Role of Environmental Factors in the Timing of Puberty

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ABSTRACT

Puberty-timing measures have historically been used as indicators of adequate nutrition and growth. More recently, these measures have been examined in relation to exposure to estrogenic or antiandrogenic agents, as well as other environmental factors. The scientific community has debated whether puberty timing is occurring earlier today than in the mid-1900s in the United States and, if so, whether environmental factors play a role; however, no one has asked a multidisciplinary panel to resolve this question. Thus, a multidisciplinary expert panel jointly sponsored by the US Environmental Protection Agency, the National Institute of Environmental Health Sciences, and Serono Symposia International was convened to examine the evidence of a secular trend, identify potential environmental factors of concern, and identify research needs regarding environmental factors and puberty timing at “The Role of Environmental Factors on the Timing and Progression of Puberty” workshop. The majority of the panelists concluded that the girls’ data are sufficient to suggest a secular trend toward earlier breast development onset and menarche from 1940 to 1994 but that the boys’ data are insufficient to suggest a trend during this same period. The weight-of-the-evidence evaluation of human and animal studies suggest that endocrine-disrupting chemicals, particularly the estrogen mimics and antiandrogens, and body fat are important factors associated in altered puberty timing. A change in the timing of puberty markers was considered adverse from a public health perspective. The panel recommended research areas to further our understanding of the relationships among environmental factors, puberty-timing outcomes, and other reproductive and adult disease at the individual and population levels.

The age of puberty has historically been used as a measure of health status of particular populations. From as early as the 1800s, data on the age of menarche have been collected and recorded in health records among specific populations in the United States1 and Europe.2 Declines in the age at menarche have been reported from the late 1800s to the mid-1900s, and these declines have been attributed to improvements in nutrition occurring over the same period (Fig 1).3,4 Contemporary and historical studies of puberty timing have focused on girls’ age at menarche, in part because it is relatively easy to collect either retrospectively or prospectively. Puberty-timing measures used in studies have expanded in the past century to include measures that capture onset and progression of puberty (eg, Tanner stages) as well as completion.5-9

Although researchers disagree about whether children are entering and/or progressing through puberty earlier today than in the mid-1900s, some recent analyses of US cross-sectional data concluded that girls are reaching puberty earlier over this time span, as measured by age at breast development stage, pubic hair development stage, and/or age of menarche.10-14 Conversely, other studies concluded that there is no compelling evidence of an earlier age of menarche when comparing data collected in the 1950s and 1960s with data collected between 1988 and 1994.15 Furthermore, for breast and pubic hair development, Sun et al16,17 argued that the studies cannot be
adequately compared or that the degree of change is not significant. Far fewer studies of puberty timing in boys are available, but 2 recent studies suggested that male puberty timing is occurring earlier.18,19

Hypotheses to explain the proposed recent population-level changes in puberty timing from the mid-1900s to the present time are controversial. One prominent hypothesis is that exposure to endocrine-disrupting chemicals (EDCs) cause an earlier age of puberty.10,20,21 EDCs are a class of chemicals that interfere with steroid hormone activity via a variety of modes of action, at a number of levels, and puberty timing has been identified as a sensitive marker of response to EDC exposure. Male and female puberty-timing end points are especially sensitive to in utero or peripubertal exposure to certain EDCs, particularly estrogens and antiandrogens in animal models.22,23 Associations between exposure to certain EDCs and puberty timing have been identified in some human studies as well.24,25 The linkage between EDC exposure and puberty-timing outcomes at the level of the individual makes intuitive sense because the full spectrum of pubertal maturation events requires the activation of the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axes in rodents, nonhuman primates, and humans. Furthermore, a change in the timing of a single measure of puberty could result from exposure to an EDC that affects hormone activity at the target tissue.26,27 In addition to the EDC hypothesis, other hypotheses include increasing obesity11,28,29 and increasing hyperinsulinemia and insulin resistance,30 but all of these hypotheses remain controversial.

The debate about the factors that are responsible for the proposed secular trend toward an earlier puberty stems from several sources. First, the question of whether a secular trend in puberty timing even exists in this time period continues to be debated. Second, the terms “puberty” and “puberty onset” have been used to indicate a variety of puberty markers (eg, “puberty onset” can indicate menarche to some and breast development to others), increasing confusion. Because puberty-timing markers can differ in their mechanistic underpinning, it is important to compare puberty-timing data for the same marker. Third, puberty timing is a consequence of a wide range of genetic31–33 and environmental factors; thus extracting the contribution of environmental factors at the population level is difficult. For example, racial/ethnic differences in the timing of puberty reflect both genetic and environmental factors (Table 1).18,19,34 Finally, inherent biases in the different interest groups have tended to polarize the debate. Specifically, iden-

