

Public Health Implications of Altered Puberty Timing

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ABSTRACT

Changes in puberty timing have implications for the treatment of individual children, for the risk of later adult disease, and for chemical testing and risk assessment for the population. Children with early puberty are at a risk for accelerated skeletal maturation and short adult height, early sexual debut, potential sexual abuse, and psychosocial difficulties. Altered puberty timing is also of concern for the development of reproductive tract cancers later in life. For example, an early age of menarche is a risk factor for breast cancer. A low age at male puberty is associated with an increased risk for testicular cancer according to several, but not all, epidemiologic studies. Girls and, possibly, boys who exhibit premature adrenarche are at a higher risk for developing features of metabolic syndrome, including obesity, type 2 diabetes, and cardiovascular disease later in adulthood. Altered timing of puberty also has implications for behavioral disorders. For example, an early maturation is associated with a greater incidence of conduct and behavior disorders during adolescence. Finally, altered puberty timing is considered an adverse effect in reproductive toxicity risk assessment for chemicals. Recent US legislation has mandated improved chemical testing approaches for protecting children's health and screening for endocrine-disrupting agents, which has led to changes in the US Environmental Protection Agency's risk assessment and toxicity testing guidelines to include puberty-related assessments and to the validation of pubertal male and female rat assays for endocrine screening.

THE TIMING OF normal puberty has a wide physiologic variation. The onset of puberty varies 4 to 5 years among normal boys and girls. The physiologic regulation of the onset of puberty is still poorly known; therefore, the reasons for the variability also remain unexplained. It is clear, however, that ethnicity, nutrition, and several environmental and genetic factors are influential. From the late 1800s to mid-1900s, there was a secular trend toward an earlier menarche. There is disagreement as to whether data indicate that the trend has continued since the mid-1900s to the current time or has leveled off in recent years (reviewed by Euling et al¹). Comparisons of some studies, from the mid- to late-1900s, indicate that breast and pubic hair development onset in US girls, particularly in black girls, is occurring at younger ages.² This has led to regional revisions of the definitions of precocious puberty in girls: the suggested age limits are 6 years in black American girls, 7 years in white American girls, and 8 years in European girls. In boys, a similar trend is not apparent, and definitions of precocity are the same around the world; however, it is pertinent to consider the consequences of early puberty in both boys and girls at the individual and population levels. Early puberty has clinical significance for individual children and their families that may necessitate counseling and intervention. On the population level, secular trends in the timing of puberty may influence behavioral disorders and adult health, which can be reflected in cancer morbidities (eg, breast, testis) and metabolic diseases (eg, polycystic ovary syndrome [PCOS], metabolic syndrome). This has implications in children's health risk assessment that need to be considered in the continuous development of guidelines for reproductive and developmental toxicity testing and screening of endocrine disruptors. This review discusses the implications of secular

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Key Words

puberty, precocious puberty, adrenarche, growth and development, breast cancer, testicular cancer, polycystic ovary syndrome, infertility, behavioral symptoms, risk assessment

Abbreviations

PCOS—polycystic ovary syndrome
HPG—hypothalamic-pituitary-gonadal
PA—precocious adrenarche
EPA—Environmental Protection Agency
MOA—mode of action

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trends in puberty timing: first, on an individual level in clinical pediatrics; second, on a population level with respect to adult health consequences; and, third, for children's health risk assessment of environmental chemicals.

ALTERED PUBERTY TIMING AS A CONCERN IN PEDIATRIC MEDICINE

Overview of Puberty

Puberty is the process by which and the period during which sexual maturation occurs and reproductive capacity is attained. It represents a dynamic physical, behavioral, and hormonal event. There are 2 seemingly related but hormonally distinct processes: the maturation of the hypothalamic-pituitary-gonadal (HPG) system, or gonadarche, and the maturation of the hypothalamic-pituitary-adrenal androgenesis system, or adrenarche. These maturational events are part of a continuum that begins during intrauterine life and extends through the life cycle. The appearance of breast tissue and the onset of rapid growth characterize the earliest components of gonadarche in girls, whereas testicular enlargement is the first pubertal event in boys. Growth of pubic or axillary hair, the development of acne or body odor, and, perhaps, a small growth velocity increment are physical findings (pubarche) associated with adrenarche in girls and boys. These physical findings may represent the onset of the aforementioned maturational events, or they may be the result of exposure of the child to endogenous or exogenous estrogens or androgens that do not necessarily arise from maturing reproductive or adrenal androgenesis systems (pseudo-puberty). The relationship of these earlier pubertal events to the ongoing epidemic of increased body fatness seems statistically clear for girls, with increased BMI associated with a trend for girls to mature earlier^{3,4}; however, in boys, a greater BMI may be associated with later onset of puberty⁴ (for review, see Kaplowitz et al⁵).

