# Endocrine-Disrupting Chemicals and Female Puberty

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In recent decades pubertal onset in girls is considered to occur at an earlier age than previously. Exposure to endocrine-disrupting chemicals (EDCs) has been associated with alterations in pubertal timing, several reports suggesting that EDCs may have a role in the secular trend in pubertal maturation, at least in girls. However, relevant studies give inconsistent results. On the other hand, the majority of girls with idiopathic precocious or early puberty present the growth pattern of constitutional advancement of growth (CAG), i.e., growth acceleration soon after birth. CAG is unrelated to exposure to EDCs and is the major determinant of precocious or early puberty. EDCs, at most, have a minor effect on the timing of pubertal onset in girls.

puberty endocrine-disrupting chemicals girls constitutional advancement of growth

## 1. Introduction

Pubertal timing is multifactorial involving a predominant effect of genetic and epigenetic factors and to a lesser—but still significant—extent, environmental factors. Although genetic factors are considered to explain 50–80% of the onset of puberty [1], genes that have been found to play a role in pubertal onset have a minor role in the onset of puberty of the population. Gene mutations, e.g.,ESR1,KISS1,KISSR1,MKRN3, are rarely identified as the cause of disordered pubertal timing; thus, these genes do not seem to determine the timing of puberty nor menarche in the female population [2]. Recently, it was shown that the onset of puberty is regulated by epigenetic mechanisms, Kiss1 expression is negatively regulated by two polycomb group proteins (Cbx7 and Eed) [3].

Environmental factors are major determinants of the onset of puberty and the age at menarche. Nutrition of the mother or/and of the infant [4], chronic diseases and chronic somatic stress, like strenuous exercise or psychological stress, e.g., violence exposure [5], or adoption of a girl from an underprivileged environment, exert a major influence on the timing of the pubertal events. Although environmental factors may result in epigenetic modifications in an organism, the epigenetic effects of the environment on the hypothalamic regulation of puberty are still to be discovered.

In girls, when pubertal onset occurs before the age of 8 years, it is considered precocious and when it occurs after 8 years but before 9 years of age, it is considered early. The causes of central precocious puberty may be organic, e.g., due to tumors of the central nervous system (CNS) or most commonly idiopathic Obviously, it is important to differentiate between organic or idiopathic precocious puberty (IPP) because the former may have dire health

consequences. On the other hand, early puberty lies on the extreme of normal variation of timing of pubertal onset [6].

## 2. Endocrine-Disrupting Chemicals

Endocrine-disrupting chemicals are compounds that can interfere with the activity of endocrine systems. EDCs action is exerted by imitating or blocking hormone signaling through the relevant hormonal receptor. EDCs may also modulate the synthesis, metabolism, and binding of natural hormones.

EDCs are usually used by industry, as plastics (bisphenol A (BPA)), plasticizers (phthalates), solvents/lubricants (polybrominated biphenyls (PBBs), polychlorinated biphenyls (PCBs), dioxins), pesticides (chlorpyrifos, dichlorodiphenyltrichloroethane (DDT), methoxychlor), fungicides (vinclozolin) and also as flame retardant additives in manufactured materials, and pharmaceutical agents, e.g., diethylstilbestrol (DES), a non-steroidal synthetic estrogen [7].

EDCs may also be made by nature, e.g., phytoestrogens, which interfere with endogenous endocrine function, are produced by plants and act primarily through estrogen receptors [8].

The abundance of EDCs and their ability to interfere with the endocrine system combined with the secular trend for earlier onset of puberty has led many researchers to associate EDCs with early puberty, especially since some EDCs have estrogenic activity.

## 3. Association between Exposure to Endocrine-Disrupting Chemicals and Timing of Puberty

Commonly used and studied EDCs are phthalates, bisphenol, pesticides and flame retardants.

BPA (bisphenol A) is found in plastics (e.g., bottles, Tupperware, etc.), and in epoxy resins coating the inside of beverage and food cans, and humans are exposed mainly through food contamination from plastic and can packaging. In experimental animals, it has been shown that BPA advances puberty [9], but on the other hand, it also has been shown it has no effect on pubertal timing [10]. Similar to the experimental animals, results of BPA on human puberty are inconsistent. studied the in-utero and peripubertal exposure to phthalates and BPA in relation to sexual maturation and did not find any association between BPA and sexual maturation, although in utero phthalate exposure impacted on earlier timing of sexual maturation [11].

In a study performed in Denmark, mothers who worked in greenhouses in the first trimester of pregnancy were prenatally categorized as exposed or unexposed to pesticides. Female offspring of exposed mothers had decreased age of breast development at 8.9 years, compared with 10.4 years in the unexposed, and 10.0 years in a Danish reference population [12]. Other researchers reported decreased menarcheal age to girls exposed in utero

to DDE [13]. Adopted or immigrant girls in Belgium, who presented central precocious puberty (CPP), had increased plasma levels of pesticides (DDE), thus CPP could be attributed to pesticide exposure [14].

