

CLINICAL PRACTICE UPDATE

The pubertal timing controversy in the USA, and a review of possible causative factors for the advance in timing of onset of puberty

Arnold H. Slyper

Department of Pediatrics, Loyola University Medical Center, Maywood, IL, USA

Summary

Previously used standards for the diagnosis of precocious puberty in girls no longer appear to be appropriate in the USA, in that a significant number of girls are being seen in paediatricians' offices with breast budding before 8 years of age. The timing of menarche, however, has changed little over the past few decades. Early maturing girls are more likely to become obese in adolescence and adulthood than normal or late maturing girls. Early maturing white girls are heavier at the onset of puberty, but this is not the case for African-American girls or boys of either race. Boys and girls with premature pubarche may be more hyperinsulinaemic than normal children, and girls with premature pubarche more likely to develop functional ovarian and adrenal hyperandrogenism. Early menarche is preceded by prepubertal hyperinsulinaemia. It is proposed that pubertal onset, although not necessarily the tempo of puberty, is influenced by hyperinsulinaemia and insulin resistance. If this hypothesis is correct, insulin resistance may be more prevalent in US children than previously recognized. An advance in timing of onset of puberty has not been noted in other countries, although it is likely that this phenomenon may become more prevalent as other countries adopt a more American lifestyle and diet.

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Has there been a secular advance in pubertal timing?

It has been the impression among paediatric health providers in the USA that girls are developing secondary sexual characteristics earlier than in previous decades. Appreciating the need for current data, the Pediatric Research in Office Settings (PROS) network from the American Academy of Pediatrics examined more than 17 000 girls from a geographically diverse group of private paediatric offices

across the USA and Puerto Rico between 1992 and 1993.¹ Of these girls, 9.6% were African-American. Distinct racial differences were noted, with mean age of onset of breast development being 9.96 years for whites and 8.87 years for African-Americans. Differences in maturation between African-American and white girls had been noted incidentally in the past, but this was the first study to document these differences precisely.^{2–5} These figures from the PROS study were about 6 months to 1 year earlier than previously reported for white girls, and about 2 years earlier for African-Americans girls. Based on earlier studies, it had been generally assumed that onset of breast development was close to 11 years for both African-Americans and whites.^{6–9}

Nevertheless, not all studies agree that there has been a secular shift in the age of onset of female puberty. This issue has also been examined using data from the National Health and Nutrition Examination Survey III (NHANES III). In this large survey, carried out in the USA between 1988 and 1994, the study population was racially more representative of the US population than the PROS study. From these data, Sun *et al.*¹⁰ reported onset of breast development to be 10.38 years for whites and 9.48 years for African-Americans, which is significantly later than the PROS study (Table 1). Essentially similar results were obtained by Wu *et al.*¹¹ using the same data sets. A subsequent report in abstract form noted no difference in age of onset of puberty for white and African-American girls between the National Health Examination Survey (NHES) conducted in 1966–1970 and NHANES III conducted in 1988–1994.^{12,13}

In view of these discrepancies, there are doubts as to the accuracy of the PROS data. One criticism of the PROS study has been that it did not select a random sample, and this could have led to ascertainment bias.¹⁰ It has been suggested, for example, that early onset of breasts or pubic hair may have been a 'hidden agenda' for the visit to the paediatrician.¹⁴ In addition, breast development was assessed by palpation in only 37% of girls in the PROS study.¹ Particularly in obese girls, adipose tissue over the chest wall can closely resemble true breast tissue. The PROS study also included no girls older than 13 years of age, thereby excluding late-maturers. By contrast, NHANES III collected no data prior to 8 years of age. Hence, depending on race, 6–30% of the girls from NHANES III had at least one secondary sexual characteristic at the youngest age data were collected.¹⁵ Statistical corrections were made in both studies to correct for this problem but biases could have occurred.

