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Link Between Body Fat and the Timing of Puberty

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ABSTRACT

Several recent studies suggest that the timing of the onset of puberty in girls has become earlier over the past 30 years, and there is strong evidence that the increasing rates of obesity in children over the same time period is a major factor. This article reviews studies from the United States that examined the age of menarche and the age of onset of breast development and pubic hair as a function of body mass index, which is a good surrogate measure of body fat. These studies are nearly all cross-sectional, so many questions remain unanswered. However, at least several studies show that girls who have relatively higher body mass index are more likely to have earlier menses, as well as a relationship between body mass index and other measures of pubertal onset. The evidence published to date suggests that obesity may be causally related to earlier puberty in girls rather than that earlier puberty causes an increase in body fat. In contrast, few studies have found a link between body fat and earlier puberty in boys. A growing body of evidence from both rodent and human studies suggests that leptin may be the critical link between body fat and earlier puberty. Leptin-deficient mice and humans fail to enter puberty unless leptin is administered, and rodent studies indicate that very low levels of leptin stimulate gonadotropin secretion both at the hypothalamic and the pituitary level. Current evidence indicates that leptin appears to play a permissive role rather than act as the critical metabolic signal initiating puberty. The linkage between body fat and the reproductive axis in girls may have evolved in mammals as a mechanism for ensuring that pregnancy will not occur unless there are adequate fat stores to sustain both the mother and the growing fetus.

HISTORICAL PERSPECTIVES

Records from several northern European countries, particularly Norway, Denmark, and Finland, document that the age of menarche, a convenient marker for the timing of puberty in girls, decreased from ~16 to 17 years during the 19th century to ~13 years by the middle of the 20th century.¹ In the United States, a decline from 14.75 years in 1877 to just under 13 years by the period of 1950 to 1970 has been reported. It has been widely assumed that improved health and nutrition associated with the coming of the Industrial Revolution were responsible for most if not all of that decline in the mean age of menarche. At the very least, these historical data suggest that the timing of puberty is not solely genetically determined but can be influenced by epigenetic factors. There have also been studies to suggest that obese girls tend to mature earlier than normal and that "thin" girls tend to mature later. For example, a significant delay in puberty and menarche is seen in girls who are very physically active and have markedly diminished body fat.² After reviewing longitudinal growth data for 181 normal girls, Frisch and Revelle³ observed that the mean weight at menarche was constant at ~48 kg for girls who reached menarche before age 12, between 12 and 13, between 13 and 14, and after age 14; however, mean height at menarche increased progressively the older the girls were at the time of menarche. These observations led Frisch to propose that a critical weight is required to initiate and sustain menses in young girls and that this relationship could explain the secular trend toward earlier menarche during the previous century. One problem with this theory is that although the average weight at menarche in this study varied little with the age at menarche, there was a broad distribution of weights (anywhere between 35 and 60 kg) at the time when individual girls reached menarche. One could interpret the same data as indicating that weight is an important factor but by no means the main determinant of age at menarche. Frisch, relying heavily on studies involving loss of reproductive function in women after weight loss, later modified her theory to suggest that there is a critical fat mass (~17% of body weight) required for menarche and a higher fat mass (22% of body weight) needed for maintenance of reproductive capacity.⁴ In contrast, Garn et al⁵ looked at skinfold

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Key Words

obesity, BMI, menarche, early puberty, leptin

Abbreviations

NHANES—National Health and Nutrition Examination Survey

DEXA—dual-energy radiograph absorptiometry

PROS—Pediatric Research in Office Settings

NHES—National Health Examination Survey

GnRH—gonadotropin-releasing hormone

LH—luteinizing hormone

FSH—follicle-stimulating hormone

DHEA-S—dehydroepiandrosterone sulfate

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TABLE 1 Percentage of 6- to 11-Year-Old Children With a BMI at >95th Percentile

Years of Study	Boys		Girls	
	White	Black	White	Black
1963–1965	5.6	2.0	5.1	5.3
1976–1980	7.9	7.9	6.4	11.3
1988–1991	10.4	13.4	10.2	16.2
1999–2000	12.0	17.1	11.6	22.2

Based on 4 national surveys spanning 5 decades.

Adapted from Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. *Arch Pediatr Adolesc Med.* 1995;149(10):1085–1091 and Ogden CL, Flegal KM, Carroll MD, Johnson CL. *JAMA.* 2002;288(14):1728–1732.

thickness of premenarcheal and postmenarcheal girls of the same age and found extensive overlap; he concluded that there was no clear evidence of a threshold level of weight or fatness that is critical for the onset of menarche. Nonetheless, evidence has accumulated in the past 30 years that points to a major influence of body fat as the timing of puberty, at least in girls. Although the role of environmental chemicals has not been adequately studied, the well-documented epidemic of obesity in American children provides a plausible explanation for the decreasing age in both the age of onset of breast development and the age of menarche. In this review, the studies presented support a link between these 2 phenomena. Although there are much fewer data concerning the possible link of obesity with early puberty in boys, this is reviewed and contrasted with the findings in girls.

INCREASING PREVALENCE OF OBESITY IN US CHILDREN

There is ample evidence for the increasing prevalence of obesity in all segments of our population, including children, in the last 30 years. Table 1 compares the prevalence of obesity, defined as a BMI >95th percentile for age and gender, for black and white boys and girls between the National Health and Examination Survey (NHANES) study from 1963 to 1965, NHANES II from 1976 to 1980, and NHANES III from 1988 to 1991 and the recently reported results of NHANES 1999 to 2000.^{6,7} In the 1963–1965 study, ~5% of the children had a BMI >95th percentile, but since then, there have been striking increases in all groups, with the greatest increase being found in black girls. In the most recent survey, 22% were obese before they even reached adolescence. It is worth noting that the greatest increase in obesity among 6- to 11-year-olds is in the very group in which the earlier onset of puberty has been noted.