Some studies from the 1980s and 1990s demonstrated that the ages at which secondary sexual characteristics (breast budding and pubic hair growth) appear in North American girls are earlier than had been previously considered normal.^{6,7} Data are less clear in boys, and, in fact, it does not seem that the tempo or rate of progression of puberty has accelerated.^{2,6,8} If there has been a secular trend toward an earlier age of puberty in girls or boys, then it is important to consider the impact of the onset of these pubertal events at ages that are earlier than normal or earlier than had been previously recognized, from the point of view of the patient and of the pediatric medical caregivers. Both aspects are briefly summarized in this section.

Consequences of Early Appearance of Secondary Sexual Characteristics

When a child develops secondary sexual characteristics at an earlier age than her or his peer group, there are clearly recognizable differences in physical appearance. Although these may be temporary and "normal," the impact on the child's self-esteem and feelings of being

set apart from the peer group could be significant. Adults or older children may insensitively point out that "it" (puberty) has started and direct undesired attention at the changes. The assumption that a more mature-appearing child will behave in a more mature manner or perform strongly academically is flawed, because the youth is unlikely to demonstrate such behaviors; then there is the perception of failure after pressure to succeed. Finally, the appearance of precocious breast development in a girl may elicit attention from potentially abusive adults.

Adrenarche

Children who develop signs of adrenarche (eg, pubic hair) early are likely to be girls (10:1 ratio), taller and heavier than peers, and black.⁹ Bone mineral content and density are greater than in nonaffected children.¹⁰ Thus, they are somewhat distinct from age-matched children. Early adrenarche is generally benign unless the androgen-mediated events are excessive (eg, acne, muscle mass, voice change), suggesting a process that is not simply slightly earlier activation of adrenal androgenesis but a pathologically excessive production of androgens, as from adrenal or ovarian tumors or late-onset congenital adrenal hyperplasia. The remainder of the pubertal process in children with early adrenarche is not accelerated (ie, they show normal ages of onset of gonadarche and occurrence of menarche with adult height achievement appropriate for family height).⁸ These data suggest that the need for an extensive endocrinologic evaluation is limited and that routine child health care should suffice; however, a clear subset is affected by the syndrome of functional ovarian hyperandrogenism that may evolve into the adult metabolic syndrome (discussed in detail in the subsequent section).

Precocious Puberty (Gonadarche)

Girls with evidence of pubertal change before age 6 (in black girls) or age 7 (in white girls) in the United States or age 8 in other parts of the world or boys with pubertal findings before age 9 are considered to have abnormally early onset of puberty.^{6,7,11} Also, US girls with secondary sexual characteristics appearing before age 8 are still viewed as having somewhat early, although not necessarily abnormal, puberty timing. Here, we focus on gonadarche, or maturation of the HPG axis. The onset of puberty may occur at or before these ages, but it is the rate of progression or the tempo of pubertal maturation that determines the intensity of the clinical evaluation. There is considerable diversity in the speed of pubertal change.^{6,11-13} In children with rapid development, endocrinologic studies are undertaken; in those with desultory progression, clinical observation is indicated. In this latter group, the impact of obesity may be considerable; breast development occurs but may be secondary to local estrogen production by adipose cell aromatization of steroid precursors. Rapid full pubertal development would be unlikely to ensue. Gene-regulated progression of hypothalamic-pituitary maturation is an important determinant of duration of puberty. This potentially

complex process often requires expert consultative management.

In consideration of the clinical impact of early pubertal maturation, a review of the management issues raised by Grumbach and colleagues^{6,14} is relevant. The cause of the early maturation must be determined. Girls comprise ~60% to 80% of cases of early maturation, and idiopathic precocious puberty is the diagnosis in the majority (60%–80%) of these girls. Idiopathic precocious puberty, especially in children close to and in the 6- to 8-year age group, presumably reflects normal pubertal physiology, although occurring at an earlier age. The remainder of patients with sexual precocity have organic causes that must be sought and treated appropriately.

Beyond diagnosis and treatment of structural organic problems, the children who remain have early pubertal development that is remarkable only in its age of onset and in the variability of its progression. Clinical impacts of the early development, nonetheless, may be substantial. In children with rapidly progressive development, skeletal maturation will be advanced and lead to impaired adult stature. In children who have markedly accelerated skeletal maturation and in whom sexual development begins before age 6, treatment with agents to arrest the pubertal progression is appropriate and will diminish the loss of height.¹⁵ In the group of children between 6 and 8 years of age, the protection of the long-term growth opportunity is less clear, and treatment must be individualized to those who have sustained maturation.¹⁶ If puberty has advanced rapidly, then menarche may occur at an early age (<10). This may not be an important consideration in some cases but generally is of great concern to parents and may require suppressive treatment.

Other issues to be considered in making therapeutic decisions in children with early sexual maturation revolve around psychosocial matters.^{6,14} The very fact of early development may be disturbing to some children because they are taller and have secondary sexual characteristics and a more mature body habitus than others in their age range. In addition, the parents of these children will be affected by additional parental anxiety. When a child has early puberty, she or he is at risk for sexual abuse or for early sexual debut (ie, age of first sexual intercourse) with its attendant consequences in girls.

