negatively correlated ($P < 0.0005$) with testosterone, FSH, or LH.

To understand whether the leptin changes were age related or puberty related, the children were divided into three stages of pubertal development based on the levels of estradiol in the girls and testosterone in the boys as previously described (17–19). The three stages were P1, prepuberty; P2, early puberty; P3 overt puberty. In the girls, a significant ($P < 0.05$) increase was observed at P2 for the four hormones measured compared with P1 (Fig. 4). Although all these parameters increased again ($P < 0.05$) when puberty was completely accomplished in the P3 stage, only LH and estradiol values increased significantly *vs.* the previous P2 stage. In particular, leptin values increased from 5.4 ± 0.2 µg/L at P1 to 7.1 ± 0.7 µg/L at P2 and 8.1 ± 0.5 µg/L at P3. Examined as percent of increase *vs.* P1 values, the leptin and FSH increments were very modest at P2 and P3, whereas

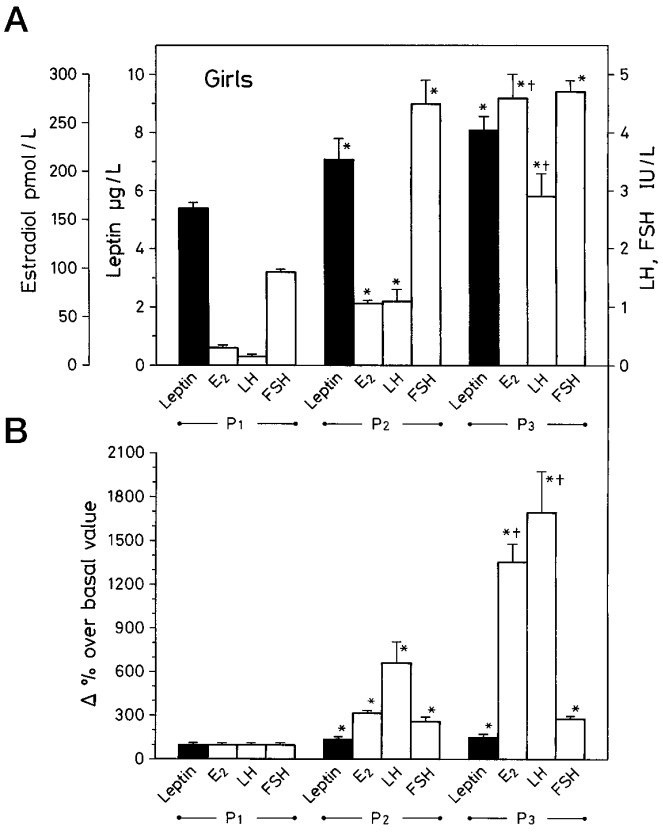

FIG. 4. A, Mean ± SEM of serum concentrations of leptin, LH, FSH, and estradiol (E_2) in normal girls in three pubertal stages studied. B, Same values depicted as percent increment over basal value at P1. *, $P < 0.05$ *vs.* respective hormone value in P1 group. +, $P < 0.05$ *vs.* respective value in P2 group.

very relevant increases were observed for LH and estradiol (Fig. 4). In the boys (Fig. 5), a significant increase *vs.* the P1 stage was observed at P2 and P3 for testosterone, LH, or FSH, with a progressive reduction in leptin levels that were lower at overt puberty ($P < 0.05$) than at the prepubertal stage. In fact, leptin values were 4.3 ± 0.2 µg/L at P1, 4.0 ± 0.4 µg/L at P2, and 2.7 ± 0.1 µg/L at P3. In the percentage of increment *vs.* the P1 values, again the most relevant increments in P2-P3 were observed for testosterone and LH (Fig. 5).

At any stage and in any group leptin levels in the boys were lower than in the girls. In both girls and boys, the subtraction of children with high weight (97% SDS-BMI) or with low weight (3% SDS-BMI) did not alter the described pattern of leptin, LH, FSH, and gonadal hormones in the age groups studied (data not shown). The multivariate analysis with a stepwise regression for leptin in the girls showed a strong influence of BMI and a minor relevance of age. In boys, a strong influence of BMI and a lower influence of age was observed and, although negative, a relevant influence of testosterone concentrations (Table 2).