EPIDEMIOLOGIC EVIDENCE FROM THE UNITED STATES THAT LINKS OBESITY AND EARLIER PUBERTY

Ideally, one would like to be able to assess directly the influence of body fat mass on indices of puberty; however, in most large-scale epidemiologic studies, fat mass has not been directly measured. BMI is a suitable surrogate for body fat, as demonstrated by a study in which both were measured in 100 boys and 92 girls between the ages of 7 and 17.⁸ For girls, the correlation between

BMI and fat mass (measured by dual-energy radiograph absorptiometry [DEXA]) was 0.94 and 0.96 for black and white girls, respectively, and for BMI versus percentage body fat, the correlations were 0.83 for both races. The correlations were lower for boys (0.85 and 0.86 for BMI versus fat mass and 0.54 and 0.50 for BMI versus percentage body fat).

The National Heart, Lung, and Blood Institute's National Growth and Health Study is a cohort study of 2379 girls divided approximately equally between white and black girls who were recruited in 1987 at age 9 from schools in Richmond, California, and Cincinnati, Ohio, and a large group practice in the Washington, DC, area. Each girl was examined yearly for height, weight, skinfold thickness, and stage of pubertal maturation. A recent analysis of this cohort showed that the mean age at menarche was 12.7 years in white girls and 12.0 years in black girls. The black and white girls were separated into 3 groups according to the age of onset of menarche. Across the entire 9- to 18-year age range studied, the earlier maturing white and black girls had consistently higher BMIs than the midonset girls, who had higher BMIs than the late-onset girls.⁹ Similar findings were reported when the sum of skinfold thickness was examined in relation to the timing of menses; however, there was no association between age at menarche and body fat distribution.

In 1997, the results of the cross-sectional Pediatric Research in Office Settings (PROS) study of female puberty were published as discussed elsewhere in this supplement.^{10,11} For testing of the hypothesis that obesity was a major predictor of earlier puberty in black and white girls, each child between the ages of 6 and 12 had her BMI calculated and then converted to a BMI SD or z score using the tables derived from the NHANES III study.¹² The values used were based on the entire sample of 2200 to 4300 girls per age group, rather than the slightly different values calculated for black, Hispanic, and white girls. For example, for 7-year-olds, the mean BMI was 16.2 ± 2.2 ; thus, a girl whose BMI was 17.3 would have a BMI z score of $(17.3 - 16.2) \div 2.2 = 0.5$. For white 6- to 9-year-old girls, the mean BMI z scores of girls with breast development were significantly greater than for age-matched girls who were prepubertal (Fig 1); the same trend was noted for black girls, but the differences were smaller.¹³ In 7- to 12-year-olds, there was a continuous relationship at each age between greater Tanner breast stage and higher mean BMI z scores (Fig 2). The same trends for increased BMI z score were found for 6- to 8-year-old white and black girls who had developed pubic hair but not breasts. When the mean BMI z score was compared for premenarcheal versus postmenarcheal 11- to 12-year-old girls, white premenarcheal girls had a mean BMI z score of -0.25 vs 0.29 for postmenarcheal girls; for black girls, the means were -0.09 vs 0.70 . One potential problem with the PROS study is that breast development was assessed by inspection and not palpation, which can cause confusion in overweight girls, in whom fat can mimic breast tissue; however, an analysis of the subset of girls (39%) in which Tanner staging by palpation was recorded showed

FIGURE 1

Mean BMI z scores in 6- to 9-year-old white girls with and without breast development, based on the PROS study data reported by Kaplowitz et al.¹³ The number of subjects represented by each bar is indicated at the top of the graph.

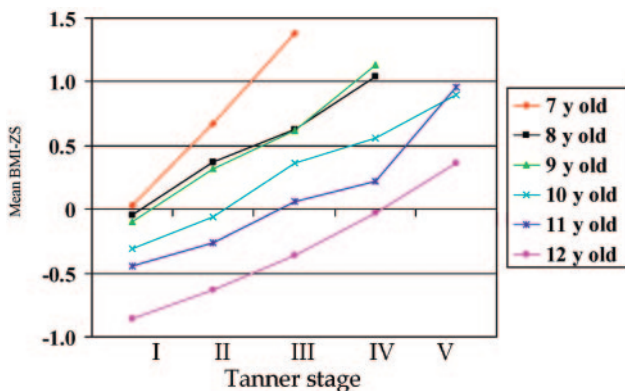
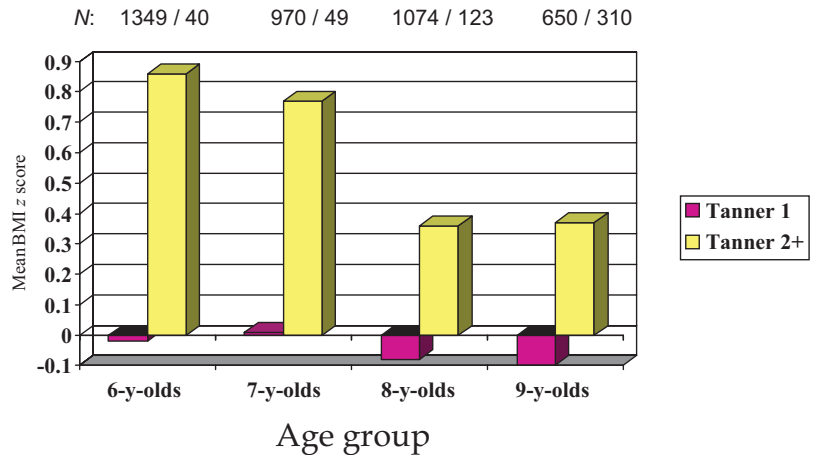


FIGURE 2

The relationship between mean BMI z scores and Tanner staging of breast development in 7- to 12-year-old girls, based on the PROS study data reported by Kaplowitz et al.¹³ The data include both white (90%) and black (10%) girls.

that the results were very similar to those found in the whole sample.¹⁴

A report from the Girls Health Enrichment Multi-site Studies, which included 147 black girls between the ages of 8 and 10, found that increasing stages of breast development (but not pubic hair) were positively related to BMI and waist circumference, as well as fat mass and percentage body fat as assessed by DEXA. Pubertal girls were 8 times as likely to have a BMI \geq 95th percentile, as were age-matched prepubertal girls.¹⁵

Another study that examined the interrelationship between menarche and the trend for increasing obesity is the Bogalusa Heart Study, in which 7 cross-sectional studies of 5- to 17-year-old girls were conducted in a semirural Louisiana community between 1973–1974 and 1992–1993. During the 20-year study period, the median menarcheal age decreased by \sim 9.5 months among black girls versus \sim 2 months among white girls.¹⁶ More important for this discussion, however, earlier age at menarche correlated negatively with BMI in both white and black girls ($r = -0.23$ and -0.24). In addition, the incidence of early menarche (before age 11) was 1.79-fold greater for girls at the 75th percentile for BMI versus girls at the 25th percentile and was 1.4 to 1.5

greater for girls with skinfold thickness at the 75th versus the 25th percentile.