Correspondence: Arnold H. Slyper, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153, USA. Tel.: 708 327 9079; Fax: 708 327 9132; E-mail: aslyper@lumc.edu

Table 1. Reported mean ages \pm SD (years) for female sexual maturation in the UK and the USA

	Number of subjects (age range in years)	Breasts at Tanner stage 2	Menarche	Pubic hair at Tanner stage 2	Comments
Marshall and Tanner (UK) (1969) ⁶	192 (8 up)	11.15 \pm 1.10	13.47 \pm 1.02		Photographs. Whites
Reynolds and Wines (USA) (1948) ⁹	49 (8–18)	10.8 \pm 1.1	12.9 \pm 1.4	11.0 \pm 1.1	Direct examination + photographs. Race not stated
Nicolson and Hanley (USA) (1953) ⁸	252	10.6	12.8	11.6	
Lee (USA) (1980) ⁷	18 (8.6–17.8)	11.2 \pm 1.6	13.3 \pm 1.3	11.9 \pm 1.5	Direct examination. Almost all whites
Billewicz <i>et al.</i> (UK) (1981) ⁷⁵	788 (9–17)	10.8 \pm 1.6	13.4 \pm 1.1		Direct examination. Whites
Roche <i>et al.</i> (USA) (1995) ²⁴	67 (9.5–17)	11.2 \pm 0.7		11.0 \pm 0.5	Whites. Assisted self-examination
Herman-Giddens <i>et al.</i> (USA) (1997) ¹	17 077 (3–12)	African-Americans 8.87 \pm 1.93 Whites 9.96 \pm 1.82	African-Americans 12.16 \pm 1.21 Whites 12.88 \pm 1.20	African-Americans 8.78 \pm 2.0 Whites 10.51 \pm 1.67	Only 9.6% African-Americans Breast development assessed by palpation in 39% of girls. Otherwise by inspection
Sun <i>et al.</i> (USA) (2002) ¹⁰	1215 (8–19)	African-Americans 9.48 Whites 10.38		African-Americans 9.43 Whites 10.57	Direct examination
Wu <i>et al.</i> (USA) (2002) ¹¹	1623–1168 (8–16)	African-Americans 9.5 Whites 10.3	African-Americans 12.2 Whites 12.6	African-American 9.5 Whites 10.6	Direct examination
Freedman <i>et al.</i> (USA) (2002) ¹⁹					
Data collected 1973–1974	1398 (7–16)		African-Americans 12.9 Whites 12.7		
Data collected 1992–1994	1230 (7–16)		African-American 12.1 Whites 12.5		
Chumlea <i>et al.</i> (USA) (2003) ¹⁶	2510 (8–20)		African-American 12.06 Whites 12.55		
Anderson <i>et al.</i> (USA) (2003) ¹⁸					
Data collected 1963–1970	1760 (10–15)		African-Americans 12.48 Whites 12.8		
Data collected 1988–1994	767 (10–15)		African-American 12.14 Whites 12.60		

It also needs to be asked – how reliable were previous standards? Most were based on relatively small studies, select populations, and possibly inappropriate age ranges, and used differing methods for pubertal staging. Most commonly cited is a 1969 study by Marshall and Tanner⁶ involving 192 white girls from a children's home in the UK, in whom breast development identified by photographs was noted at 11.15 years. However, these girls were from a low socio-economic sector, may have lived previously in unsatisfactory home conditions, and were not completely representative of the British population, in that they were reaching menarche 4 months later than the population of London. Nevertheless, this figure seems to be in line with other early surveys, including those from the USA (Table 1).^{7–9}

There has been less discussion in the literature as to whether the appearance of pubic hair has advanced in females, although this does seem to be the case, pubarche having advanced by at least 6 months (Table 1). The PROS study found stage II pubic hair to be apparent in African-American females at a mean age of 8.78 years and 10.51 years in whites.¹ Conclusions from NHANES III data from 1988 to 1994 are in broad agreement with these figures, at least for whites, ages quoted being 9.43 years for African-Americans, 10.57 years for whites, and 10.39 years for Mexican-Americans.¹⁰ Previous standards were based on the same studies as for the appearance of breasts and the same criticisms could be levelled. The Fels Research Institute reported in the 1940s that pubic hair was apparent shortly after the appearance of breasts at a mean age of 11.0 years.⁹ Lee's small study from the early 1970s quoted a figure of 11.9 years for mainly whites.⁷