ALTERED PUBERTY TIMING AS AN ADULT DISEASE RISK FACTOR

In addition to problems that are presented to parents and clinicians by a child with altered puberty timing, population health risks need to be taken into consideration.

Metabolic Syndrome and PCOS

There seems little doubt that a history of precocious adrenarche (PA) in girls is a clear indicator of increased risk for development of metabolic syndrome and/or ovarian hyperandrogenism/PCOS in adulthood.⁹ PCOS is a complex disorder that is characterized by infertility,

hirsutism, obesity, and menstrual effects (eg, oligomenorrhea, amenorrhea, anovulation) and is usually associated with both ovaries enlarged and with atretic follicles. In turn, this puts the girls at increased risk for adult complications arising from these changes, namely obesity, type 2 diabetes, dyslipidemia, and cardiovascular disease (metabolic syndrome), and infertility and hirsutism associated with PCOS, although this remains to be demonstrated categorically in longitudinal studies.^{9,17,18} Some of these changes (eg, hyperinsulinemia, insulin resistance) are evident at approximately the time of puberty.^{19,20} Girls who exhibit these features are frequently obese (notably those of black or Caribbean Hispanic origin),²¹ and ~30% have marked hyperandrogenism; those with the more marked hyperandrogenism tend to exhibit the greatest insulin resistance and hyperinsulinemia, even after correction for BMI.^{22,23} Girls who have PA and remain obese are at risk for developing PCOS,²¹ particularly when PA itself was preceded by low birth weight.^{9,18} A recent US study showed that early menarche (<12 years) is also associated with increased BMI, hyperinsulinemia, and elevated blood pressure, but the relationship to PA was not reported.²⁴ One study showed that boys with PA may also exhibit increased evidence of risk factors for developing metabolic syndrome and associated complications,²⁵ whereas another study reached the opposite conclusion.²⁶

This evidence points clearly to PA/premature menarche as a risk factor for adult onset of metabolic syndrome; however, another interpretation of the data is that PA (and perhaps premature menarche) is simply another clinical manifestation of metabolic syndrome. In this regard, PA, like metabolic syndrome, is often preceded by low birth weight, and a combination of PA and low birth weight increases risk for developing the adult disorders outlined already.^{9,18,27} Ibáñez et al^{27,28} suggested that PA can be interpreted as a childhood risk factor for a polyendocrine-metabolic disorder of prenatal origin. This seems highly plausible, but more supporting evidence is required, because 1 French study failed to find a link between PA and either low birth weight or insulin resistance, although it did confirm that PA was a risk factor for PCOS.²⁹

Behavioral Disorders

Timing of puberty has long been a topic of research for psychologists and psychiatrists. Some of these studies examined children with clinically precocious or delayed puberty, but most studied general populations that were assessed for puberty timing in a variety of ways. Because the studies vary in their purpose, historical era, and design, general conclusions are difficult to present.

IQ and Psychopathology

Intelligence is known to reach stable levels that reflect genetic background during adolescence. Several studies documented an IQ or school achievement advantage in children (primarily girls) with early puberty³⁰ or clinically precocious puberty.^{31–34} Recently, a small sample of children with precocious puberty demonstrated a de-

crease in IQ scores during treatment with gonadotropins.³⁵ Rovet³⁶ found that children with abnormal pubertal timing (clinically precocious or delayed) had impaired verbal abilities. Spatial abilities were advanced in girls but impaired in boys.

Psychosocial and psychosexual adjustment is obviously of great concern in girls with precocious puberty. Reviews of studies of girls with untreated precocious puberty^{34,37,38} concluded that age-appropriate psychosocial and psychosexual adjustment were commonly achieved; however controlled studies were limited. Characteristic personality traits of the girls with untreated or treated^{35,39–41} precocious puberty included poor self-image and internalizing symptoms.

Because schizophrenia is often first diagnosed in late adolescence, theoretical links have been drawn among pubertal timing, altered adolescent brain maturation, and schizophrenia.^{42–50} Questionnaire studies⁵¹ have found no relationship between an overall “psychosis proneness” score and puberty timing, but some studies found a correlation between age at menarche and age at onset of symptoms.^{42,52,53} Altered pubertal timing was not found in children who received a diagnosis of schizophrenia before age 12.⁵⁴ No relationship between timing of puberty and symptom onset was found in boys with schizophrenia.

Little has been done to investigate brain maturation in early- and late-maturing children. In electroencephalogram studies of adults,^{55,56} electroencephalogram coherence, which increases in adolescence and reflects synaptic pruning, was greater in the later maturers, particularly males. In addition, the latency of the visual event related potential, which increases during adolescence, was shorter in early-maturing females.⁵⁶

Adolescent Affect and Risk

More recent attention has focused on puberty timing in relation to affective disorders and incidence of risk behaviors (eg, substance abuse, cigarette smoking, multiple sexual partners, conduct disorder) in adolescence. These studies are associated with large-scale cohorts of adolescents (Table 1) but vary widely in social context, sample size, method of assessing puberty, and end points considered.