As mentioned elsewhere in this supplement, recent comparison of data from the National Health Examination Survey (NHES; data collected 1963–1970) and NHANES III (collected 1988–1994) shows that, using probit analysis, the average age at menarche dropped from 12.75 to 12.54 years during the 25-year period.¹⁷ At the same time, the percentage of girls who were 10 to 15 years of age and had a BMI $>$ 85th percentile increased from 16% to 27%. Additional analyses were needed to determine whether these 2 findings were related. Similar to what was found in the PROS and Bogalusa studies, premenarcheal girls at each age between 10 and 15 had a significantly lower BMI z score than postmenarcheal girls in both the NHES and NHANES III, the main difference between the studies being the higher BMI z scores in NHANES III. Table 2 shows data for ages 11 to 13, for which there were sufficient numbers of girls to provide good statistical comparisons; all differences were significant at $P < .01$ or greater.

In a logistic regression model, an increased BMI z score was associated with a significantly greater likelihood of a girl's having reached menarche, after adjustment for age and race. The most striking finding, however, was that of the relationship between BMI z score and age of menarche derived from the NHES data; the

TABLE 2 Relationship Between Age at Menarche and Mean BMI z Score in 11- to 13-Year-Old Girls

Age, y	NHES				NHANES III			
	Premenarcheal		Postmenarcheal		Premenarcheal		Postmenarcheal	
	n	BMI z Score	n	BMI z Score	n	BMI z Score	n	BMI z Score
11	441	-0.22	65	0.75	204	0.17	57	0.83
12	295	-0.28	245	0.52	96	-0.15	127	0.63
13	153	-0.56	422	0.34	29	-0.33	181	0.71

Data are from the NHES and NHANES III studies. All differences between premenarcheal and postmenarcheal girls were significant at $P < .01$.

Adapted from Anderson SE, Dallal GE, Must A. *Pediatrics*. 2003;111(4 pt 1):844–850.

TABLE 3 Prevalence of Obesity (BMI >95th Percentile) Among Girls and Boys in the NHANES III Who Were Early Maturers Versus Average and Late Maturers (Others)

Parameter	Girls, %		Boys, %	
	Early Maturers ^a	Others	Early Maturers ^a	Others
Children (aged 8 to 11)	14	8	8	14
Adolescents (aged 12 to 14)	17	8	8	17
White	13	5	6	13
Black	20	12	8	19

^a A boy or girl was classified as an early maturer when he or she reached a certain stage of sexual maturation earlier than the median age for that stage in the population. For example, a girl with Tanner 2 breast development was early when her chronological age was less than the median for breast stage 2.

Adapted from Wang Y. *Pediatrics*. 2002;110(5):903–910.

authors predicted, on the basis of the higher BMIs in NHANES III, that the average age at menarche in NHANES III would be 12.56 years, quite close to the actual figure of 12.54 years. This analysis suggests that there is a causal relationship between increasing obesity and the modest decline in average age at menarche during a 30-year period in US girls.

A different analysis of the puberty/obesity relationship using the NHANES III data was reported by Wang.¹⁸ Both boys and girls were categorized as early maturers when they reached a certain stage of genital (boys) or breast (girls) development earlier than the median age for that stage. Children (aged 8–11) and adolescents (aged 12–14) were analyzed separately. Table 3 shows the percentage of obese children (BMI >95th percentile) who were early maturers versus the combined average and late-maturing children. Similar differences were found between early maturers and the others in the percentage of children who had a BMI >85th percentile. For example, in 8- to 11-year-old girls, 32% of early maturers and 20% of the others met the definition of overweight. It was concluded that fatness (measured as both BMI and skinfold thickness) was related to sexual maturation in both boys and girls, with early-maturing boys being thinner and early-maturing girls being fatter than their late-maturing counterparts.

IS OBESITY RELATED TO EARLIER PUBERTY IN BOYS?

In contrast to the large number of studies pointing to a relationship between obesity and early puberty and menses in girls, there are few, if any, data pointing to a similar relationship in boys. The previously cited study based on the NHANES III data¹⁸ points to the possibility that obesity may actually result in later rather than earlier puberty in boys; however, these results should be interpreted with caution because of problems with the ascertainment of genital stage in the boys in NHANES III. This study seems to show that puberty is starting earlier in boys as well as girls, on the basis of the observation that 25% of 8-year-old boys were already at genital stage 2¹⁹; however, clinicians have noted no recent increase in the number of boys being evaluated for precocious puberty, which is defined as the onset of testicular enlargement at <9 years of age and which is still uncommon.

Thus, it seems possible that criteria for attainment of stage 2 genital development in boys were not adequately defined in NHANES III, resulting in an overclassification of prepubertal boys as early pubertal. In an earlier study from Italy, 141 obese boys and 162 obese girls (defined as weight 20% greater than that expected for height and age) were evaluated for growth, bone maturation, and pubertal staging.²⁰ Although, as expected, the obese girls were advanced in puberty relative to normal-weight Italian girls and had a mean age of menarche of only 11.4 years, the obese boys did not mature earlier than normal; in fact, 19% had delayed genital development and 16% had delayed pubic hair. A Spanish study that focused on boys between the ages of 11 and 14 and girls between the ages of 10 and 13 found a positive relationship between age of pubertal onset and BMI in boys but not in girls; however, the sum of skinfolds and the percentage body fat did not differ according to the age of pubertal onset in either boys or girls.²¹ Furthermore, when Laron²² compared obese and age-matched control Israeli boys and girls, he found that the obese children were taller up to age 14, but there was no difference in the age of appearance of pubic hair or facial hair or the age at testicular or genital enlargement in obese boys or in the age of menarche or the appearance of breasts or pubic hair in obese girls. The last 2 studies suggest that the relationship between obesity and the timing of puberty may differ depending on the population studied in both boys and girls.

