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Endocrine Disrupters and Pubertal Timing

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Abstract

Purpose of review—This review summarizes recent epidemiologic data demonstrating the effects of endocrine disrupting compounds (EDCs) on the timing of puberty and highlights the complexity of understanding the interplay of environmental and genetic factors on pubertal timing.

Recent findings—In girls, there have been mixed results, with some exposures being associated with earlier timing of puberty, and some with later puberty.

In boys, prepubertal exposures to non-dioxin-like PCBs accelerate puberty while levels of insecticides, dioxin-like compounds, organochlorine pesticides, and lead delay puberty.

Summary—The effects of EDCs on pubertal timing are sexually dimorphic, compound specific, and varies according to the window of exposure. These studies confirm that low level exposures to a mix of environmental compounds may mask the effects of individual compounds and complicate our ability to translate data from animal studies to human health and to fully understand the clinical implications of environmental epidemiology studies.

Keywords

Puberty; endocrine disrupting compounds; dioxins; pesticides; breast development; menarche; sexual maturation; genital staging

INTRODUCTION

Puberty is a fundamental process of maturational changes that mark the transition from sexual infancy to reproductive maturity. It is now recognized that the age of onset of breast development, exemplifying an early stage of puberty in girls, has declined in recent decades, although the age of menarche, an advanced pubertal milestone, has not changed significantly (1, 2, 3). The data on pubertal timing in boys is inconsistent, with some reporting an earlier onset and others finding no changes in the age of pubertal development in recent decades (4,

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5). While genetic factors remain the predominant determinant of pubertal timing, the shift towards an earlier age of puberty in the past century coincided with improvements in public health and nutrition, and more recent changes have been attributed to obesity. It has also been speculated that endocrine disrupting compounds (EDCs) are potential contributors to the observed shifts in pubertal timing (1, 2, 5, 6). Here we review publications from 2016 and 2017 that examine EDC associations with pubertal milestones, focusing on possible environmental triggers of puberty in both males and females.

General principles of EDC actions

A number of different classes of exogenous compounds with endocrine active properties interfere with endogenous hormone action (7). These Endocrine Disrupting Compounds (EDCs) can bind hormone receptors and affect their synthesis, transport, metabolism, and/or elimination. Among the various types of EDCs are persistent organic compounds that bio-accumulate through the food chain and have half-lives of years to decades. These chemicals, pesticides (dichloro-diphenyl-trichloroethane [DDT], pyrethroids), dioxins, polychlorinated biphenyls (PCBs), and flame retardants (polybrominated diphenyl ethers [PBDEs]), are present ubiquitously across the ecosystem and detectable in humans worldwide (reviewed in (5, 7). Other EDCs, such as phthalates and phenols, have shorter biological half-lives and are measurable for only a short duration post-exposure, but may still exert long-term health effects. EDCs are not natural ligands, and therefore do not have the same binding specificity and affinity as endogenous hormones, and may elicit non-receptor mediated effects. They exert antagonistic and agonistic actions on hormonal axes and pathways, and may have divergent effects at low versus high concentrations- consistent with their non-monotonic dose response curves. Both acute and delayed (latent) effects of EDCs have been reported. The prenatal, infancy, and childhood periods are considered critical windows of susceptibility due to ongoing developmental processes that are vulnerable to EDCs. The specific health consequences are dependent on the life stage at the time of exposure, particular compound, the endogenous hormonal milieu, and which health outcomes are being examined.

Phenols and phthalates

Phthalates and phenols include a number of hormonally active chemicals with anti-androgenic and estrogenic activity that are present at relatively high concentrations compared to pesticides and other industrial chemicals.

Bisphenol A (BPA) is the phenol that has drawn the most public interest (reviewed in (8)). BPA and other phenols are plasticizers used in both medical products and consumer goods, such as medical tubing, plastic bottles and toys, dental sealants, and linings of metal container. BPA is now banned in the production of infant food and beverage containers such as baby bottles, and has been removed from many consumer products. At lower concentrations, BPA and other phenols have weak estrogenic properties but can also compete with endogenous estrogens for binding, and at higher concentrations, they have been shown to have anti-androgenic properties.