In contrast to breast budding, there is general agreement that there has been less change over the years with respect to menarche (Table 1).¹⁵ The PROS study (with data collected between 1992 and 1993) concluded that age of menses was 12.16 years in African-American and 12.88 years in white girls.¹ From NHANES III data collected between 1988 and 1994, Chumlea *et al.*¹⁶ found that mean age of menarche was 12.43 years, with African-Americans beginning menses earlier (12.06 years) than white (12.55 years) and Mexican-American girls (12.25 years). This is an advance of 4 months compared to NHES data collected between 1963 and 1970.¹⁷ An analysis of these data by Anderson *et al.*,¹⁸ using a slightly different analytical

approach, concluded that the average age of menarche advanced by 0.21 years (about 2½ months) between data collected from 1963 to 1970 and 1988 to 1994. Bogalusa Heart Study data indicate that age of menarche advanced by 9.5 months for African-American girls and 2 months for white girls between 1973 and 1994.¹⁹ With close attention to racial differences, Anderson and Must concluded that there was almost no change in age of menarche for whites and African Americans from 1988 to 1994 and from 1999 to 2002, with a 0.15 year decline for Mexican-Americans.²⁰

Boys also seem to be developing earlier than previously, possibly by more than a year. From NHANES III data on boys aged 8–19 years, it is apparent that the mean age of onset of male genital development based on visual inspection is now approximately 9.3 years for African-Americans, 10.0 years for whites, and 10.3 years for Mexican-Americans.¹⁰ These figures are in line with the conclusions of Herman-Giddens *et al.*²¹ from the same data sets but using a different statistical analysis. White boys and white girls therefore seem to be commencing puberty at approximately the same age. This conclusion is somewhat surprising, in that early male maturation has not attracted attention as a clinical concern. As pointed out by Reiter and Lee,²² however, their examinations did not include testicular volume assessment, and a one-stage variance was permitted between the physician's assessment and quality control standard. There is therefore the possibility that genital development in the NHANES III survey was overrated in the younger age groups.

Earlier observations from the UK and the USA suggested that the mean age of male genital development was between 11.2 and 11.9 years, which was somewhat later than for female breast budding.^{7,23,24} However, the UK subjects from the important study of Marshall and Tanner²³ were not completely representative of the UK population, in that they were living in a children's home, came from a lower socio-economic sector of the population, and may have received suboptimal care before entering the home. In addition, pubertal staging was determined from photographs. Nevertheless, their data seem to be in line with other early studies, although the lack of standardization for assessing genital development is a concern (Table 2).²⁵ Like girls, there has been little change in the age at which puberty is completed, suggesting a slowing in the tempo of male puberty.²²

Table 2. Reported mean ages ± SD (years) for male sexual maturation in the UK and the USA

	Number of subjects (age range in years)	Genitalia Tanner stage 2	Pubic hair Tanner stage 2	Comments
Marshall and Tanner (UK) (1970) ²³	228	11.64 ± 1.07	(13.44 ± 1.09)	Photographs (and hence data for pubic hair questionable). Whites
Lee (USA) (1980) ⁷	36 (9–17.5)	11.9 ± 1.1	12.3 ± 0.8	Direct examination. Almost all whites
Roche <i>et al.</i> (USA) (1995) ²⁴	78 (9.5–17)	11.2 ± 0.7	11.2 ± 0.8	Whites. Assisted self-examination
Biro <i>et al.</i> (USA) (1995) ⁷⁶	515 (10–15)	12.2		African-American and whites
Herman-Giddens <i>et al.</i> (USA) (2001) ²¹	2114 (8–19)	African-Americans 9.5 Whites 10.1	African-Americans 11.2 Whites 12.0	Direct examination
Sun <i>et al.</i> (USA) (2002) ¹⁰	500 (8–19)	African-Americans 9.20 Whites 10.03	African-Americans 11.16 Whites 11.98	Direct examination

