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

Chemicals in Personal Care Products Tied to Early Puberty in Girls

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precocious puberty in girls, which is often used to make
which leads to later menarche [7,16-18].

Bisphenol A is another phenol associated with
precocious puberty in female children. Meanwhile, in vitro and animal studies have
inhibited sulfation of estrogens [39]. Parabens can be excreted
also in vivo, due to their uterotrophic effects, the
esterogenicity 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

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
term 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
contentrations 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
esterogenicity 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 diethy stilbestrol (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 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 diethyl stilbestrol (DES), one of the synthetic estrogens, elevates the risk of early menarche [41,44].

References

43. BLANCK, H. M., MARCUS, M., TOLBERT, P. E., RUBIN, C., HENDERSON, A. K., HERTZBERG, V., ... & CAMERON, L. Epidemiology, 11, no. 6, 2000, p. 641.

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