Discussion

Puberty is a slow evolutionary process that probably begins years before the first signs or biochemical changes are detected. The initiator of puberty is controversial (1–3), but there is a coherent body of evidence suggesting that a certain

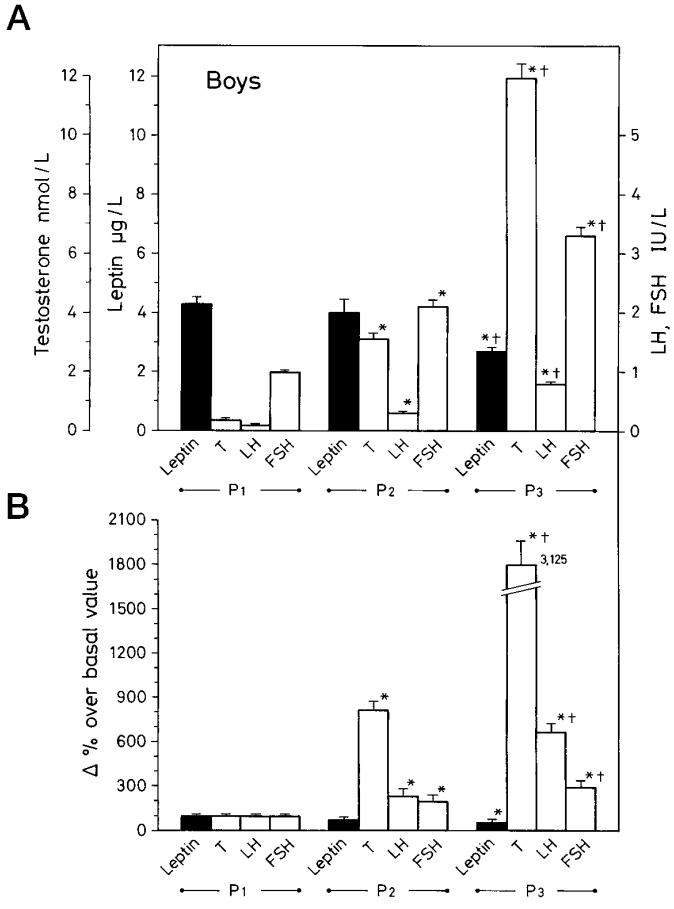

FIG. 5. A, Mean ± SEM of serum concentrations of leptin, LH, FSH, and testosterone (T) in normal boys in three pubertal stages studied. B, Same values depicted as percent increment over basal value. *, $P < 0.05$ *vs.* respective value in P1 group. +, $P < 0.05$ *vs.* respective value in P2 group.

TABLE 2. Multivariate analysis and stepwise regression for leptin values and other relevant parameters. Leptin, LH, FSH, and estradiol data were log transformed.

Parameter influencing leptin values	Girls		Boys	
	F ratio	*P*	F ratio	*P*
Age	9.51	<0.05	10.62	<0.05
Weight	0.033	NS	4.19	<0.05
BMI	366.0	<0.005	67.88	<0.05
LH	0.53	NS	1.41	NS
FSH	0.47	NS	6.10	<0.05
Estradiol	0.33	NS		
Testosterone			60.18	<0.05

NS, Not significant.

degree of body development or maturation is mandatory before puberty may proceed. In female rats, a controlled food restriction that maintains the prepubertal animals at 45% of their expected body weight impedes puberty. When such restricted animals are given unlimited access to food, LH pulses begin and puberty immediately ensues (6, 7). This link between fat reserves and gonadal function did not seem to apply to male rats, because food restriction did not delay male puberty (8). As has been suggested by several authors, calorie intake, body composition, or the adipose tissue reserves somehow control the hypothalamic secretion of GnRH and may be exerting a permissive action in the initiation of puberty (20, 21).