The issue is less clear for age of onset of male pubic hair. NHANES III data for boys indicate that the mean age of onset of pubic hair development is 11.2 years for African-Americans, 12.0 years for whites and 12.3 years for Mexican-Americans.^{10,21} Marshall and Tanner²³ reported on a 15-year longitudinal study of 228 white British boys commencing in the 1950s, and reported a mean age of 13.44 years. However, their data were obtained from photographs and early pubic hair would not have been detectable. Lee gives a figure of 12.6 years for mainly whites.⁷

In conclusion, the issue as to whether there has been an advance in the onset of female puberty remains controversial, with no general consensus. Nevertheless, despite their manifest deficiencies, older studies did permit calculations of normality that have served paediatricians and paediatric endocrinologists well for many years. Female sexual precocity has been regarded as the onset of breast development before 8 years irrespective of race (2.5 standard deviations from the mean).^{26,27} It is difficult to ignore the fact that 15.4% of African-Americans and 5% of white girls are now presenting to their paediatricians' offices between 7 and 8 years of age with breast budding.¹ This is very different from the 0.06% of girls of this age that would be anticipated from the previous standards. Furthermore, differences between the PROS study and NHANES III may not be as great as first apparent. The percentage of white girls with breast development by ages 8–9 years from the PROS study was 10.5% and from NHANES III 11.4%.^{1,11} For African-American girls, the figures were 37.8% from the PROS study and 27.8% from NHANES III. Although these numbers differ, the trend is very similar. Based on previous standards, the cut-off for female premature pubarche would be 8 years. However, the PROS study found that 17.7% of African-American and 2.8% of white girls had Tanner 2 or greater pubic hair between 7 and 8 years of age, again suggesting that previous standards are no longer relevant to the current situation.¹ The disparity between previous standards and recent surveys is even more striking for male development, although, as mentioned, there is considerable doubt as to the accuracy of the recent survey. Based on the older standards, male sexual precocity has been considered as testicular enlargement before 9½ years of age.²⁶ This is very different from the 29.3% of white, 27.3% of Mexican-American and 37.8% of African-American males that now have Tanner stage 2 genitalia at 8 years of age as reported from NHANES III.²¹

It has been argued that the PROS study's findings of little change in age of menarche despite an earlier onset of puberty cast doubts on the reliability of their figures for onset of puberty.¹⁴ However, given the fact that menarche has undergone only slight change over the decades, it is equally likely that there has been a slowing in the overall tempo of female pubertal development.^{15,16,18–20} A similar phenomenon may have occurred in males.²⁵

Not surprisingly, the popular press has picked up on the phenomenon of early female maturation and discussed its societal implications.²⁸ A recently formed paediatric endocrine advisory committee felt it appropriate to revise the definition of female sexual precocity to 7 years for white girls and 6 years for African-American girls.²⁹ This would obviate the need for endocrine testing of many otherwise normal girls. Many paediatric endocrinologists, however, feel these new recommendations to be inappropriate, given the doubts as to the applicability of the PROS data.¹⁴

Mention should be made of the study of Midyett *et al.*³⁰ who, under the title 'Are pubertal changes in girls before age 8 benign?', reported that of 223 girls aged 7–8 years for whites and 6–8 years for African-Americans, 12.3% had a pathological explanation for their sexual precocity. The authors conclude that revision of well-established recommendations on the basis of a single study (the PROS study) was premature and could lead to under-diagnosis of significant pathology. There is, however, much to discuss regarding this conclusion. Previous recommendations were used in the main to distinguish those patients who would benefit from radiological studies to rule out an organic central cause for their sexual precocity. This was found in only one of Midyett *et al.*'s patients.³⁰ Previous recommendations clearly did not obviate the need for a clinical evaluation to rule out such entities as neurofibrosis (one patient) and McCune–Albright syndrome (two patients). It is also telling that 4.2% of Midyett *et al.*'s patients with isolated breast development, 8.4% with pubic hair, and 6.7% with breast and pubic hair were diagnosed with acanthosis nigricans/hyperinsulinism. Also that 35.2% of the girls with both breasts and pubic hair had bone ages greater than 3 standard deviations above the mean. The fact that 'normality' may have changed does not negate the possibility that the physiological processes leading to these changes are neither normal nor benign.