One reason that data on obesity and the timing of puberty in boys may be limited is that because there is no easily defined pubertal event, such as menarche, in boys, it is simply more difficult to study this relationship. One needs a large sample of healthy boys with recorded heights and weights and physical examination with Tanner staging done by experienced personnel or longitudinal growth records detailed enough to allow one to determine accurately the time of the pubertal growth spurt, and very few growth studies are suitable for obtaining this information. Furthermore, data using only BMI in boys as a measure of body fat may be misleading, because the correlation between BMI and body fat is much lower in boys than in girls.⁸ This may be because during male puberty, the increasing muscle mass related to the anabolic effect of rising testosterone levels will cause an increase in weight and BMI independent of any increase in body fat.

IS INCREASED BODY FAT THE CAUSE OF EARLY PUBERTY IN GIRLS OR THE RESULT OF IT?

All of the studies that show a relationship between early puberty and obesity in girls do not answer the question of whether increased body fat predisposes girls to earlier puberty or earlier puberty in some girls leads to an estrogen-mediated increase in body fat. A review of the effects of gonadal steroids on body composition in adults concluded that estrogens and possibly progesterone largely account for the greater degree of body fatness in women as opposed to men, because these hormones seem to work together to favor the storage of excess calories as fat, with estrogens promoting deposition of fat

in peripheral adipose tissue depots.²³ Thus, it is possible that the early pubertal girl produces enough gonadal steroids to result in greater BMI and greater body fat than would be found in age-matched prepubertal girls; however, there is evidence from 2 longitudinal studies that the increase in obesity precedes the onset of early puberty in girls. In a large population-based study done in Sweden, growth data were collected in a sample of children using physician records until age 6 and school records from ages 7 to 18. From these data, the age at peak height velocity, which is an early puberty marker in girls but a late puberty marker in boys, could be determined for each child as a measure of the timing of puberty. There was a negative correlation between the change in BMI between the ages of 2 and 8 and the age of the peak height velocity.²⁴ An increase of 1 BMI unit between ages 2 and 8 was associated with an average of 0.11 years earlier for peak height velocity, and for children with higher changes in BMI, the effect on the timing of puberty was as great as 0.6 years in boys and 0.7 years in girls. This study suggests that overnutrition in early childhood can result in an earlier onset of puberty; in this study, the effect seemed to apply to both girls and boys.

Two recent studies with very different methods reached similar conclusions. A group of 197 5-year-old girls in central Pennsylvania were recruited through advertisement and enrolled in a longitudinal study at age 5 and then reexamined at ages 7 and 9.²⁵ Fat mass and body fat percentage were calculated from a formula using height, weight, subscapular and the triceps skinfold thickness, and bioelectrical impedance. At age 9, girls were classified as earlier ($n = 44$) or later ($n = 136$) maturers on the basis of breast development stage examined by inspection, serum estradiol levels, and a parent-assessed pubertal development scale. It was found that girls with a higher percentage of body fat at age 5 and girls with higher body fat or higher BMI percentiles at age 7 were significantly more likely than their peers to be classified as having earlier pubertal development at or by age 9. The strongest Spearman rank correlation (0.53) was between percentage body fat at age 7 and breast development at age 9. The most recent and best longitudinal study of this relationship examined 354 girls whose heights and weights were recorded from age 3 until sixth grade. The authors defined early puberty as any breast development by fourth grade, Tanner 3 breast development by fifth grade, or menarche by sixth grade. They found that increased BMI as early as age 3, plus the increase in BMI between the ages of 3 and 6, were significant risk factors for whether a girl would be earlier than average in entering puberty.²⁶

The mechanisms by which adrenal androgen secretion is activated in 6- to 10-year-old girls and boys, leading to the appearance of pubic hair, are incompletely understood and likely involve intra-adrenal changes in the activity of certain adrenal steroidogenic enzymes. They are distinct from the activation of estrogen secretion by the ovaries, which is under control of hypothalamic gonadotropin-releasing hormone (GnRH) and pituitary luteinizing hormone (LH) and follicle-stimulating

hormone (FSH) secretion. For investigation of whether obesity and nutritional factors might influence this process, 42 white children who participated in a longitudinal study in Dortmund, Germany, had yearly 24-hour urine samples analyzed for the main adrenal androgen dehydroepiandrosterone sulfate (DHEA-S).²⁷ BMI was tracked by yearly measurements and was related to levels of urinary DHEA-S production. Although there was no association in the cross-sectional analysis between BMI and urinary DHEA-S, it was observed that there was a significantly higher increase in DHEA-S during the year when a child had the highest rise in BMI compared with the year when the BMI rise was lower. This suggests that an increase in body fat may play a critical role in the "turning on" of adrenal androgen secretion. A study from France found that 32.5% of girls with appearance of pubic hair between the ages of 4 and 8 had a BMI of ≥ 2 SD and that the correlation between BMI z score and serum DHEA-S was highly significant ($P = .004$).²⁸

CRITICAL ROLE OF LEPTIN

An excellent review of the studies that address the role of obesity and leptin in the onset of puberty was published.²⁹ In this section, animal studies are reviewed first before turning to human studies.

Rodent Studies

Rat studies have shown that body weight and food intake have important effects in regulating the onset of puberty and that there is a close relationship between weight and the timing of first estrus in females.³⁰ A more recent study³¹ investigated the effects of intrauterine malnutrition (induced by uterine artery ligation at day 17 of gestation and postnatal food restriction) on the onset of puberty in male and female rats. In both male and female rats with intrauterine growth-restriction, the onset of puberty was delayed relative to control rats, whereas postnatal food restriction onset delayed puberty in the male rats only. Body weight at the onset of puberty did not consistently correlate with the timing of puberty. The authors concluded that the perinatal period is a critical time for maturational events that affect the timing of puberty.