Thus, body composition or a certain volume of adipose tissue in humans also may be either a triggering signal to start puberty, or more likely, a permissive factor allowing puberty to fully develop. Because pregnancy requires 50,000 kilocalories above normal requirements and lactation half of that amount each month, puberty should only advene when the woman is endowed with the adipose reserves necessary to carry out a successful pregnancy and lactation. Epidemiological studies support the connection between fat deposits and gonadal function, because in wealthy societies menarche appears earlier, following a secular trend, and taller and heavier girls have menarche earlier than their counterparts (21). On the other hand, a negative calorie balance, like that in high-performance athletes or in anorexia nervosa patients, induces a puberty delay. In this context, leptin may be the link conveying information on the state of adipose tissue to the hypothalamus to initiate puberty. In fact, leptin is exclusively produced in the adipocytes to regulate the satiety centers in the hypothalamus causing a decrease in appetite and increase in energy expenditure (10). Serum leptin concentrations directly correlate with BMI and the amount of body fat; obese subjects show higher levels than normal subjects and underweight subjects have extremely reduced leptin levels, which rise after partial weight recovery (11, 22, 23). Finally, in rodents leptin was able to fully restore the gonadal function of infertile animals (16, 17), accelerate puberty (24), and reverse starvation-induced gonadal failure (25).

This background was the basis for the present work in which the circulating levels of leptin were assessed in a population of healthy children under two different frames: chronological variation and stages of pubertal development. The population studied was healthy and nonobese, as was shown by the normality of BMI, SDS-BMI, and WFHA during the study. Similarly, the corrected BMI ($Kg/m^{2.88}$), which has been postulated as a better index to assess adiposity in children (16), was virtually horizontal throughout the study. When serum leptin concentrations were plotted in a chronological way in the 343 girls and 446 boys studied, a striking divergent pattern depending on gender was observed. In the girls, leptin levels increased progressively in an ordered age-related way, following a pattern that paralleled body weight. It then appears that leptin levels in the girls increased according to the increase in body weight and, logically, with the increase in of adipose tissue that occurs with age, because a direct correlation was observed for leptin with body weight and BMI. Except for the logical differences in BMI caused by their lower age, no differences in leptin were observed between children and adults (23). In the boys, leptin levels were always lower than in the girls, which was evident even from the first time period studied (age 5–6 yr). Because no sex-related hormonal changes are present at such early life periods, and because no differences in weight, height, age, or adiposity were observed between the boys and the girls in this study, a gender-based factor would explain such differences. Until age 10 yr, leptin levels in the boys increased in parallel with body weight, in a similar

pattern to the girls, but after that time a striking inflexion occurred, with the leptin values in boys being progressively lower. After submission of this work, a similar observation was reported by others in a longitudinal study of eight boys (26). No auxological data, *i.e.* age, height, weight, BMI, etc., can explain the age-related changing pattern of leptin in the boys. It is true that, contrary to the girls, the ratio of lean mass/fat mass changed and became higher as boys approached puberty. However, this reflects because of a larger increment in muscle mass and no decrement (even a small progressive increase) in adipose stores occurs (27). It appears that an unknown factor operating after the age of 10 yr was inhibitory on leptin secretion, making leptin levels no longer a direct expression of the amount of adipose tissue present in these boys.

The age-related evolution of leptin in relation with gonadal hormones, LH, and FSH was studied. Overall, in the girls a parallel increase in the four hormones was observed, with no strident divergence among them. However, a time lag was evident, leptin being the first hormone to rise followed later by FSH. After the age 10-yr period, LH and estradiol started to increase. In the boys also, leptin was the first hormone to progressively increase, followed 2 yr later by FSH and 4 yr later by LH and testosterone. Interestingly enough, the negative inflexion in leptin levels occurred after the testosterone rise, suggesting a direct inhibitory action of this steroid hormone on leptin production at the adipose tissue. Obviously, it is unlikely that either FSH or LH is responsible for the inhibition of leptin values, considering the lack of action observed in the girls. In the same way, it is evident that after the initial events of prepuberty in the boys studied, leptin was no longer necessary to complete puberty, a fact that fits well with the known data in experimental animals, in which once puberty has started, food restriction in males is not detrimental to the completion of puberty (7).

