Chemicals in Personal Care Products Tied to Early Puberty in Girls

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Precocious puberty is defined as the onset of menarche before 9 years of age, or the appearance of secondary sex characteristics before 8 years of age. It is associated with many psychosocial disturbances and adverse health outcomes such as: cardiovascular disease, shorter adult stature, an increased risk of type 2 diabetes and breast cancer. There is a general tendency to a progressive decrease in age of reaching puberty, specifically the onset of thelarche and menarche, girls being 10 times more affected than boys. This actual tendency can be explained by the increasing prevalence of childhood obesity and also by increasing environmental exposure to endocrine disruptor chemicals in household and personal care products.Phenols, phthalates, parabens and other compounds, such as polybrominated biphenyls and diethylstilbestrol are associated with precocious onset of puberty in girls, in case of in-utero or peripubertal exposure. These chemicals are frequently found in toothpaste, cosmetics, soups, shampoos, perfumes and other personal care products, interfering with sex hormones and puberty timing. This is why pregnant women should be more aware and avoid products based on these chemicals.

Keywords: precocious puberty, phenols, parabens, phthalates, in-utero exposure, EDCs

Puberty is defined as a complex process of development which makes the transition from childhood to adolescence. It consists in the appearance of secondary sexual characteristics, behavioral changes, accelerated growth and ultimately the reproductive capacity [1,2]. Puberty is marked by a maturation of the hypothalamic- pituitary-gonadal axis, which is responsible for the increased levels of hypothalamic gonadotropin releasing hormone (GnRH). GnRH leads to a rise in pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. Gonadotropin release is a trigger for the gonads, the final result being the onset of ovulatory menstrual cycles [1,3,4].

The available studies showed a progressive decrease in age of reaching puberty, specifically the onset of menarche and breast development [5,6]. Precocious puberty consists in the onset of menarche before 9 years of age, or the appearance of secondary sex characteristics before 8 years of age [2].

The prevalence of precocious puberty is 1 in 5000 children and girls are 10 times more affected than boys [2]. An earlier onset of menarche has been associated with adverse health and social outcomes, such as shorter adult stature, an increased risk of type 2 diabetes, adult-onset asthma, cardiovascular disease and an increased risk of breast cancer and reproductive tract cancers [7-10]. Precocious puberty is also associated with many psychosocial disturbances, like an increased incidence of depression, withdrawal and internalizing disorders [2,11]. A study which compared a group of girls with early onset of the menarche with those who had menarche after 11 years of age has shown major differences at age 13 and 15, reporting many more episodes of rule-breaking at home, at school and during leisure time among the early maturing girls. The group of girls with precocious puberty also showed more school discipline problems, school fatigue and an earlier sexual debut with a greater incidence of abortions by the age of 16 years [11].

The two main hypotheses for the actual tendency towards earlier menarche are: the increasing prevalence of childhood obesity and increasing environmental exposure to endocrine disruptor chemicals (EDCs) in household and personal care products [7,8,12].

Endocrine disruptor chemicals (EDCs)

EDCs are synthetic or natural environmental chemicals which are introduced into the human body through foodstuffs, water and air. They also can be transferred from the mother to the baby via breast milk and to the fetus via placenta [6,7,13]. These chemicals are highly spread in personal care products, in household products and household cleaners, leading to high exposures in the population through behaviors and daily activities [7,14]. The mechanisms of action of endocrine disruptors can be explained by their hormone-like characteristics. The endocrine function and development are affected by these chemicals in an agonist- or antagonist- specific manner [6,7]. They affect puberty through their androgenic, anti-androgenic, estrogenic or anti-estrogenic effects. Endocrine disruptors have also direct effects on the gonadotropin-releasing hormone (GnRH). The estrogenic effects may be exerted either directly by binding to estrogen receptors, leading to an increase of aromatase activity and finally increasing estrogen sensitivity or indirectly, rising the endogenous estrogen production by influencing the GnRH. The final result of all of these mechanisms is the precocious puberty [6]. Several examples of chemicals which are known to disrupt estrogen receptor signaling in vitro and in animal studies are parabens, triclosan, dichlorophenols and certain benzophenones. These compounds exert their action by modulating the downstream signaling processes, or by binding directly to

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the receptor itself [7]. The androgenic and anti-estrogenic effects of the endocrine disruptors are exerted through inhibition of steroidogenic enzyme production and aromatase enzyme activity. The anti-androgenic effects of these chemicals may be explained by the suppression of testicular steroidogenesis and androgen-receptor blockade. Because of these multiple mechanisms of action, endocrine disruptors not only lead to precocious puberty, but also interfere with delayed puberty and with many sexual differentiation disorders [6]. Phthalates and bisphenol A are examples of compounds which have a demonstrated role in disrupting androgen-dependent processes. Additionally, bisphenol A is involved in both estrogenic and anti-androgenic responses [7].