### TABLE 1


<table>
<thead>
<tr>
<th>Pubertal Event</th>
<th>Non-Hispanic White</th>
<th>Black</th>
<th>Mexican American</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age, Mean (95% CI), y</td>
<td>Age, Mean, y^a</td>
<td>Age, Mean (95% CI), y</td>
</tr>
<tr>
<td>Pubic hair^b</td>
<td>10.6 (10.4–10.9)</td>
<td>10.5</td>
<td>9.5 (9.2–9.8)</td>
</tr>
<tr>
<td>Breast development^b</td>
<td>10.3 (10.0–10.5)</td>
<td>10.3</td>
<td>9.5 (9.3–9.8)</td>
</tr>
<tr>
<td>Menarche^b</td>
<td>12.6 (12.4–12.8)</td>
<td>12.7</td>
<td>12.2 (12.0–12.4)</td>
</tr>
<tr>
<td>Menarche^c</td>
<td>12.7 (12.5–12.8)</td>
<td>12.7</td>
<td>12.4 (12.2–12.5)</td>
</tr>
</tbody>
</table>

NHANES III indicates Third National Health and Nutrition Examination Survey; CI, confidence interval.

^a Estimated with application of weights for the examination sample of NHANES III.

^b Estimated by using probit model for the status quo data of the puberty measurements.

^c Estimated by using failure time model for the recalled age at menarche.

tification of a secular trend in puberty timing would have very different consequences for 2 main groups that are interested in this issue: health scientists and clinicians. For health scientists, the finding of a secular trend would identify a new public health concern for investigation of potential causes. For clinicians, the finding of a secular trend could influence the normative guidelines for puberty timing. A finding of a secular trend toward an earlier average age of puberty might lower the ages considered precocious, which in turn could potentially affect treatment protocols and/or decrease the number of children treated.35,36

Current US pediatric endocrinology guidelines cite age limits for precocious puberty as secondary sexual characteristics before 8 years of age for girls8 and before 9 years for boys,9 but some have recommended reducing the US age limit for defining precocious puberty to breast or pubic hair development before 7 years in white girls and before 6 years in black girls.37

The US Environmental Protection Agency, the National Institute of Environmental Health Sciences, and Serono Symposia International convened an expert panel workshop to discuss and attempt to resolve some of these issues. Panelists represented a wide range of expertise, perspectives, and countries, including clinicians, epidemiologists, toxicologists, anthropologists, biologists, risk assessors, and statisticians. The goals of the workshop were to develop consensus, defined as characterizing areas of agreement and disagreement, on 2 main questions: (1) Are there sufficient data to suggest or establish a secular trend in the timing of puberty onset or progression in boys or girls from 1940 to 1994 in the United States? (2) What are the priority research needs for environmental factors and puberty timing for human and animal studies? The panel also considered the implication of its findings with respect to children’s health protection, including clinical guidelines for precocious and delayed puberty and children’s health risk assessment. This workshop is the only one, thus far, to have evaluated puberty and children’s health risk assessment. This workshop is the only one, thus far, to have evaluated puberty timing, especially for male puberty onset (eg, genetic and environmental factors on puberty timing. The panel concluded that an altered timing of puberty onset or progression, including isolated precocious breast development, was considered an adverse outcome; however, the increment of change in puberty timing considered biologically meaningful was not agreed on for either humans or an animal model. Finally, a recurring theme in the discussions was the value of multidisciplinary and international efforts to design and perform studies and analyze data.

These 4 articles provide a summary of the findings of the expert panel and, perhaps more important, illuminate gaps in our understanding of the interplay between genetic and environmental factors on puberty timing. Specific research needs highlighted in each article will allow us to understand better this important public health issue. Research recommendations focused on 3 areas: (1) studies to explore further the relationship between environmental factors and puberty timing, including basic research to understand the initiating event of puberty, longitudinal studies, and toxicology studies at dosages that are relevant to human exposure; (2) studies to explore further the relationship between puberty-timing alterations and adult disease, including animal and human studies of precocious puberty, delayed puberty, or isolated precocious breast development and later disease outcomes, particularly reproductive cancers (eg, breast development onset and breast cancer), and studies to determine the degree of change in puberty timing that is biologically meaningful with respect to later disease; and (3) methods development, including more sensitive puberty biomarkers with less variability in timing, especially for male puberty onset (eg, genomics methods, hormonal assays) and methods to discriminate more reliably fat from breast tissue. The goal of the recommended research is to develop a more complete picture of the complex interrelationships among dosage and time of exposure to environmental factors, genetic factors, puberty-timing outcomes, other reproductive outcomes, and adult disease, at the individual and population levels.

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