The discovery of the protein leptin, which is produced by fat cells and is missing in a well-described mouse model of obesity, the *ob/ob* mouse, provided a molecular basis for the suspected link between body fat and reproductive function. Leptin was initially thought to regulate primarily energy balance, by decreasing appetite and food intake and increasing thermogenesis.³² When fat stores are low, decreased leptin leads to increased appetite, helping to restore body fat and body weight to normal. The female *ob/ob* mouse is both overweight and sterile, and "thinning" them by restricting their diet does not restore fertility, but injection of leptin into these mice allows them to ovulate, become pregnant, and have offspring.³³ Barash et al³⁴ showed that restoration of fertility in both female and male *ob/ob* mice was associated with increases in serum levels of LH in females and of FSH in males.

When leptin was injected into normal prepubertal female mice, they grew at a slower rate than controls, most likely as a result of the hormone's thinning effects, but they reproduced up to 9 days earlier than controls.³⁵ Another study in which leptin was given daily to prepubertal mice gave a more complex picture.³⁶ Leptin resulted in a 20% reduction of food intake, and measures of pubertal maturation were delayed in non-leptin-treated pair-fed animals, but leptin reversed this delay, and the timing of puberty was similar in the leptin-treated and ad libitum-fed mice. However, when both leptin-treated and pair-fed mice were fed 70% of what the control mice were fed, the delay in puberty was only partially reversed. The same group subsequently reported their failure to find any developmental changes in either serum leptin levels or expression of the leptin receptor gene in the hypothalamus of the female rat at the time of puberty.³⁷ The authors proposed that in the rodent, leptin might act in a permissive manner to allow puberty to progress if fat stores were adequate and that its presence may be necessary but not sufficient to initiate sexual maturation. Yet another approach to establishing the leptin-reproduction link was the study of transgenic "skinny" mice that overexpressed the leptin gene.³⁸ These mice with little if any adipose tissue exhibit accelerated puberty and earlier fertility, but, at older ages, they develop a hypogonadism characterized by a decreased activity of the entire hypothalamic-pituitary-gonadal axis.

For better defining the effect of leptin on the hypothalamic-pituitary-gonadal axis, hemianterior pituitaries from adult male rats were incubated for 3 hours with very low concentrations of leptin. A peak effect on LH release was seen with 10^{-11} M leptin, and a peak effect on FSH was seen with 10^{-9} M; higher concentrations of leptin failed to stimulate gonadotropin secretion.³⁹ When leptin was incubated with hypothalamic explants, concentrations in the range of 10^{-12} to 10^{-10} M caused a significant release of GnRH. Furthermore, injection of leptin into the third ventricle of ovariectomized female rats caused a significant increase in LH (but not FSH) secretion after 10 to 50 minutes. In the prepubertal rat, exposure of hypothalamic explants to leptin results in more frequent pulses of GnRH secretion but no change in pulse amplitude.⁴⁰ Thus, these studies indicate that leptin exerts its effects on the reproductive axis at both the hypothalamic and the pituitary levels.

Primate Studies

Although many studies on the regulation of GnRH, LH, and FSH secretion were originally done in monkeys, there has been less work in primates on possible role of leptin in primate puberty, and most of those studies examined male rhesus monkeys. The exception is a study in which juvenile female rhesus monkeys were treated with a daily injection of leptin from 12 to 30 months of age and compared with age-matched controls. There was an earlier rise in LH and an earlier increase in estradiol and onset of menarche in the leptin-treated monkeys.⁴¹ Despite the increase in nocturnal LH after

leptin treatment, it was still lower in the leptin-treated monkeys than in ovariectomized monkeys, suggesting that leptin may act by reducing the gonadal negative feedback suppression of LH. The authors interpreted the results as suggesting, as in rodents, that leptin has an important but mainly permissive role in advancing primate female puberty.

In immature male rhesus monkeys, leptin levels were determined every 1 to 2 weeks from 18 to 30 months of age in both intact and castrate animals. The time at which either testosterone levels or, in the castrate animals, gonadotropin levels increased was not accompanied by any rise in circulating leptin levels.⁴² Mann et al⁴³ reported in the same species that leptin declined until the onset of puberty and that there was no significant rise or fall in leptin in association with the pubertal rise in LH and testosterone, but seasonal fluctuations in leptin after the achievement of sexual maturity were observed. The authors of both studies concluded that increasing leptin levels do not trigger the onset of puberty in the male rhesus monkey; however, Suter et al⁴⁴ found in the agonadal male rhesus monkey that whereas daytime leptin did not increase, nocturnal levels did increase in the late prepubertal period. Finally, prepubertal agonadal rhesus monkeys were observed for 16 days when recombinant leptin was infused intravenously, but there was no precocious release of GnRH as assessed by monitoring of LH secretion.⁴⁵ Although the issue is not completely settled, the weight of evidence suggests that in the male primate, a rise in circulating leptin is not the signal that triggers the onset of puberty.

Human Studies That Link Leptin, Puberty, Adrenarche, and Body Fat

As the role of leptin in rodent physiology was being elucidated, many studies examined the factors that affect leptin levels in adults and children. Not surprising, leptin levels were found to be much higher in obese children than in children with normal BMI, and the correlation between leptin and BMI was 0.88.⁴⁶ The gender and stage of puberty were also found to affect leptin, with levels in female pubertal children higher than in male children even after correction for obesity.⁴⁶ In parallel with the ob/ob mouse, humans who have rare mutations of the leptin gene and are very obese remain prepubertal⁴⁷ unless given recombinant leptin, which restores pulsatile gonadotropin secretion, have been discovered.⁴⁸

Several studies, both cross-sectional and longitudinal, have shown a marked rise in serum leptin concentrations in young girls starting as early as age 7 and continuing as they progress through puberty at least until age 15.⁴⁹⁻⁵¹ In contrast, in boys, leptin levels seem to rise transiently and then decrease after Tanner stage 2 to prepubertal levels that are approximately one third of those seen in late-pubertal girls. These changes in leptin levels are paralleled by increasing body fat during female puberty and decreasing body fat during male puberty. In at least 1 cross-sectional study, the rise in serum leptin was well established 2 years before clear increases in

serum LH and estradiol levels were observed.⁵⁰ This would be consistent with the hypothesis that higher leptin levels are one of the factors that are critical in allowing puberty to progress, rather than a result of the hormonal increases of puberty.