To investigate the associations of BPA exposures with puberty, a Thai study compared urinary BPA concentrations in 41 girls with precocious puberty to 47 age matched controls (9). The girls with precocious puberty had higher urinary BPA levels than controls, and among the group with early puberty, those who were obese or overweight had higher values than those of normal weight. One challenge with this study is that the investigators used a relatively advanced cut-off of 8–9 years to define early puberty. In addition, samples were collected at the time of the exam, reflecting contemporaneous exposures rather than exposure assessment prior to the outcome measure- the onset of puberty.

Miao and colleagues also conducted a cross-sectional study to investigate the association between BPA exposure and pubertal development in 655 girls aged 9–18 years in Shanghai, China (10). Urinary BPA levels were measured and categorized according to whether they were unmeasurable (<LOD) or measurable (>LOD). If they were measurable, they were grouped as “above” or “below” the median concentrations for the cohort. A physician assessed pubertal development by Tanner staging and collected self-reported age at menarche. After adjusting for potential confounders, girls with higher values of BPA were more likely to have delayed menarche compared to girls with undetectable urinary BPA levels. Girls aged 9–12 years with measurable urinary BPA levels were more likely to have reached pubic hair stage 2; while among girls aged >15 years, those with detectable urinary BPA were less likely to have reached pubic hair stage 5. These authors concluded that contemporaneous BPA exposures were associated with delayed menarche and with earlier onset of P2 but later attainment of P5. Again a limitation of this study was that the exposure assessment occurred concurrently with the outcome assessment, making it difficult to establish causality.

BPA and phthalate levels were compared in 42 Turkish girls with idiopathic central precocious puberty, 42 girls with peripheral precocious puberty, and 50 healthy non-obese age-matched girls as controls (11). The authors did not find any differences in mean values of urinary BPA, LH, FSH or estradiol among the three groups. However, they reported that plasma DEHP and MEHP, were higher in the group with central precocious puberty than in the other two groups, suggesting a potential central site of action for these phthalate metabolites.

A longitudinal US puberty cohort study based at three centers (the Bay area in northern California, Cincinnati, Ohio, and Manhattan, NY was established through the Breast Cancer Environmental Research Program (BCERP) to examine the role of EDCs on pubertal development (12). 1051 girls had urinary levels of phenols and phthalates measured at age 6–8 years and were followed annually (13). Higher 2,5-dichlorophenol was associated with a 7-month earlier onset of menarche, while mono-3-carboxypropyl phthalate (MCPP) was associated with a 4–5 month later age of both thelarche and menarche, that was greater in lean girls. The association of MCPP with delayed pubertal onset and menarche was a new and unanticipated finding. MCPP is a metabolite of several phthalates and exposures is through household products as well as diet. These authors also reported that triclosan, an anti-bacterial and anti-fungal agent in soaps and personal care products, and benzophenone-3, a ketone in cosmetics for UV protection were both associated with earlier thelarche but not menarche (13).

Wang and colleagues evaluated the association of urinary BPA with pubertal development in 671 Chinese boys aged 9 to 18 years (14). Urinary BPA levels were categorized as <LOD, LOD to the 75th%ile and >75th%ile levels. The boys were grouped according to sexual maturity staging as early-, mid-, and late puberty. Of note is that all 13 years olds recruited were already in early puberty and that none of the boys < 11 years of age had progressed to late puberty. Moderate levels of urinary BPA correlated with earlier onset of pubic hair and genital stage 2, and showed a trend towards testicular enlargement. Urinary BPA was associated with later attainment of mature milestones, suggesting an association of moderate levels of urinary BPA with slower pubertal progression. These authors concluded that BPA exposure was associated with earlier age of adrenarche and genital stage 2, but delayed attainment of genital stage 5. Adjusting for BMI did not alter these associations.

Flame retardants/polybrominated diphenyl ethers (PBDEs)

Another class of EDCs of particular interest are the flame retardants, or polybrominated diphenyl ethers (PBDEs) used in carpeting, clothing, and furniture. The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) was a birth cohort in California established to investigate the health effects of gestational and childhood exposures to agricultural pesticides and other environmental chemicals (15). This paper examined the association of flame retardants with pubertal timing in Latino low income mothers in this agricultural community. Four PBDEs were measured in maternal serum during pregnancy or at delivery as a measure of prenatal exposures and childhood exposures were assessed in PBDE measurements at age 9 years in the offspring. The children were seen every 9 months from 9–13 years of age for pubertal staging, and menarche was self-reported. In this cohort of 309 boys and 314 girls, prenatal PBDE exposure was associated with later menarche in girls and earlier pubarche in boys. Associations were stronger for normal weight girls. Childhood PBDE exposure showed a similar trend towards later menarche but it was not statistically significant, and no association was found at all for boys. There was no association between prenatal or childhood PBDE exposure and thelarche or pubarche in girls. These results are similar to those reported for the BCERP cohort, the only other longitudinal cohort study of girls' PBDE exposure (12). In the CHAMOCOS cohort, maternal PBDE levels were also associated with higher LH values in the boys at age 12 years (16).