Although it is difficult to compare results across studies, early-maturing girls seem to be consistently identified as being at higher risk for depression and eating disorders (internalizing disorders) as well as substance use and conduct disorders (externalizing disorders). The studies of Kaltiala-Heino et al^{57–59} are particularly key because of the large sample size and the use of a graded scale of age at puberty in the statistical analysis; however, the results may reflect characteristics of contemporary Finnish society that do not generalize in detail to all populations. Studies using a similar framework (internalizing and externalizing symptoms) are rare in clinical precocious puberty samples, but 1 study⁶⁰ supported a similar conclusion.

How far from normal does pubertal age need to be to suggest a risk? Most of the studies did not allow an estimate of the degree of “earliness” associated with altered incidence of behavioral syndromes; however 1 study⁶¹ found a difference of 5 months in reaching Tanner stage 3 between girls with and without “internalizing symptoms” (eg, eating disorders, panic attacks, depression).

Design problems must be taken into consideration when interpreting this type of study. One major design problem is confounding of current stage of development with timing of puberty in cross-sectional studies.⁶² For example, Angold et al⁶³ found that the incidence of depression in girls increases after midpuberty. Thus, a subgroup with earlier puberty in a cohort of like-age girls would demonstrate more depression because they are at a later stage of pubertal development. Inappropriate self-perception/reporting of pubertal development in children with behavior problems such as anorexia nervosa⁶⁴ is another problem. Finally, some attention has been given to the idea that antecedents of adolescent problems in childhood (ie, family stress) could precipitate early puberty.⁶⁵

A number of studies have looked at psychological variables that could be considered mediators/modifiers of the influence of pubertal timing on affective disorders, including self-esteem, attitude toward eating, complexity of thinking, psychological distress, attention, and social interaction.^{66–72} In general, these relationships were

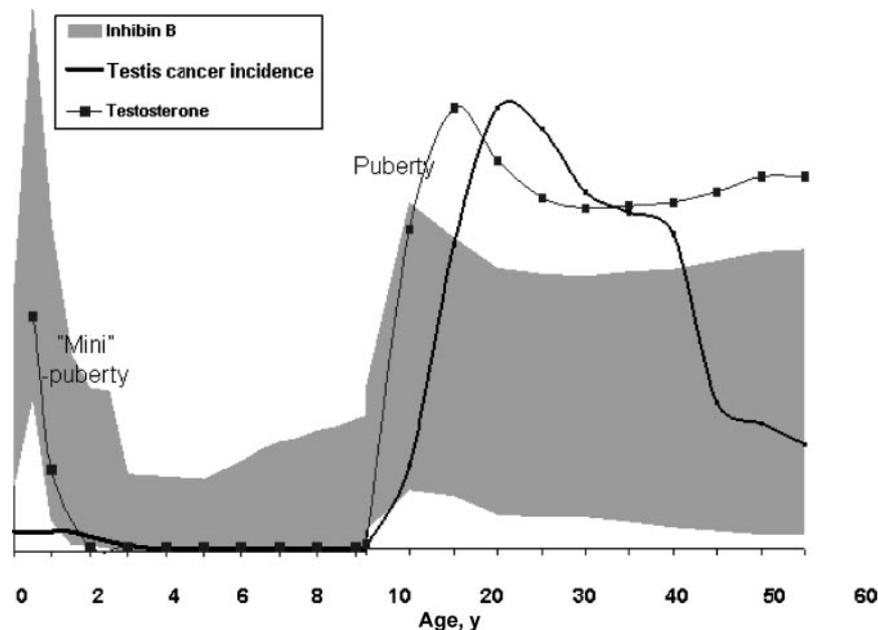
TABLE 1 Large-Scale Studies of Pubertal Timing and Adolescent Risk Behaviors

Reference	Region/Study/Sample	Outcomes	Puberty Measure	Finding
Kaltiala-Heino et al ^{57–59} (2003, 2001, 2003)	Finland/School Health Promotion Study/N = 36 000 14- to 16-y-olds	Depression, anxiety, psychosomatic symptoms, bulimia, drunkenness, drug use, smoking, truancy	Age at menarche, oigarche ^a (<10, 11, 12, 13, and 14 y)	Increased incidence of all problems with decreasing age at puberty in both genders
Williams and Dunlop ¹⁴⁴ (1999)	Britain/N = 99 14-y-old boys	Questionnaire on conduct problems, norm violations, and illegal acts	Pubertal Development Scale (growth spurt, body hair, skin change, facial hair, voice change)	More delinquency in early or late maturers
Wichstrom ⁷¹ (2000)	Norway/Young in Norway Study/N = 9679 12- to 20-y-olds	Suicide, suicide attempts	Self-perception of pubertal timing (earlier or later than peers)	Increased incidence of suicide behavior with early maturation in girls, late maturation in boys

^a First ejaculation.