If the relationship between body fat and earlier menarche in humans is mediated by leptin, then one would predict that leptin levels would be related to age at menarche. This was examined in a study of 343 healthy, white girls from central Ohio who were recruited at Tanner stage 2 of puberty between the ages of 8.3 and 13.1.⁵² Menstrual history, height and weight, body composition by DEXA, and leptin were measured every 6 to 12 months during a 4-year period. As expected, leptin was highly correlated with body fat mass ($r = 0.81$). Higher leptin levels up to a level of 12 ng/mL were associated with a decline in the age of menarche by approximately 1 month per 1-ng/mL increase in leptin. In addition, the group of girls who remained premenarcheal for the entire 4 years of the study had significantly lower leptin levels than the groups of girls who reached menarche during the study. The authors concluded that a threshold blood level of leptin in girls may be needed for establishment of normal menses.

The role of leptin in the regulation of the onset of adrenal androgen secretion has also received recent attention. A preliminary study of 7 US girls with premature adrenarche and 8 age-matched control subjects showed a higher BMI and a greater than twofold increase in leptin in the girls who were in adrenarche.⁵³ In contrast, a Berlin study compared 26 obese prepubertal girls with 26 normal-weight prepubertal girls and 30 girls with premature adrenarche with 30 age-matched control subjects. Before the onset of the appearance of pubic hair, adrenal androgen levels were to some extent related to higher BMI and leptin; however, in children with premature adrenarche, no clear correlation was found between increased adrenal androgen secretion and leptin or BMI.⁵⁴ If a relationship between leptin and adrenarche is verified, then there is already a possible molecular explanation. In vitro studies with human adrenal NCI-H295R cells expressing a leptin receptor showed that low-dosage leptin caused a significant increase in 17,20-lyase activity without a significant sustained influence on the 17 α -hydroxylase activity.⁵⁵ The 17,20 lyase enzyme is a key step in adrenal androgen biosynthesis.

Several studies also suggest a role for insulin resistance in the pathogenesis of premature adrenarche, which has been associated with an increased risk for development of polycystic ovary syndrome in adolescence.⁵⁶ Whether the insulin resistance found in girls with premature adrenarche is secondary to the girls' tendency to be obese or is a separate risk factor for an early increase in adrenal androgen secretion is not clear at this time.

EVOLUTIONARY IMPLICATIONS FOR LINKING BODY FAT AND PUBERTY TIMING

The link between leptin and puberty and reproduction is clearly not a new development in mammalian evolu-

tion, because there is strong evidence for this connection, reviewed previously, in rodents. Reproduction, although essential to survival of a species, is expensive in terms of energy expenditure. It makes sense for mammalian females to be able to turn off their reproductive systems when the food supply is inadequate or marginal, resulting in decreased body fat mass, leading to lower leptin levels. These results (at least in rodents) showing a downregulation of gonadotropin secretion would either delay the onset of sexual maturation in young rodents or result in an inability to ovulate. It does not make sense for mammals to be pregnant at times of low food availability, because the offspring would have a poor chance of surviving and pregnancy might endanger the female's survival as well. That fat mass and percentage of body fat rise progressively during puberty in the human female underscores its likely role in preparing women for childbearing. Now, however, food scarcity has been replaced with food excess in the developed part of the world. The resulting increase in body fat may (assuming that leptin represents a "metabolic gate" for puberty) have the effect of lowering the age at which breast development and menses begin.

The evolutionary implication of body fat with regard to mammalian males is somewhat different. Providing the sperm is essentially the only contribution that the male makes to a pregnancy; therefore, whether the male maintains adequate food intake and fat stores has no direct bearing on the likelihood of the pregnancy's being successful and healthy offspring's being born. Thus, there may be no evolutionary reason to have a tight linkage between fat stores and reproductive function in males. In fact, as testosterone levels increase during male puberty, fat mass as a percentage of total body mass decreases and leptin levels decline. One cannot with the current information rule out the role of leptin in initiation of male puberty, but it is almost certainly not required for its progression.

CONCLUSIONS

Evidence from several different epidemiologic studies in the past 30 years indicates a relationship between earlier puberty in girls and increased BMI, which is the most commonly available indirect measure of obesity and body fat stores. Most of these studies examined the age of menarche as the primary marker for the timing of puberty, because it requires only a recollection of its timing by the child and no physical examination; however, analysis of the PROS and NHANES III studies suggested that increased BMI is also correlated with earlier attainment of other markers of female puberty, including breasts and pubic hair. Although the question of whether earlier puberty is the cause or the result of increased body fat has not been resolved, at least 2 longitudinal studies suggested that increased body fat or a rapid increase in BMI predicts earlier onset of puberty. Although many details need to be filled in, it is increasingly clear that leptin has direct effects on gonadotropin secretion and provides the link between body fat stores and the timing of puberty, in both rodents and humans. Current evidence suggests that a threshold level of leptin

may be required for initiation of puberty, but an increase in leptin does not seem to be the triggering event in the onset of puberty. This formulation is consistent with clinical observations in humans. Many girls with true precocious puberty are not overweight, and although mean leptin levels in girls with central precocious puberty were slightly elevated compared with those in BMI-matched control subjects, leptin levels in most of these girls fell within the reference range.⁵⁷ Thus, although obesity is not the only factor contributing to early puberty in girls, the downward shift in the United State during the past 30 years in the age of onset of puberty and the age of menarche in girls could well be explained by the higher prevalence of obesity. The studies cited in this review indicate that the relationship between obesity and early puberty in boys is not at all clear. One reason that there may be fewer data for boys than for girls is that there is no convenient marker for puberty in boys that can be obtained in an interview as menarche provides for girls. Therefore, studies of boys must rely on physical examinations with accurate staging of pubic hair and genital development, and such studies are more difficult to perform on a large scale.