Can the secular trend to earlier pubertal maturation be explained by obesity?

Over 35 years ago, Frisch and Revelle proposed that the onset of the female adolescent growth spurt and menarche require a critical weight.^{31–33} This hypothesis was subsequently refined to incorporate body fat.³⁴ There are, however, multiple explanations for menstrual-related phenomenon, and the notion of a threshold level of fatness in relation to menarche was subsequently discredited.^{35–37} Nevertheless, some form of linkage between nutrition and pubertal timing seems evident from the following observations.

A number of studies have shown that early maturation is associated with the eventual development of obesity. Wang³⁸ noted that early maturing girls demonstrate an increase in body mass index (BMI), skinfold thickness, and prevalence of obesity (BMI equal to or greater than the 95th percentile) between 8 and 14 years of age compared to normal and late maturing girls. Adair and Gordon-Larsen³⁹ found the prevalence of overweight (BMI at or above the 85th percentile) was significantly higher in adolescents who had experienced an early menarche, and that the prevalence of overweight was lower in later maturing girls. Early maturing girls were nearly twice as likely to be overweight than average maturing girls, with the overweight state being particularly high among early maturing African-American adolescents (57.5%).⁴⁰ de Ridder *et al.*⁴¹ demonstrated a negative relationship between body fat mass and the time interval from breast stage 3 to menarche. It has also been noted that earlier maturing girls are heavier and more obese in early adulthood than later maturing girls.^{42,43}

A more contentious issue is whether increased body fatness is aetiologically related to early puberty. This is an important question as it would link the secular shift in pubertal development to the current paediatric obesity epidemic in the USA. This idea was proposed by Kaplowitz *et al.*,⁴⁰ who, on re-examination of the PROS data, noted

a stronger correlation between maturational stage and BMI than between chronological age and BMI. Pubertal 6- to 9-year-old white girls also had markedly higher BMI z-scores than prepubertal girls of the same age. Nevertheless, such observations do not necessarily point to a causal relationship between BMI and maturation, and may indicate no more than that early puberty in girls leads to increased body fatness, as noted by other investigators. Furthermore, their hypothesis breaks down for African-American girls. African-American girls mature earlier than white girls.^{1,10,11} However, in the PROS study, differences in BMI z-scores between prepubertal and pubertal black girls were much smaller than for whites, and reached significance only for 9-year-olds. This difference between early maturing African-American and early maturing white girls was ascribed by the authors to an artefact due to the small number of African-Americans girls in the PROS study.⁴⁰ However, their observations appear to be very real. From analyses of NHES and NHANES III data, Anderson *et al.*¹⁸ found that a higher BMI z-score was strongly associated with an increased likelihood of reaching menarche, after controlling for age and race. However, for African-American girls, age of menarche was independent of the effect of BMI z-score, even though African-American girls were reaching menarche earlier than whites.

On theoretical grounds, longitudinal studies should be of greater value than cross-sectional studies in determining whether body weight influences the onset of pubertal maturation. Davison *et al.*⁴⁴ studied 183 white American girls from ages 5 to 9 years and followed their BMI, waist circumference and percentage body fat (as determined from weight, skinfold thickness and bioelectrical impedance). The prevalence of overweight and obesity increased slightly among girls from ages 5 to 9 years, with the greatest increase occurring between 7 and 9 years. Girls with a higher percentage of body fat at 5 years and a higher percentage of body fat, higher BMI percentile and greater waist circumference at 7 years were more likely to show advanced pubertal development at 9 years. Nevertheless, it should be noted that these girls were no more likely to be overweight or obese at ages 5 or 7 years than the general population. Analysing longitudinal data from the Bogalusa Heart Study, Frontini *et al.*⁴⁵ compared two groups of girls, those who had achieved menarche before and those who had achieved menarche after 12 years of age. Their population was 65% white and 35% black. Significant differences in BMI were apparent for the early menarche girls when they were 5–7 years of age, and differences in BMI remained significant up to and beyond menarche. Nevertheless, in this study also, mean BMI for the girls with early menarche while in the 5–7-years age group was neither in the obese nor overweight range, and only reached the overweight range at 19–37 years of age.