FIGURE 1

Age-adjusted incidence of testicular cancer related to activity of selected hormones. Incidence rate of testicular cancer starts to increase in puberty after gonadotropins have stimulated the testes to produce testosterone and inhibin B. Data are from reference value data at the University Department of Growth and Reproduction, Copenhagen, Denmark.¹⁴⁶



not strong enough to identify clearly a single mediating factor. Another possibility is that these effects are mediated by altered brain development before puberty that sets the stage for behavior problems to emerge in adolescence.

Testicular and Prostate Cancer

Testicular cancer is the most common malignancy in young men of several Western countries.⁷³ Incidence of testicular cancer has increased rapidly during the past few decades in the white population, but there are large geographic differences (eg, the incidence in Denmark is fourfold higher compared with that of Finland⁷⁴⁻⁷⁶). Epidemiologic studies suggest that the risk for testicular cancer is strongly associated with the year of birth and that each younger generation has an increased risk compared with the previous ones.^{75,77,78} Currently, the highest age-adjusted incidence of testicular cancer occurs at 25 to 30 years of age, and the risk declines rapidly after the peak age.

The cause of testicular cancer is still poorly understood, but there is strong evidence that the disease has its origin in fetal life, when the development of primordial germ cells or gonocytes, precursors of spermatogenic cells, goes awry and gives rise to carcinoma in situ cells.^{79,80} These cells remain quiescent until they are stimulated to proliferate by gonadotropin-mediated signals and form germ cell tumors either in infancy or after puberty in young adulthood. Gonadotropin action is an essential permissive factor for tumorigenesis, and occurrence of testicular cancer in men with hypogonadotropic hypogonadism (low gonadotropin production) is extremely rare. Ninety-five percent of testicular tumors derive from germ cells that do not have gonadotropin receptors⁸¹ but depend on testicular growth factors that are produced under gonadotropin stimulation. Gonadotropin levels are high during infancy, decline rapidly

after 3 months of age,⁸² and remain very low until puberty, when they rise to adult levels. The age-adjusted incidence of testicular cancer follows closely the changes in gonadotropin levels, which suggests that tumorigenesis depends on permissive action of gonadotropins in the testis (Fig 1). A secular trend in the onset of puberty is also reflected by the change in age-adjusted incidence rates of testicular cancer that occur earlier than previously thought. Thus, it is to be expected that if the secular trend to younger age at the onset of puberty continues, then the peak incidence rate of testicular cancer would also move to a younger age.

Indeed, a low age at puberty is associated with an increased risk for testicular cancer according to several epidemiologic studies⁸³⁻⁸⁶; however, a Canadian population-based, case-control study did not find a clear association with early puberty but provided strong evidence that delayed puberty had a protective effect on risk for testicular cancer.⁸⁷ In Denmark, a significant increase in the incidence of testicular cancer was found among adolescent boys, whereas no increase occurred among children up to 4 years of age.⁸⁸ Maoris, who have the highest incidence of testicular cancer among the nonwhite populations,⁸⁹ start puberty late compared with the white population in New Zealand.⁹⁰ This contradiction suggests that other factors, such as intrauterine growth restriction and a possible unfavorable hormonal milieu, may contribute to the cancer incidence among Maoris. Maoris have relatively lower birth weights than white individuals, and their mothers are frequently obese, which is associated with high estrogen levels.⁹⁰⁻⁹²

Whereas timing of puberty has a strong association with the age at the peak incidence of testicular cancer, the correlation to cancers of other reproductive organs is less clear. A population-based, case-control study in Australia reported that markers of delayed androgen action, such as delayed growth spurt in puberty, were

associated with decreased prostate cancer risk.⁹³ Similar epidemiologic findings have also been published from other parts of the world.^{94,95} Early age at first sexual intercourse, often reflecting early puberty, is also associated with an increased prostate cancer risk.^{96–98} Extensive databases on growth records in Denmark will make it possible to analyze the association of age at peak growth velocity, which is closely linked to timing of puberty, and the incidence of prostate cancer.

Breast Cancer

As with testicular cancer, breast cancer may well have origins in early life. Estrogens are critical to the proliferation of breast tissue and development of the mammary gland, and early age of menarche, as well as late menopause, and late age at first birth are proxies for estrogen burden and known risk factors for breast cancer.^{99–101}

Early environmental exposures that mimic estrogens, such as bisphenol A,¹⁰² atrazine,¹⁰³ and polycyclic aromatic hydrocarbons,¹⁰⁴ may be related to earlier breast development, thereby putting the rapidly proliferating mammary tissue at risk. Chemicals that are associated with early menarche, such as polybrominated biphenyls¹⁰⁵ and dichlorodiphenyldichloroethylene,¹⁰⁶ are also of interest.