Phenols

Phenols are endocrine disruptors commonly found in many personal care products. An important phenol is triclosan, which is still used in toothpaste, although it was banned from the antibacterial soap in the US [15]. Measuring the urinary concentrations of triclosan and 2,4-dichlorophenol in pregnant women, it was demonstrated that in-utero exposure to these compounds is associated with earlier menarche in girls [16]. Also, a study measuring the urinary concentration of triclosan in pregnant women has shown that for every doubling in concentration, the menarche of their daughters was one month earlier [15]. In addition, peripubertal exposure to triclosan is linked not only to earlier menarche, but also with earlier breast development in girls [8,16,17].

Another compound, 2,5-dichlorophenol was associated with precocious onset of pubarche, thelarche and menarche in girls at ages 6-8 [16-18] and only with earlier menarche in girls at ages 12-16 [7,16]. Meanwhile, another study found that 2,5-dichlorophenol was correlated with earlier age at menarche [7, 18].

Bisphenol A (BPA) is another phenol associated with precocious puberty in girls, which is often used to make household products [4,19]. Animal studies have demonstrated estrogenic properties for BPA, this compound being associated with earlier onset of puberty in female rats, leading to a precocious vaginal opening [12,20,21]. Human studies found a correlation between BPA and earlier age at menarche and thelarche in girls [12,22-24].

There are studies which describe contradictory results regarding the effect of phenols to the pubertal timing in girls. For example, benzophenone-3 which was linked to later thelarche and menarche and enterolactone, a phenol which leads to later menarche [7,16-18].

Phthalates

Phthalates are also used in personal care products as softeners [25-27]. Three of the most used phthalates are di-n-butyl phthalate (DnBP) and di-iso-butyl phthalate (DiBP), which are more frequently found in cosmetics and nail polish, and diethyl phthalate (DEP), which is used in perfumes, shampoo, deodorants and soaps [28].

Human studies have shown a relationship between phthalates, allergic response and behavior changes in children. Meanwhile, in vitro and animal studies have marked the estrogenic and anti-androgenic effects of the phthalates [29].

Phthalates plasticizers lead to early puberty in female rats, affecting the female reproductive system through a weak estrogenic effect [22]. A recent study of female rats has shown a correlation between an earlier onset of puberty and neonatal and prepubertal exposure to dibutyl phthalate [30]. Another animal study found an earlier ovarian development and estrous in female rats which have been exposed in utero to di(2-ethylhexyl) phthalate (DEHP) [12,31,32].

In human studies, there is described a link between phthalate exposure and early onset of puberty in girls. For example, a study on Puerto Rican girls has shown a correlation between premature breast development and phthalate exposure, the most prevalent phthalate being di-2-ethylhexyl phthalate (DEHP) [33]. There are also evidences of high blood levels of DEHP in girls with precocious puberty [12].

Another study has assessed the impact of phthalate exposure during in utero development and peripubertal on the serum concentrations of sex hormones and on the timing of sexual maturation. It was demonstrated that in utero exposure to some phthalates (DEHP and butylbenzyl phthalate) can lead to premature onset of puberty and adrenarche. There have been measured the urinary phthalate metabolites among mothers, during their third trimester of pregnancy and among their girls at 8-13 years of age. It was found that in utero exposure to DEHP leads to increased concentrations of dehydroepiandrosterone sulfate (DHEA-S), which is an important precursor to pubarche [30]. In addition, there are evidences that each doubling of urinary concentration of a phthalate indicator in pregnant women leads to 1.3 months earlier onset of the pubarche in their daughters [15]. In contrast, another study has found that urinary concentrations of high-molecular weight phthalate (high-MWP) metabolites including di(2-ethylhexyl) phthalate (DEHP) are linked to later pubarche [34].