Because circulating leptin levels are also tightly linked to the amount of adipose tissue in children (28), obesity could have been a confounding factor in assessing the evolution of leptin through the pubertal process. The problem is that in children it is by no means clear where the limits between normal weight variation and pathology are located (29), and even more so in a period like peripuberty in which considerable changes in body shape occurs. In the present work the exclusion by arbitrary criteria of children with body weight higher than the 97 percentile of the SDS-BMI gave an age-related evolution of leptin, FSH, LH, and gonadal hormones nearly identical to the evolution in all children. This observation suggests that the age-dependent leptin variation observed was not dependent on the proportion of individuals with elevated body weight in the groups of higher age.

Regarding the initial question on the possibility that leptin could be the trigger for starting puberty in humans, or at least a permissive factor, the present work can not provide an unambiguous demonstration. But in experimental animals it has been recently demonstrated that leptin induces early puberty (30). If a signal for inducing puberty or a permissive factor must be in the circulation some time before the initial biochemical events of puberty appear, leptin truly behaved in such a way. In fact, in the transversal study presented here leptin rose years before any other hormone implicated in puberty. These observations may be taken as inferential evidence that leptin is the message by which the body informs the hypothalamus that the energy reserves have attained a safe level, and it may start the complex events that will produce puberty several years after. Once pubertal development starts, elevated leptin levels are no longer necessary in boys to complete puberty or to maintain the reproductive function, but in girls leptin levels may need to be above a definitive level, not only to complete puberty but even to maintain the normal reproductive function.

In conclusion, in the girls studied leptin levels rose progressively in an age-related pattern paralleling increased body weight. Initially, the boys had lower leptin levels than the girls but showed a similar pattern of increase. However, after the age of 10 yr an inflection at the time of testosterone increase occurred. Leptin may well be a permissive factor for the initiation of pubertal events.

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Conference on the Diagnosis and Treatment of the Unborn Child
The Buttes, Tempe, Arizona
Saturday, April 18–Monday, April 20, 1998

Participants: Maria I. New (Chairman), New York, NY; Arleen Auerbach, New York, NY; Ted Brown, New York, NY; Frank Chervenak, New York, NY; Jessica Davis, New York, NY; Robert Desnick, New York, NY; Miroslav Dumic, Zagreb, Croatia; Mark I. Evans, Detroit, MI; Alan W. Flake, Philadelphia, PA; Maguelone G. Forest, Lyon, France; Judith Hall, Vancouver, BC; Margaret Hilgartner, New York, NY; Eric Hoffman, Pittsburg, PA; Sheila Innis, Vancouver, BC; Y. W. Kan, San Francisco, CA; Josuha Lederberg, New York, NY; Lucio Luzzatto, New York, NY; Arno Motulsky, Seattle, WA; John Opitz, Salt Lake City, UT; Darwin J. Prockop, Philadelphia, PA; David L. Rimoin, Los Angeles, CA; Joe Leigh Simpson, Houston, TX; Jean Wilson, Dallas, TX; Don Wolf, Beaverton, OR.

The Conference will include: Genetic Disorders in Ashkenazim; Hemophilia Problems in Carrier Identification and Fetal Diagnosis; Fragile X Syndrome; Fanconi Anemia; Inherited Variation in Susceptibility to Cancer in the Unborn Child; Smith Lemli-Opitz Syndrome, Marfan Syndrome, Androgen Receptor Defects, Skeletal Dysplasias, Muscular Dystrophies, Congenital Adrenal Hyperplasia, Uniparental Disomy, Diagnosis and Treatment of Fetal and Neonatal Malnutrition, Fetal Cells in Maternal Blood to Diagnose Aneuploidy; Fetal Cells in Maternal Blood to Diagnose Hemoglobinopathy; Open Surgery; Percutaneous Approaches, Stem Cell Therapy, Stem Cell Techniques, Preimplantation Genetic Diagnosis, Ethical Fetal Therapy; New Obligations of Physicians in Genetics, Cloning and Ethics.

The deadline for abstracts of poster presentations is December 15, 1997.

For further information, please contact Maria I. New, MD, Prenatal Diagnosis Conference—Arizona '98, Ross Professional Services, 40 Old Ridgebury Road, Ste. 309, Danbury CT 06810; telephone 203-730-8724; fax 203-778-1121.