It is abundantly clear that much more research needs to be done in this area. First, the most recent published data on the subject based on the PROS, NHANES III, and Bogalusa studies were collected at least 10 to 15 years ago, and during that time, the incidence of obesity has continued to climb in American children.⁷ More contemporary data from the United States are desperately needed, as well as comparable studies from other parts of the world, both where the secular trend for earlier puberty has been detected and where it has not been observed. Second, the staging of puberty by investigators needs to be more reliable and less subjective; in particular, breast development needs to be staged by palpation, not just inspection, and testicular measurements need to be incorporated into the staging of puberty in boys. Third, there should be less reliance on BMI as the only measure of obesity and more emphasis on measures of body fat, including skinfold thickness and bioelectrical impedance. The age of the children studied should range from as early as 6 or 7 years up to 13 or 14 years, at least for girls, to capture the onset of puberty in the increasing proportion of girls who start having breast and pubic hair development before 8 years of age. Fourth, there is an obvious need for new longitudinal studies to examine the relationship between body fat and puberty in girls in more detail. In the long run, the best hope is the National Children's Study, a longitudinal study of a nationally representative sample of children and the environment (www.nationalchildrensstudy.gov). This study will recruit parents during pregnancy or before and follow >100 000 children until 21 years of age. Environment has been broadly defined, including the chemical and physical environment, social and cultural influences, genetics, and a variety of other factors. Recruitment of centers is still in process, and each center will have 4 years to enroll the required number of participants, so it will unfortunately be many years before any information relevant to the onset of pu-

erty becomes available. Eventually, the National Children's Study and perhaps other studies could not only confirm that increased body fat increases the risk for early puberty but also assess whether there is a critical window or sensitive period during which increased body fat is most likely to result in earlier puberty. Finally, data that will allow an estimation not only of total energy intake as it relates to the timing of puberty but also of intake of specific foods that may be important as possible sources of both estrogenic and antiestrogen chemicals need to be collected.

REFERENCES

1. Wyshak G, Frish RE. Evidence for a secular trend in the age of menarche. *N Engl J Med*. 1982;306(17):1033-1035
2. Warren MP. The effects of undernutrition on reproductive function in the human. *Endocr Rev*. 1983;4(4):363-377
3. Frisch RE and Revelle R. Height and weight at menarche and a hypothesis of menarche. *Arch Dis Child*. 1971;46(249):695-701
4. Frisch RE. Body fat, menarche, fitness and fertility. *Hum Reprod*. 1987;6:521-533
5. Garn SM, LaVelle M, Pilkington JJ. Comparison of fatness in premenarcheal girls of the same age. *J Pediatr*. 1983;103(2):328-331
6. Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. Overweight prevalence and trends for children and adolescents: the National Health and Nutrition Examination Surveys, 1963 to 1991. *Arch Pediatr Adolesc Med*. 1995;149(10):1085-1091
7. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999-2000. *JAMA*. 2002;288(14):1728-1732
8. Daniels SR, Khoury PR, Morrison JA. The utility of body mass index as a measure of body fatness in children and adolescents: differences by race and gender. *Pediatrics*. 1997;99(6):804-807
9. Biro FM, McMahahon RP, Striegel-Moore R, et al. Impact of timing of pubertal maturation on growth in black and white female adolescents: the National Heart, Lung, and Blood Institute Growth and Health Study. *J Pediatr*. 2001;138(5):636-643
10. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatrics Research in Office Settings network. *Pediatrics*. 1997;99(4):505-512
11. Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics*. 2008;121(3 suppl):S172-S191
12. Rosner B, Prineas R, Loggie J, Daniels SR. Percentiles for body mass index in U.S. children 5 to 17 years of age. *J Pediatr*. 1998;132(2):211-222
13. Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SE, Herman-Giddens ME. Earlier onset of puberty in girls: relation to increased body mass index and race. *Pediatrics*. 2001;108(2):347-353
14. Kaplowitz PB, Oberfield SE, Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. *Pediatrics*. 1999;104(4 pt 1):936-941
15. Himes JH, Obarzanek E, Baranowski T, Wilson DM, Rochon J, McClanahan BS. Early sexual maturation, body composition, and obesity in African-American girls. *Obes Res*. 2004;12(suppl):64S-72S

16. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of menarche to race, time period, and anthropomorphic dimensions: the Bogalusa Heart Study. *Pediatrics*. 2002;110(4). Available at: www.pediatrics.org/cgi/content/full/110/4/e43
17. Anderson SE, Dallal GE, Must A. Relative weight and race influence average age at menarche: results from two nationally representative surveys of US girls 25 years apart. *Pediatrics*. 2003;111(4 pt 1):844–850
18. Wang Y. Is obesity associated with earlier sexual maturation? A comparison of the association in American boys vs girls. *Pediatrics*. 2002;110(5):903–910
19. Herman-Giddens ME, Wang, L, Koch G. Secondary sexual characteristics in boys: estimates from the National Health and Nutrition Examination Survey III, 1988–1994. *Arch Pediatr Adolesc Med*. 2001;155(9):1022–1028
20. Vignolo M, Naselli A, Di Battista E, Mostert M, Aicardi G. Growth and development in simple obesity. *Eur J Pediatr*. 1988;147(3):242–244
21. Vizmanos B, Marti-Henneberg C. Puberty begins with a characteristic subcutaneous body fat mass in each sex. *Eur J Clin Nutr*. 2000;54(3):203–208
22. Laron Z. Is obesity associated with early sexual maturation? *Pediatrics*. 2004;113(1 pt 1):171–172
23. Rosenbaum M, Leibel RL. Role of gonadal steroids in the sexual dimorphism in body composition and circulating concentrations of leptin. *J Clin Endocrinol Metab*. 1999;84(6):1784–1789
24. He Q, Karlberg J. BMI gain in childhood and its association with height gain, timing of puberty, and final height. *Pediatr Res*. 2001;49(2):244–251
25. Davison KK, Susman EJ, Birch LL. Percent body fat at age 5 predicts earlier pubertal development among girls at age 9. *Pediatrics*. 2003;111(4 pt 1):815–821
26. Lee JM, Appugliese D, Kaciroti N, Corwyn RF, Bradley RH, Lumeng JC. Weight status in young girls and the onset of puberty. *Pediatrics*. 2007;119(3). Available at: www.pediatrics.org/cgi/content/full/119/3/e624
27. Remer T, Manz F. Role of nutritional status in the regulation of adrenarche. *J Clin Endocrinol Metab*. 1999;84(11):3936–3944
28. Charkaluk ML, Trivin C, Brauner R. Premature pubarche as an indicator of how body weight influences the onset of adrenarche. *Eur J Pediatr*. 2004;163(2):89–93
29. Shalitin S, Phillip M. Role of obesity and leptin in the pubertal process and pubertal growth: a review. *Int J Obes (Lond)*. 2003;27(8):869–874
30. Kennedy GC, Mitra J. Body weight and food intake as initiating factors for puberty in the rat. *J Physiol*. 1963;166:408–418
31. Engelbregt MJ, Houdijk ME, Popp-Snijders C, Delemarre-van de Waal HA. The effects of intra-uterine growth retardation and postnatal undernutrition on onset of puberty in male and female rats. *Pediatr Res*. 2000;48(6):803–807
32. Halaas JL, Gajiwala KS, Magherita M, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science*. 1995;269(5223):543–546
33. Chehab FF, Lim ME, Lu R. Correction of the sterility defect in homozygous obese female mice by treatment with human recombinant leptin. *Nat Genet*. 1996;12(3):318–320
34. Barash IA, Cheung CC, Weigle DS, et al. Leptin is a metabolic signal to the reproductive system. *Endocrinology*. 1996;137(7):3144–3147
35. Chehab FF, Mounzih K, Lu R, Lim ME. Early onset of reproductive function in normal female mice treated with leptin. *Science*. 1997;275(5296):88–90
36. Cheung CC, Thornton JE, Kuijper JL, Weigle DS, Clifton DK, Steiner RA. Leptin is a metabolic gate for onset of puberty in the female rat. *Endocrinology*. 1997;138(2):855–858
37. Cheung CC, Thornton JE, Nurani SD, Clifton DK, Steiner RA. A reassessment of leptin's role in triggering the onset of puberty in the rat and mouse. *Neuroendocrinology*. 2001;74(1):12–21
38. Yura S, Ogawa Y, Sagawa N, et al. Accelerated puberty and late-onset hypothalamic hypogonadism in female transgenic skinny mice overexpressing leptin. *J Clin Invest*. 2000;105(6):749–755
39. Yu WH, Kimura A, Walczewska A, Karanth S, McCann SM. Role of leptin in hypothalamic-pituitary function. *Proc Natl Acad Sci USA*. 1997;94(3):1023–1028
40. Lebrethon MC, Vandersmissen E, Gerard A, Parent AS, Junien JL, Bourguignon JP. In vitro stimulation of the prepubertal rat gonadotropin-releasing hormone pulse generator by leptin and neuropeptide Y through distinct mechanisms. *Endocrinology*. 2000;141(4):1464–1469
41. Wilson ME, Fisher J, Chikazawa K, et al. Leptin administration increases nocturnal concentrations of luteinizing hormone and growth hormone in juvenile female rhesus monkeys. *J Clin Endocrinol Metab*. 2003;88(10):4874–4883
42. Plant TM, Durrant AR. Circulating leptin does not appear to provide a signal for triggering the initiation of puberty in the male rhesus monkey. *Endocrinology*. 1997;138(10):4545–4508
43. Mann DR, Akinbami A, Gould KG, Castracane VD. A longitudinal study of leptin during development in the male rhesus monkey: the effect of body composition and season on circulating leptin levels. *Biol Reprod*. 2000;62(2):285–291
44. Suter KJ, Pohl CR, Wilson ME. Circulating concentrations of nocturnal leptin, growth hormone, and insulin-like growth factor-1 increase before the onset of puberty in gonadal male monkeys: potential signals for the initiation of puberty. *J Clin Endocrinol Metab*. 2000;85(2):808–815
45. Barker-Gibb ML, Sahu A, Pohl CR, Plant TM. Elevating circulating leptin in prepubertal male rhesus monkeys does not elicit precocious gonadotropin-releasing hormone release, assessed indirectly. *J Clin Endocrinol Metab*. 2002;87(11):4976–4983
46. Hassink SG, Sheslow DV, de Lancey E, Opentanova I, Considine RV, Caro JF. Serum leptin in children with obesity: relationship to gender and development. *Pediatrics*. 1996;98(2 pt 1):201–203
47. Strobel A, Issad T, Camoin L, Ozata M, Strosberg AD. A leptin missense mutation associated with hypogonadism and morbid obesity. *Nat Genet*. 1998;18(3):213–215
48. Farooqi IS, Jebb SA, Langmack G, et al. Effect of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med*. 1999;341(12):879–884
49. Blum WF, Englaro P, Hanitsch S, et al. Plasma leptin levels in healthy children and adolescents: dependence on body mass index, body fat mass, gender, pubertal stage, and testosterone. *J Clin Endocrinol Metab*. 1997;82(9):2904–2910
50. Garcia-Mayor RV, Andrade A, Rios M, Lage M, Dieguez C, Casanueva FF. Serum leptin levels in normal children: relationship to age, gender, body mass index, pituitary-gonadal hormones, and pubertal stage. *J Clin Endocrinol Metab*. 1997;82(9):2849–2855
51. Ahmed ML, Ong KK, Morrell DJ, et al. Longitudinal study of leptin concentrations during puberty: sex differences and relationship to changes in body composition. *J Clin Endocrinol Metab*. 1999;84(3):899–905
52. Matkovic V, Ilich JZ, Skugor M, et al. Leptin is inversely related to age at menarche in human females. *J Clin Endocrinol Metab*. 1997;82(10):3239–3245
53. Cizza G, Dorn LD, Lotsikas A, Sereika S, Rotenstein D, Chrousos GP. Circulating plasma leptin and IGF-1 levels in girls with premature adrenarche: potential implications of a preliminary study. *Horm Metab Res*. 2001;33(3):138–143

54. l'Allemand D, Schmidt S, Rousson V, Brabant G, Gasser T, Gruters A. Associations between body mass, leptin, IGF-I and circulating adrenal androgens in children with obesity and premature adrenarche. *Eur J Endocrinol.* 2002;146(4): 537–543
55. Biason-Lauber A, Zachmann M, Schoenle EJ. Effect of leptin on CYP17 enzymatic activities in human adrenal cells: new insights in the onset of adrenarche. *Endocrinology.* 2000;141(4): 1446–1454
56. Saenger P, Dimartino-Nardi J. Premature adrenarche. *J Endocrinol Invest.* 2001;24(9):724–733
57. Palmert MR, Radovick S, Boeplle PA. Leptin levels in children with central precocious puberty. *J Clin Endocrinol Metab.* 1998; 83(7):2260–2265

Link Between Body Fat and the Timing of Puberty

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