It has been shown a correlation between the monoethyl phthalate (MEP) in pregnant women and an earlier onset of pubarche in their daughters [14]. Studying the effect of peripubertal exposure to MEP in overweight or obese girls, it has been demonstrated that this compound leads to earlier menarche [8,14].

On the other hand, exposure to another compound, diethyl phthalate (DEP) was linked to earlier onset of pubic hair and breast development [35].

In a case-control study comparing girls with thelarche with controls, it was observed a detectable serum level of phthalates in two-thirds of the cases and only in 14% of the controls [36,37].

Parabens

Parabens are esters of p-hydroxybenzoic acid, often found in cosmetics, foods and pharmaceuticals as antimicrobial preservatives [38]. Types of exposure to parabens include: dermal contact, inhalation and ingestion [38]. Although there are described a lot of compounds, the two of the highly used parabens are methyl paraben (MP) and propyl paraben (PP) [38]. Parabens have been linked to endocrine disruption and reproductive toxicity, but concentrations up to 0.8% in mixtures or up to 0.4% if used alone are considered safe as cosmetic ingredients [38]. It is known that parabens have estrogenic effects in vitro but also in vivo, due to their uterotrophic effects, the estrogenicity increasing with side chain length [39]. Parabens may lead to enhancing estrogen effects, being associated with breast cancer etiology [25,40]. This is possible because of the elevation of free estradiol levels, through inhibition of sulfotransferase enzymes (SULTs). This finding leads to an explanation of how parabens can inhibit sulfation of estrogens [39]. Parabens can be excreted in the urine as intact esters, but also as a conjugated form of p-hydroxybenzoic acid, a nonspecific metabolite of all

parabens. There are considered valid human exposure biomarkers the concentrations of all (both free and conjugated) urinary compounds of the parent parabens [38].

It has been shown that peripubertal exposure to methyl paraben is associated with an earlier onset of pubarche, menarche and telarche, while propyl paraben is only associated with earlier pubarche [16]. Meanwhile, other studies have shown no association between peripubertal exposure to parabens and earlier onset of puberty [7,16-18].

For example, a study including female participants 12-16 years of age has shown no relationship between total parabens exposure and the age of menarche [7].

Other compounds

It has been demonstrated a correlation between exposure to polybrominated biphenyls (PBBs) in pregnant women and earlier menarche in their daughters. Meanwhile, there was not found an association with thelarche [41]. In addition, another study found no correlation between exposure to PBB and breast development, but it was observed an earlier onset of pubarche and menarche in girls exposed to high levels of this compound in utero or by breastfeeding [42,43].

It has been shown that prenatal exposure to diethylstilbestrol (DES), one of the synthetic estrogens, elevates the risk of early menarche [41,44].

Conclusions

The increasing prevalence of precocious puberty can be explained by exposure to different chemicals frequently used in personal care products, such as parabens, phenols and phthalates.

Phenols are having different effects to the pubertal timing in girls, in-utero exposure to triclosan and 2,4-dichlorophenol leads to earlier menarche of the offspring, while peripubertal exposure to triclosan was linked with earlier thelarche. In contrast, there are some phenols linked to later menarche and thelarche, such as benzophenone-3 or only with later age at menarche, such as enterolactone.

Phthalates are also playing an important role in precocious puberty in girls. Exposure to monoethyl phthalate, 2-ethylhexyl phthalate and butylbenzyl phthalate of the pregnant women leads to earlier menarche and pubarche in their daughters and there are some evidences of later pubarche linked to high-molecular weight phthalate metabolites such as di(2-ethylhexyl) phthalate.

There are contradictory results regarding the role of the parabens in precocious puberty in girls. Propyl paraben has been associated with earlier pubarche, while methyl paraben was linked not only with earlier development of pubic hair, but also with earlier age at menarche and precocious breast development.

Prenatal exposure to other chemicals such as diethylstilbestrol is also associated with earlier menarche in girls, while polybrominated biphenyls can lead not only to precocious onset of menarche, but also of pubarche, in case of in-utero exposure or transfer by breastfeeding in girls.

The effects of these chemicals are modulated by the genetic predisposition and by the timing of the exposure. Although they are spread in many products, consumers and especially the pregnant women should avoid these compounds, in order to prevent the adverse outcomes on the puberty timing.

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