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What is in our environment that effects puberty?

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ABSTRACT

Recent studies indicate that the onset of puberty is occurring at increasingly younger ages. Many etiologies have been hypothesized to be involved, but environmental exposures are among the most worrisome. Multiple organizations have endorsed the need to study and provide clinical awareness regarding the effect of a child's environment on pubertal timing. This review article summarizes the current understanding of the major environmental influences on pubertal timing, focusing on factors for which the most scientific evidence exists. The research reviewed addresses *intrinsic factors unique to each individual*, *naturally occurring endocrine disruptors* and *chemical endocrine disruptors*. In each category, evidence was found for and against the involvement of specific environmental factors on pubertal timing. Ultimately, an individual's environment is likely comprised of many aspects that collectively contribute to the timing of puberty. The need for research aimed at elucidating the effects of numerous specific yet disparate forms of exposures is emphasized.

1. Introduction

Puberty is a time of dramatic developmental changes during which a child's body progresses through a sequential set of stages to reach mature adult reproductive function. Although the stages of puberty delineated by Tanner et al. in 1969 have not changed, the timing of puberty has become dramatically altered over the last several hundred years. Pubertal maturation begins with increasing GnRH pulses from the hypothalamus that stimulate the production of sex steroids and the progression of secondary sex characteristics resulting in the adult phenotype and reproductive capabilities [1,2]. These pulses herald the end of the dormant hypothalamic–pituitary–gonadal (HPG) axis period of childhood. Breast development, also known as thelarche, was identified by Tanner as the first sign of puberty in girls whereas testicular enlargement and thinning of the scrotum were noted to be the first signs of puberty in boys [3]. Recent research has identified key players involved in triggering puberty such as leptin, kisspeptin, genetics, nutrition and the presence of environmental stimuli [1,2,4,5]. However, precisely what ultimately starts puberty remains enigmatic.

1.1. Secular trends

Historical data have demonstrated a definite decrease in the age at puberty initiation from the 1800s to the mid 1900s [6]. More recent studies show a questionable continual decrease in the age at the start of puberty. These studies have been flawed by issues related to participant selection, poor comparison between groups and a lack of uniform methodology for the assessment of pubertal development [7]. An expert panel in 1994 concluded that there was sufficient evidence to establish a secular trend of earlier thelarche, but not menarche for girls and that there was insufficient evidence for earlier puberty in boys [7]. Indeed, thelarche occurred one year earlier in 2006 as compared to 1991 in a study of 2095 girls in The Copenhagen Puberty Study which was not explained by BMI or hormone levels, leading the researchers to postulate that other factors were involved [8]. These findings have been corroborated in multiple other studies leading to the question of why the onset of thelarche is continuing to decline [9–13]. An alteration in the tempo of pubertal progression has also been noted as thelarche is occurring earlier but the age of menarche appears to be constant. There are fewer studies evaluating pubertal timing in boys making it harder to form conclusions. In addition, there is no seminal event in boys that is analogous to menarche that allows for retrospective studies on puberty timing. However, pubertal onset in boys was recently brought into question by a large national study

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Abbreviations: HPG, hypothalamic–pituitary–gonadal; EDC, endocrine disrupting chemical; EPA, environmental protection agency; FDA, food and drug administration; SGA, small for gestational age; CPP, central precocious puberty; PBB, polybrominated biphenyls; BPA, bisphenol-A; DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyl dichloroethane.

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examining timing of secondary sexual development in relation to ethnic background [14]. Although boys were observed to develop a pubertal testicular size from 6 months to 2 years earlier than previous norms, some of the study's findings are internally inconsistent and the age at achievement of Tanner V development was virtually identical to historical reports and unaltered by ethnicity. Nonetheless, these data are intriguing and require further investigation prior to declaring a younger puberty trend in boys. Despite the observations of earlier pubertal onset, most pediatric endocrinologists still adhere to the traditional lower age limits of normal, which are 8 years in girls and 9 years in boys.

1.2. Role of environmental exposures

Multiple studies and cross-sectional reviews have identified environmental exposures and endocrine disruptors as likely contributors to the international secular trend in earlier pubertal development. Evidence for a central role of the environment has included the contemporaneous rapid increase in obesity rates over the last fifty years, geographical differences in pubertal timing, epidemics of earlier puberty concurrent with specific exposures, an increase in manufacturing during this time period and the identification of endocrine disruptors in pollutants and industrial compounds [15–17]. Due to heightened concern, a 2008 expert panel was convened by the US Environmental Protection Agency (EPA), the National Institute of Environmental Health Sciences and the Serono Symposia International to examine the relationship between environmental influences and pubertal timing and identify crucial research needs [18]. Endocrine disruptors and body weight were identified as the most concerning factors involved. Although existing data were felt to be highly suggestive of a link between endocrine disruptors and pubertal timing, it has also been readily acknowledged that association does not prove causality [18]. For example, although higher phthalate levels have been found in girls diagnosed with central precocious puberty (CPP) compared to age matched controls without CPP, this does not establish that phthalates cause CPP. Particular areas targeted for future investigation include etiologies of earlier puberty, critical exposure times and mechanisms of disrupting agents [19].