Puberty is a critical period of ductal morphogenesis that may be a window of vulnerability for the developing mammary gland with respect to future cancer risk. Pubertal girls who are exposed to carcinogens in the presence of a changing hormonal profile may be at high risk as a result of susceptibility of the mammary epithelial cells to early insults and mutations that make them vulnerable to carcinogenesis. Genetic factors and environmental stressors may affect repair of the insults. The National Toxicology Program rodent bioassay suggests that there are ~40 chemicals that may cause breast cancer,^{107,108} although developmental exposures are not included in this protocol. Cigarette smoking during the prepubertal period may also be related to future breast cancer risk. Furthermore, the time between age at first signs of breast development and ovulation, which is influenced by both genetic and environmental factors, may be related to differences in adult breast cancer risk.^{104,107,109}

Toxicologic studies show that dosing with endocrine-disrupting chemicals during different periods in an animal's life produces different effects on the mammary gland and hormone levels.^{102,103,110} The importance of early exposure is illustrated by data from women who were exposed to radiation from the atomic bomb in Hiroshima. Girls at highest risk for breast cancer (ninefold increased risk) were those who were aged ≤ 4 years at the time of the bomb blast.¹¹¹

Early life exposures are difficult to study in humans. Epidemiologic studies of breast cancer in adult women may not be able to provide reliable data on the relationship between early-life factors and cancer risk because of the inherent limitations of timing and memory, as well as a lack of awareness at the time of the exposure. Biomarkers cannot accurately capture past exposures to short-lived chemicals that occurred decades before diag-

nosis; therefore, a series of studies using different designs and different age groups is needed. Fortunately, cohort studies that are already in progress as part of the Centers for Children's Environmental Health and Disease Prevention Program¹¹² can address this need. Biological specimens were collected during pregnancy or at birth and stored for 5 cohorts. The offspring of these cohorts are being examined periodically to assess growth and development. As these children age, anthropometric assessments, puberty biomarkers, and hormonal measurements could be added. Lead, polycyclic aromatic hydrocarbons, cotinine, and pesticide assays have been conducted on the specimens that were collected during pregnancy or early life. New analyses could be performed as needed on banked specimens or newly collected specimens as the children age to test emerging hypotheses. Genotyping could also be done on DNA specimens and candidate genes to assess the role of genetic influences.

Also valuable is the Breast Cancer and the Environment Research Centers Program, a new initiative that will study the effects of a variety of environmental chemicals, dietary factors, and other environmental exposures on mammary gland growth and development. Also, 3 longitudinal studies of young girls will study the interplay of genetics and environment during puberty in an attempt to provide a better understanding of the role of early-life exposures on the risk for breast cancer. Other studies that are ongoing in the United States and internationally, including the National Children's Study, will afford opportunities to study these issues.

In addition, it is necessary to examine the influence of anthropometric and nutritional factors on the mammary gland during development, because trends in sexual maturation may be modulated by temporal changes in body size, weight, and adiposity in young girls in recent decades. Obesity is associated with increased circulating estrogens and other hormones. Two pathways to puberty with differing first signs of puberty, thelarche (breast development first) and adrenarche (pubic hair development first), have been defined.¹¹³ It would be of interest to know whether girls who go through these distinct pathways have differing breast cancer risks.

ALTERED PUBERTY TIMING IN CHILDREN'S HEALTH RISK ASSESSMENT

In addition to parents and physicians, government agencies have the responsibility of determining the potential consequences of altered puberty timing and instituting safeguards against conditions that promote altered puberty timing. The US Environmental Protection Agency (EPA) includes this function in its programs for children's health risk assessment.

Children's health risk assessment uses the standard risk assessment paradigm to focus on issues of importance to children, particularly the specific vulnerability of children versus adults. In 1996, the Federal Food Quality Protection Act and the Safe Drinking Water Act Amendments mandated improved approaches to protecting children's health. These included a call for specific assessments based on adverse health effects and

FIGURE 2

Pubertal female rat protocol. Intact weanling females are dosed by gavage from 22 to 43 days of age. The age and weight at vaginal opening (VO) (puberty) are determined, estrous cycles are monitored after puberty, and the females undergo necropsy at 43 days of age. Necropsy includes an assessment of reproductive (uterus and ovaries) and nonreproductive (liver, kidney, adrenals, thyroid) organ weights and histology (uterus, ovaries, and thyroid). Serum is taken for thyroxine and thyrotropin analyses. This protocol is designed to detect inhibition of steroidogenesis including aromatase, antithyroid, and (anti)estrogenic activities and altered HPG maturation. (Adapted with permission from International Union of Pure and Applied Chemistry from Gray LE Jr, Foster PM. *Pure Appl Chem.* 2003;75:2130.)