European studies have also found no increase in BMI in girls with a history of premature pubarche at ages 6–18 years (although increased central fat was noted).⁴⁶ The American PROS study did find that 6–9-year-old white girls with pubic hair alone had significantly higher BMI and z-scores than prepubertal girls without pubarche, but this was not the case for African-American girls.¹

In conclusion, there is much evidence that early maturing girls are more likely to become obese in adolescence and adulthood.^{38,39,41} Recent studies indicate that early maturing white girls are also heavier at the onset of puberty, although not necessarily overweight or obese.^{44,45} Nevertheless, an early relationship to BMI is not apparent

in early maturing African-American girls.^{1,18} Furthermore, although early maturation is associated with eventual obesity and overweight in girls, the association is a negative one in boys, in that early maturing boys have a reduced risk for obesity and overweight than nonearly maturers.³⁸ The evidence therefore that early pubertal development is directly related to the paediatric obesity epidemic is far from compelling.

Could there be a role for hyperinsulinaemia and insulin resistance in the secular shift in onset of puberty?

Is it possible to link together these many observations on early puberty and body weight for both sexes and for all racial groups, and develop a unifying hypothesis that incorporates not only early maturing white girls but also early maturing African-American girls and early maturing boys?

There is evidence, albeit far from complete, that it is not body fatness that induces early maturation, but hyperinsulinaemia and insulin resistance:

1 Prepubertal and pubertal African-Americans are more insulin resistant than age- and BMI-matched white children.^{46–50} As discussed above, African-American females mature and reach menarche earlier than whites.^{1,16}

2 Some of the strongest evidence for this hypothesis relates to the association between early pubarche, hyperandrogenaemia and hyperinsulinaemia. Pre- and postpubertal girls with a history of premature pubarche have a more hyperinsulinaemic response to an oral glucose tolerance test than other girls matched for age and BMI.^{51–53} Hyperinsulinaemia persists throughout all stages of puberty, and is accompanied by decreased levels of SHBG and IGFBP-1, both indicators of hyperinsulinaemia and insulin resistance.^{53–56} Throughout puberty, girls with a history of premature pubarche also have increased levels of triglyceride, very low density lipoprotein (VLDL)-triglyceride, total cholesterol, VLDL-cholesterol, and decreased high density lipoprotein (HDL) compared to controls matched for pubertal stage, bone age and BMI, this being further evidence of pubertal hyperinsulinaemia.⁴⁶ Boys with premature pubarche, defined in this study as the appearance of pubic hair and/or axillary hair before age 9 years, are also more insulin resistant and have higher fasting and postglucose load insulin values compared to controls after adjustment for BMI z-score.⁵⁷

It should be noted, however, that the majority of the studies on female premature pubarche were carried out in a single centre in Europe. Many of these children had been of low birthweight and the development of insulin resistance could have been the effect of foetal programming.^{58,59} Hence, the extent to which their observations reflect the current situation in the USA is unclear.

3 Just under 50% of girls with premature pubarche develop a postpubertal functional ovarian hyperandrogenism, characterized by increased ovarian 17-hydroxyprogesterone and androstenedione responses to GnRH analogue stimulation.⁶⁰ This pattern of steroid secretion is typical of the ovarian dysfunction seen in adult polycystic ovary syndrome (PCOS), in that administration of a GnRH analogue to females with polycystic ovary syndrome typically leads to a large and sustained secretion of endogenous gonadotrophins with a predominant LH response and a large resulting increase in gonadal

steroids.^{61,62} Hyperinsulinaemia and insulin resistance are an integral component of PCOS, even in the absence of obesity, and insulin has a direct stimulatory effect on ovarian steroidogenesis.^{61,63–69}