The EPA defined an endocrine disrupting chemical (EDC) as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental processes" [20]. The Endocrine Society published a scientific statement in 2009 regarding EDCs and the evidence that they potentially impact many aspects of endocrinology including male and female reproductive organ formation and the HPG axis [20]. The FDA and EPA are in charge of controlling the risk of environmental substances, which is a significantly daunting task in light of how little is known regarding the effects of the numerous chemicals we are exposed to every day [21]. In addition to the Endocrine Society, the European Society for Pediatric Endocrinology and the Pediatric Endocrine Society have also endorsed position statements calling for basic and clinical research, epidemiologic studies and the recognition of EDCs in clinical practice [20,22,23]. These statements highlight the need to examine the consequences of EDCs and other types of environmental exposures during critical periods of development including the prenatal period, infancy and throughout childhood. In addition to post-natal exposures, fetal programming has also been proposed as a possible mechanism for reproductive effects seen later in life due to endocrine disrupting agents. Other mechanisms are thought to be direct effects of environmental exposures on hypothalamic, pituitary or gonadal hormones [17]. Other factors may also be at play as recent scientific advances have brought the relatively young field of epigenetics to attention as a key process that is impacted by environmental EDCs [24]. Epigenetics is the study of changes to the DNA code that do not alter the underlying sequence but induce silencing or activation of gene transcription utilizing DNA methylation and histone deacetylation [24]. The DNA changes can be environmentally induced and inherited by multiple generations independent of subsequent individual exposures [25]. Interestingly, genome wide methylation studies have suggested that epigenetic mechanisms are intrinsically involved in the neuroendocrine control of female puberty [26]. Moreover, both human and animal studies have implicated epigenetic changes resulting from exposures to different types of EDCs in the genesis of altered pubertal timing, as will be discussed in a later section of this review [27,28]. Collectively, there is resounding unanimity among governmental agencies and the scientific community regarding the importance of exploring the link between environmental exposures and human health. This article will summarize the current understanding of the major environmental influences on pubertal timing with a focus on physiologic HPG axis activation rather than variants such as premature adrenarche. We have organized these as *intrinsic factors unique to each individual*, *naturally occurring endocrine disruptors* and *chemical endocrine disruptors*. While an exhaustive description of every purported modifier is beyond the scope of this article, we have aimed to delineate factors within each of these categories for which the most scientific evidence exists.

2. Intrinsic factors unique to individuals

An individual's genetics have been identified as the primary determinant of the timing of pubertal onset and the tempo of progression. However, it is known that many other aspects of an individual's life and environment will affect this developmental stage [15,29]. Many association studies examining a host of factors ranging from the intrauterine environment to psychosocial and nutritional exposures have been conducted. As discussed below, these have reported earlier puberty, later puberty or no effect.

2.1.1. Body weight

One of the most enduring observations is that being overweight is associated with earlier puberty in girls. However, these findings have not been substantiated in boys [30–33]. In fact, there are actually conflicting data with one study showing slightly earlier puberty in obese boys [34] and others finding precisely the opposite [32,35]. Proposed physiologic mediators of the link between obesity and pubertal timing include leptin, adipocytokines and gut peptides [31,36]

2.1.2. Prenatal growth

There has been increasing interest in the effects of intrauterine growth, birth weight and the pace of early weight gain on fetal programming and subsequent pubertal development. In one study, small for gestational age (SGA) status was found to be an independent risk factor for idiopathic CPP in girls [37]. This effect has been explained through the concept of increased metabolic efficiency imparted by low weight in infancy and evidenced by greater insulin resistance and higher IGF-1 levels in SGA infants who have subsequent rapid weight gain [38,39]. The "thrifty gene" hypothesis states that SGA children are born with the need to take advantage of calories and therefore will gain weight more easily promoting increased BMI and earlier puberty. However, another study reports that girls with a longer and leaner size at birth, not just SGA status, achieve menarche earlier than their shorter and heavier counterparts [40]. The observation that a lower birth weight alone does not increase a child's chance for earlier puberty but that being longer