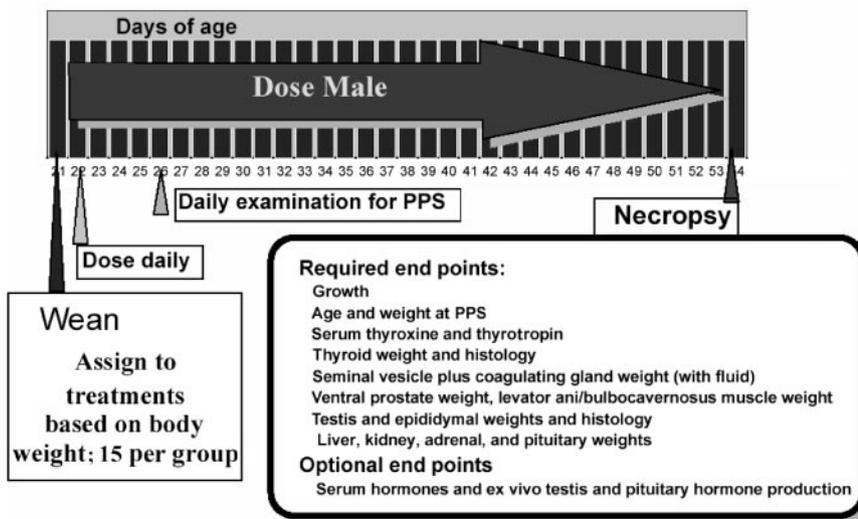
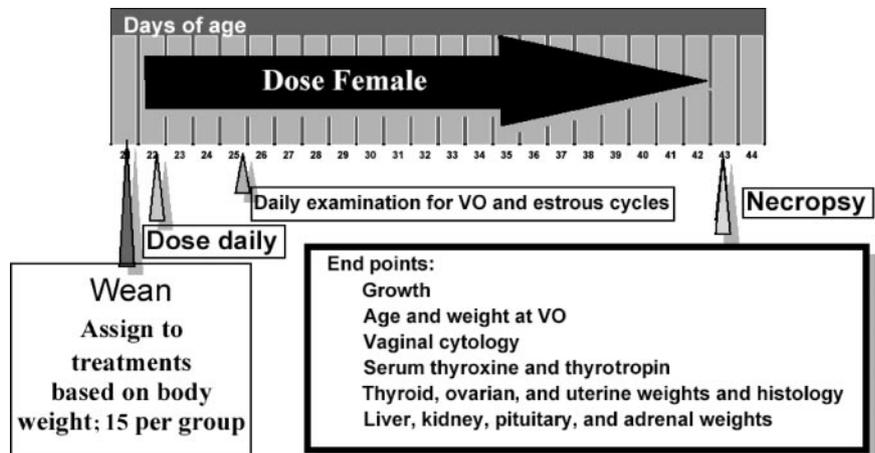


FIGURE 3

Pubertal male rat protocol. Weanling males are dosed by gavage from 22 to 53 days of age. The age and weight at preputial separation (PPS) (puberty) are determined, and the males undergo necropsy at 52 to 55 days of age. Necropsy includes an assessment of reproductive (testes, epididymides, ventral prostate, seminal vesicles, Cowper's glands, levator ani plus bulbocavernosus muscles) and nonreproductive (liver, kidney, adrenals) organ weights and histology. Serum is taken for thyroxine and thyrotropin analyses. Thyroid weight and histology also are evaluated. This protocol is designed to detect inhibition of steroidogenesis, antithyroid and (anti)androgenic activities, and altered HPG maturation. (Adapted with permission from International Union of Pure and Applied Chemistry from Gray LE Jr, Foster PM. *Pure Appl Chem.* 2003;75:2131.)

exposures in children and a mandate for endocrine disruptor screening and testing, both of which are relevant to altered puberty.

The data used in assessing risks to children come from both human and animal studies. Adequate human data are preferred, but more often the data available are from animal studies. Changes in federal animal testing guidelines that are relevant to detecting altered puberty timing are discussed next.

Assessment of Puberty in Toxicologic Studies

The primary animal testing studies that are used to assess reproductive and developmental toxicity are the prenatal developmental toxicity study, the 2-generation reproduction study, and the developmental neurotoxicity study.¹¹⁴⁻¹¹⁶ Until the early 1990s, there were no specific testing guidelines for assessing puberty. End points were incorporated into the developmental neurotoxicity testing protocol,¹¹⁶ originally published in 1991, and included an assessment of age at vaginal opening in female F₁ rodent offspring and the separation of the prepuce

from the glans penis in male offspring. These same end points were incorporated into the EPA multigeneration reproduction study protocol in 1998¹¹⁶ (published in draft form in 1996) as indicators of the timing of pubertal development.

In addition to animal toxicology testing changes, 1996 legislation mandated an endocrine screening and testing program. The Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) to the EPA developed a tiered screening and testing strategy. Tier 1 includes a specific pubertal female assay in rats¹¹⁷⁻¹²⁰ (Fig 2), and a pubertal male rat assay has been proposed as 1 of the alternative assays. In the pubertal female assay, weanling rats are dosed daily by gavage with the test agent for ~20 days. The age at vaginal opening (a marker of the initiation of puberty) and the onset of estrous cycles are monitored. Additional measurements enable the detection of alterations in thyroid hormone status, HPG function, and inhibition of steroidogenesis (including aromatase), together with the identification of estrogens and antiestrogens.^{121,122} The pubertal male

rat assay^{119,120,123–129} (Fig 3) also is designed to detect alterations in thyroid function, HPG axis maturation, steroidogenesis (but not aromatase), and steroid hormone function. Weanling males are exposed to the test substance for ~30 days, the age at puberty is determined, and reproductive tissues are evaluated and serum is taken for hormonal analyses.