4 In just over a third of cases of premature pubarche, a functional adrenal hyperandrogenism is also evident at adolescence, with increased dehydroepiandrosterone (DHEA) and androstenedione responses to ACTH stimulation.⁶⁷ This type of adrenal response is also found in just over 50% of hyperandrogenic adult women and 16% of hyperandrogenic adolescents girls.^{51,67,68}

5 Lazar *et al.*⁷⁰ reported that 44.6% of 112 Israeli girls with idiopathic central precocious puberty had exaggerated 17-hydroxypregnenolone levels and 17-hydroxypregnenolone/17-hydroxyprogesterone ratios in response to combined ACTH and GnRH stimulation tests compared to 14.3% of controls. Many girls with premature pubarche have a similar type of response.⁷¹ Lazar *et al.*⁷² also studied 49 mature Israeli girls with a history of precocious puberty (i.e. Tanner stage 2 or 3 breast development before age 8 years and/or menarche before 10 years), many of whom had been treated with GnRH analogue therapy, and noted that 40.8% of the girls fulfilled at least three of the four clinical criteria for PCOS (irregular menses, hirsutism, acne and obesity).

6 The study of Frontini *et al.*,⁴⁵ quoted previously, which compared girls from the Bogalusa Heart Study who reached menarche before and after 12 years of age, is of considerable interest as this is the only study to follow sequential insulin levels in children in relation to onset of menarche. Levels of insulin and homeostasis model assessment (HOMA)-determined insulin resistance were higher at all ages in the earlier maturing girls, but were significantly higher in the 5–7 and young adulthood age groups. Early menarche was also associated with a 1.8-fold higher prevalence in young adulthood of clustering of 3–4 risk factors constituting the metabolic syndrome, namely fasting insulin, BMI, systolic or mean arterial blood pressure, total cholesterol to HDL-cholesterol ratio, and triglycerides to HDL-cholesterol ratio. On multivariate analysis, fasting insulin, BMI and triceps skinfold thickness showed independent associations with early menarche. In a longitudinal study of a similar nature that separated the closely linked aspects of weight gain and insulin, the Fels Longitudinal Study examined the influence of body composition (fat-free mass and percentage body fat) in 391 girls, and showed that girls with early menarche developed greater adiposity, greater hyperinsulinaemia, and less favourable cardiovascular disease risk factor changes during puberty compared to girls with average or late menarche.⁷³ Girls with early menarche had higher insulin levels at the onset of puberty compared to the other two groups, with differences reaching statistical significance at 10–12 years of age.

Conclusions

American girls are presenting to their physicians' offices with evidence of breast budding at a younger age than would be anticipated from previously used standards, and a secular shift in age of onset of female puberty seems to be very real. However, there has been little change in the timing of menarche, suggesting a slowing in the overall tempo of female pubertal development. The evidence that the advance in the onset of female puberty is due to obesity is far from conclusive, and can be excluded for African-American girls and boys

of any race. There is evidence, albeit incomplete, that early maturation could be related to hyperinsulinaemia and insulin resistance.

A possible relationship between pubertal timing and the later development of the metabolic syndrome is of considerable importance and further studies are clearly necessary. There are numerous longitudinal data on the development of the metabolic syndrome following early menarche, but little information regarding the extent to which hyperinsulinaemia and the metabolic syndrome develop after early breast budding. In this respect, the reports of Lazar *et al.*^{70,72} from Israel relating early puberty to PCOS are provocative and warrant study in other countries. It is also unclear how common premature pubarche is in early maturing American boys and girls.

The notion that secular changes in the onset of puberty are the 'canary in the mine' may be a very pertinent one. If the hypothesis is correct that early pubertal maturation in boys and girls is related to insulin resistance, it follows that insulin resistance resulting from changes in lifestyle and nutrition may be more widespread in the USA than previously appreciated. An advance in the timing of onset of puberty has not been noted in other countries, although it can be speculated that this phenomenon could become more prevalent as other countries adopt a more American lifestyle and diet.⁷⁴

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