A cross sectional case-control study from Italy compared serum PBDEs in children referred for idiopathic central precocious puberty (n=37) and premature thelarche (n=56) to 31 prepubertal control girls (17). Serum was collected for PBDE measurement at the time of physical exam. They found that girls with premature thelarche had higher PBDE levels than girls with precocious puberty and controls. This study had the same limitations as the other cross-sectional studies described above, ie they did not assess exposure prior to pubertal onset, and also used a relatively late age of 8 years to define precocious puberty onset. The authors conclude that their findings suggest that PBDE has a peripheral estrogenic action but no central action on the hypothalamic-pituitary-ovarian axis.

PCBs and Dioxins

Eskanazi and colleagues also reported the association of organochlorine chemicals with pubertal timing and reproductive hormones in the CHAMACOS boys, examined at ages 9 to 12.75 years for pubertal staging (16). Of the 312 boys who completed the 12 year visit, 234 provided a blood sample for hormone analysis. A 10-fold increase in maternal DDT levels was associated with an 18% decrease in boys' LH and testosterone values, while a 10-fold increase in DDE (a DTT metabolite) was associated only with a decrease in LH. Conversely, higher prenatal PCBs were associated with higher 12 year old FSH values in the boys. These associations between the boys' chemical levels at age 9 years and hormone values at 12 years was mediated by the boys' BMI.

The longitudinal Russian Boys Study cohort examines the associations of mixed childhood exposures with pubertal development (18). 473 boys had serum dioxin-like compounds (DLCs) and PCBs measured at 8–9 years of age. Genital staging and testicular volume determination was assessed at annual follow-up visits until age 18 years. The highest quartile of TEQs (a measure of dioxin potency) compared to the lowest was associated with a delay in pubertal onset and maturation by 11.6 months for testicular volume (TV >3 ml for onset; >20 ml for sexual maturity) and 10 months for genital staging (defined as G2 and G5) (19). Conversely, non-dioxin-like PCBs co-adjusted for TEQs, were associated with earlier pubertal onset by 8.3 months (TV) and 6.3 months (G2) and earlier sexual maturity by 6–7 months. These compounds were not associated with changes in timing of pubic hair development. In this cohort, higher quartiles of TCDD and PCDD TEQs were also associated with lower sperm concentration, total sperm count, and total motile sperm count (p-trends ≤ 0.05) (20), suggesting that childhood exposures to these organochlorines not only altered pubertal timing but were also associated with poorer semen parameters, raising concerns about long term effects of EDCs on reproductive function and fertility.

Dietary exposures

One area of particular interest to parents is whether dietary exposures through dairy, meat or soy intake can alter the timing of puberty. A longitudinal study of 515 Chilean girls recruited at ages 3–4 years investigated the relationship between dairy intake and pubertal changes (21). Breast DXA was performed in 290 girls and 324 girls reported age of menarche. Breast volume was highest in girls who drank more sweetened milk-based drinks and lowest in those who ate the most yogurt. Consumption of yogurt and low fat milk was associated with later menarche by 4.6 months. Another group looked at 367 mother-daughter dyads in the UK Avon Longitudinal Study of Parents and Children (22). Six phytoestrogens were measured in urine collected during pregnancy. Enterodiol (a lignan metabolite) was associated with lower risk of earlier menarche, defined as <11.5 years of age, while O-DMA (a daidzein metabolite) was associated with an increased risk of earlier menarche, The four other lignans studied, including enterolactone were not associated with age of menarche. This study controlled for timing of sample collection, race, maternal education, age at menarche delivery, BMI, diet and smoking history, infant feeding (maternal breast milk vs soy milk), childhood BMI and vegetarianism. These findings contrasted with the BCERP data that showed an association of enterolactone, a lignan metabolite, both a 4–5 month later age of menarche as well as later thelarche (13). This association was more marked in leaner

girls and the authors speculate that the conflicting findings may be due to different exposure windows (gestational versus childhood) or sample size.