Alterations in Puberty as Adverse Effect

Results from the endocrine disruptor tiered screening are usually considered to indicate a change in endocrine status, rather than an adverse response; however, the EPA has used alterations in puberty (a 2-day delay in prepubertal separation), supported by other endocrine and reproductive alterations and data on mechanism,^{125,130} as an adverse effect in their risk assessment for vinclozolin, a fungicide. Because the concern for setting regulatory limits for chemical exposures is based on defining adverse effects, it has been important to define what is meant by “adverse” in the regulatory context. “Adverse” has been defined as a treatment-related alteration from baseline that diminishes an organism’s ability to survive, reproduce, or adapt to the environment¹³¹ and as a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism or reduces an organism’s ability to respond to an additional environmental challenge¹³² (Table 2). Causal criteria are used for determining adversity as a result of toxicant exposures.¹³¹

EPA reproductive¹³³ toxicity risk assessment guidelines¹³⁴ indicate that evidence of altered puberty timing, precocious or delayed, should be considered adverse effects for the purposes of risk assessment. In females, end points include alterations in age at vaginal opening in laboratory animals, onset of estrus, estrous/menstrual cyclicity, or onset of an endocrine or behavioral pattern consistent with alterations in estrous or menstrual cyclicity in humans or laboratory animals. In males, delay or failure of testis descent, delays in age of prepubertal separation (laboratory animals), or appearance of sperm in expressed urine or ejaculates are considered adverse effects. The guidelines do leave open the question of the

biological relevance of small changes (eg, a 1- to 2-day delay in these end points). Such small changes must be weighed along with other data and scientific judgment used to decide in which cases these should be considered adverse and used as the basis for a hazard characterization and dose-response assessment. A similar situation exists for human studies, in which isolated precocious thelarche and changes in age at menarche of a few weeks are considered a point of departure for risk assessment.

Relevance of Animal Data for Humans

The relevance of animal data to humans for indices of puberty has been addressed in a few instances. Species concordance is indicated for delay in female puberty as a result of lead,¹³⁵ based on animal^{136,137} and human^{138,139} studies. In the case of polybrominated biphenyls, the effects in humans (early female puberty¹⁰⁵) and animals (delayed female puberty^{140–142}) are inconsistent. Because there are sparse data on comparisons of pubertal changes in animals and humans, 1 of the basic assumptions used in risk assessment is that effects in animals are predictive of effects in humans, although the effects may be reflected in different end points. Differences between laboratory animals and humans, such as the absence of peripubertal adrenarche in rodents, need to be considered in determining relevance.

Dose-Response Assessment: Using Mode of Action (MOA) Information

Once an agent or mixture of agents has been determined to cause adverse effects, including effects on puberty, the dose-response curve is defined to the extent possible with the existing data. An important consideration is the choice of linear versus nonlinear modeling for the dose-response curve. Nonlinear modeling has historically been used for all noncancer effects, but recent guidance¹⁴³ emphasizes the importance of considering MOA in making this determination. For agents that affect the endocrine system and alter puberty, several possibilities for MOA may influence the dose-response approach

TABLE 2 Comparison of Reproductive and Developmental Toxicity

Parameter	Reproductive Toxicity	Developmental Toxicity
Definition	Biologically adverse effects on the reproductive systems of females or males that may result from exposure to environmental agents; may be expressed as alterations to the female or male reproductive organs, the related endocrine system, or pregnancy outcomes ¹³⁴	Adverse effects on the developing organism that may result from exposure before conception (to either parent), during prenatal development, or postnatally to the time of sexual maturation; may be detected at any point in the life span of the organism ¹¹⁴
Manifestations	Adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, lactation, developmental toxicity, premature reproductive senescence, or modifications in other functions that depend on the integrity of the reproductive systems ¹³⁴	Death, structural abnormalities, altered growth, functional deficits, or cancer ^{114,143,145}

used. For a hormone agonist, for example, the MOA is likely to be additive to an endogenous mechanism and have a linear low-dosage relationship, whereas an antagonist that subtracts from the endogenous mechanism is more likely to have a nonlinear relationship or threshold. A DNA-reactive agent is likely to be mutagenic, leading to the assumption of a linear relationship, unless there are clear data for compensation and repair. Guidance for using such information and the choice of approaches has not been developed, but additional research and investigation of appropriate extrapolation methods are needed.

CONCLUSIONS

Secular trends in puberty timing can be associated with disturbed early development that is reflected in many health consequences, such as endocrine-related cancer and metabolic syndrome. Early puberty itself may bring psychosocial and other health problems to children by compromising growth, increasing the risk for behavioral disorders, increasing the risk for early sexual debut and potential abuse, and putting the child in a position of inappropriate expectations. It is important to find out the mechanisms of the puberty timing and the reasons for its alterations. This understanding will provide tools for improved children's health risk assessment. The current secular trends in puberty timing seem to be associated with adverse health implications, which necessitates continued surveillance of human populations, chemical screening and toxicity testing in animals, and additional studies on the underlying mechanisms.

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