Flame-retardant chemicals are added to manufactured materials (plastics, textiles, surface finishes and coatings) intended to prevent or slow the further development of ignition with their physical and chemical properties. Among them, organohalogen compounds such as polybrominated diphenyl ethers (PBDEs) are lipophilic persistent endocrine disruptors exhibiting estrogenic as well as androgenic properties. It has been proposed that PBDEs might alter pubertal timing resulting in later menarche in girls [15][16] but earlier pubarche in boys [16]. Curiously, girls with idiopathic central precocious puberty, particularly those with higher body mass index (BMI) have been found with higher serum concentrations of PBDEs [17].

Thus, the inconsistency of the results of the various studies examining the association of endocrine disruptor chemicals with the onset of puberty [18] makes it imperative that more studies on the subject are performed.

## 4. Is There an Association between EDC Exposure and CAG?

Most girls with idiopathic precocious puberty present the growth pattern of constitutional advancement of growth (CAG), i.e, growth acceleration soon after birth. Since CAG is associated with early growth acceleration, if there was an association between EDCs and CAG it would be related to fetal exposure during pregnancy or early postnatal exposure.

Several studies have examined the association of fetal exposure to EDCs, especially phthalates and BPA, and fetal growth. These compounds, besides hormonal perturbations, may cause oxidative stress and epigenetic modifications that might have a deleterious effect on fetal growth [19][20][21]. In a longitudinal study that examined the relationship between average exposure measures and fetal growth [22], researchers observed inverse associations between head and abdominal circumferences, femur length, and estimated fetal weight and Di (2-ethylhexyl) phthalate (DEHP) metabolites. In our studies on CAG girls, there was no difference in birth weight or length compared to control girls.

What about the effect of postnatal exposure on growth? In a study in which chlordecone (an organochlorine insecticide with estrogenic properties) was measured at cord blood and in breast milk at the age of 3 months, postnatal exposure in girls was associated with lower height at 3, 8 and 18 months [23].

Taking into account that girls with CAG present growth acceleration soon after birth, it is unlikely that growth acceleration is induced by estradiol. In neonatal life and early infancy increased estrogen levels are experienced by all normal girls, hence the period of the first 6 months of life is termed as mini-puberty. Despite increased estradiol levels, mini-puberty is not associated with growth acceleration contrary to puberty occurring during childhood.

(GH) is necessary for normal growth after the age of 2 to 3 months [24]. However, the majority of small for gestational age (SGA) infants present catch-up growth in length since early postnatal life placing them at or above

the 3d percentile for length by 6 months of age [25]. However, from the 3d day of life SGA neonates present functional hypersomatotropism, i.e., increased GH and insulin growth factor 1 (IGF-1) levels relative to appropriate for gestational age neonates, suggesting that the somatotropic axis is fully operational since the first days of life [26] [27]. In line with a functional GH/IGF-1 axis from the first days of life is the observation that, in healthy full-term neonates, the postnatal growth velocity is positively related to a spurt in immediate postnatal life IGF-1 levels [28].

SGA children presenting catch-up growth are more prone to insulin resistance and development of metabolic syndrome [29]. Recently a study on Sprague–Dawley rats examined whether a post-receptor crosstalk of GH and insulin signaling might affect insulin resistance in catch-up growth SGA animals [30]. The authors demonstrated that catch-up growth SGA rats exhibit increased insulin resistance associated with an impaired IRS-1-PI3K-AKT signaling pathway, which resulted from GH signaling-induced upregulation of SOCS3 expression. Thus, these data suggest a link between increased GH levels and insulin resistance in catch-up growth.

Constitutional advancement of growth presents similarities to catch-up growth only that the CAG children are, auxologically, appropriate for gestational age. Accordingly, they are susceptible to developing obesity during childhood, therefore we suggested that the growth pattern of CAG may be a predictor, not only of early puberty, but of childhood obesity as well [31]. Moreover, it has been reported that earlier menarche was associated with greater height, adiposity, and significantly increased serum IGF-1 at 8 years of age, even after adjustment for height and BMI [32]. Thus, these data allow us to speculate that the growth pattern of CAG is induced by the early activation of the GH/IGF-1 axis.

From the data presented in this review, it is clear that the major determinant of early puberty, at least in girls, is the presentation of the growth pattern of constitutional advancement of growth, which is unrelated to EDC exposure. Therefore, if there is a role of EDCs on female pubertal timing it seems, at the most, to be a minor one.

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