A prospective study of 456 girls in Bogota, Columbia, investigated the association of red meat intake at ages 5–12 and age at menarche via food-frequency questionnaires (23). They found earlier menarche with higher red meat consumption. Those who ate meat more than twice daily had significantly earlier menarche than those who ate it less than four times per week. The investigators also found that those who ate canned tuna/sardine intake more than once per week had later menarche than those who ate them less than once per month. Average age of menarche was 12.4 years in this study. Intake of dairy, poultry, eggs, and other fish were not significantly associated. The meat effect was attenuated when adjusted for BMI.

Pesticides

Another area of considerable interest is whether there is a difference between organic food and conventional food. A study examined 3-phenoxybenzoic acid (3-PBA), a nonspecific metabolite of 18 pyrethroids in 305 9–15 year old Chinese girls with self-reported pubertal staging and menarche status (24). These insecticides can be both estrogenic and anti-androgenic, and are used in homes and for agriculture. Exposure occurs via diet as well as through skin. Higher 3-PBA was associated with later pubertal development for breast development, pubic hair, and menarche. The Avon Longitudinal Study examined gestational exposures to weakly estrogenic organochlorines (24). Exposure occurs through fatty foods (meat, fish, dairy), as well as via the placenta and maternal breast milk. This nested case-control study measured maternal serum organochlorine concentrations at random times in pregnancy. Among 3682 girls who self-reported age at menarche; 218 girls were ‘early’ (menarche before 11.5 years), and 230 were “controls” (ages 11.5 years or older). There were no associations between in utero exposure to organochlorines and early menarche. The investigators controlled for race, mother’s BMI, mother’s age at menarche and at delivery, SES, birth order, child’s BMI at age 7, duration of breastfeeding, child’s birth weight, and trimester of sample collection.

The associations of insecticides measured as urinary metabolites (3-PBA) with self-reported pubertal staging and self-measured testicular volumes were examined in 463 Chinese boys, ages 9–16 years (24). 3-PBA was detected in 98.7% of all urine samples and was inversely correlated with the frequency of organic food intake. After controlling for confounders such as SEC, age, and other birth history factors, higher levels of 3-PBA were associated with increased odds of being at a more advanced stage of puberty and having higher urinary gonadotropins.

Air pollution

Lastly, the BCERP group published two studies on the effects of tobacco exposure and air pollution. Prenatal and contemporary second-hand tobacco exposure was assessed by questionnaire and urinary cotinine measurement at enrollment. Girls with higher prenatal and secondhand smoke exposure have earlier pubarche but not thelarche. Pubarche occurred 10 months earlier in the highest vs the lowest prenatally exposed groups (25). To examine

the effects of exposure to the polycyclic aromatic hydrocarbons in air pollution, residential proximity to traffic metrics was used as a proxy measure (26). Proximity to major roads at age 6–8 years was associated with earlier PH across all ethnic groups, controlling for confounders. Higher exposed girls had pubarche 2–9 months earlier than lower exposed. There was no association with thelarche timing.

CONCLUSION

In summary, we have provided a brief overview of the types of EDCs being investigated for potential health effects related to puberty and reproductive development. These recent papers reinforce the complexity of studying this relationship and demonstrate that most studies have only been able to identify correlations with alterations in the timing of different pubertal milestones but that causality is difficult to glean from environmental epidemiology studies. Contrary to the original hypothesis that EDCs may be responsible for the earlier onset of puberty reported in girls over recent decades, several of the associations have been for later pubertal milestones and others have shown earlier onset but slower maturation. The effects reported depend on the exposure window, the specific compound studies, the particular pubertal milestone being considered, and are gender specific.

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Key Points

Exposure to a broad mixture of environmental contaminants is ubiquitous.

EDCs are hormonally active substances that can act via several mechanisms to perturb puberty--peripherally on target organs or via the HPG axis

Some of the shifts in pubertal timing may be mediated by exposures to EDCs at critical developmental windows.

The exposure window, ie gestational, infancy, early childhood, or peripubertal may lead to differing effects on reproductive health outcomes.