

## HEALTH EFFECTS

## REVIEW

## The Effects of Phthalates on Precocious Puberty in Girls

**Introduction**

Precocious puberty is a condition where pubertal changes occur at an age earlier than expected. In girls, these changes generally include the appearance of breast tissue, pubic hair, and menstruation, also known as thelarche, adrenarche, and menarche, respectively [1]. The onset of puberty is usually triggered by the pituitary, a pea-sized gland located near the base of the brain, and the production of gonadotropins and sex hormones. Only in a small percentage of cases is there an underlying medical condition such as a pituitary tumor. The majority of the cases have no known cause [1].

The age at which pubertal changes occur has declined worldwide over the last few decades. In the Netherlands, the median age for a girl's first menstruation was 13.66 years in 1955, 13.40 years in 1965, 13.28 years in 1980, and 13.15 years in 1997 [2]. In Puerto Rico, which has the highest reported incidence of premature breast development, girls less than 2 years of age comprise the majority of precocious puberty cases [3]. As a result of the alarming increase in incidence, Puerto Rico is home to the only world registry for the study of premature sexual development.

Nutrition, physical exercise, and weight are factors associated with the decline in age of pubertal changes. In addition to a global decline in age over time, researchers have observed specific patterns in certain populations. African-American girls tend to reach puberty earlier than other races [4]. The use of hormone-containing hair product has been indicated as one possible factor in precocious puberty in African American girls. [5].

Environmental contaminants have also been implicated in altering the timing of natural sexual maturation. The chemical phthalate esters is ubiquitous in the environment, and exposure can occur via ingestion, inhalation, and dermal absorption [6]. Although human data is limited, experimental studies have shown that this chemicals can cause female reproductive toxicity in exposed laboratory rats. We describe phthalates below and summarize the results of studies investigating the association with precocious puberty.

**Defining 'Precocious'**

While the development of breasts at 2 years of age strikes many as early, just how early is 'earlier than expected'? A study by Marshall and Tanner in 1969 is often used as a standard to define the age of normal puberty [7]. Using a rating system constructed by Tanner, photographs were examined to determine the development of 192 white British girls, primarily of lower socio-economic status.

The authors concluded that the first sign of puberty appeared between 8.5 years and 13 years in 95% of the girls. The mean for stage 2 breast and pubic hair develop-

ment was 11.15 years and 11.69 years, respectively [7]. Based on this study's results, sexual development in girls before 8 years of age is considered precocious puberty.

A more recent (1997) study by Herman-Giddens et al. shows a decline in the age of onset of pubertal changes [8]. This large cross-sectional study analyzed data for 17,077 African-American and white girls examined by clinicians belonging to Pediatric Research in Office Settings Network. The clinicians used the system devised by Tanner to determine the development of pubertal changes.

The mean age for stage 2 breast and pubic hair development was 9.96 years and 10.51 years respectively in white girls and 8.87 years and 8.78 years respectively in African-American girls. These ages are significantly earlier than those presented by Marshall and Turner. The study also illustrates the effect race has on age of puberty.

The trend toward earlier onset of puberty in girls raises an important issue: should the age defining precocious puberty be revised? The Marshall and Tanner study, which sets the standard of eight years for precocious puberty, has been described as unrepresentative of the population [9]. The girls in the study were residents of children's homes and may have been more likely neglected or mistreated before relocating to the home. Socioeconomic stress and a poor diet may have contributed to a later onset of pubertal changes.

The study by Herman-Giddens et al. suggests that pubertal changes at seven years of age in white girls represents the lower range of normal puberty, not eight years [8]. For African-American girls, the range begins even lower at six years of age. Most girls that show signs of precocious puberty fall within the age range of normal puberty set by Herman-Giddens; they would not be considered precocious if the age limit was redefined. However, the study by Herman-Giddens may be biased because the subjects were not randomly selected. Currently, the standard remains set at eight years, but diagnosis is often subject to the discretion of the pediatrician or pediatric endocrinologist.

Proper diagnosis of precocious puberty is important to determine if treatment is necessary. Precocious puberty can be psychologically painful and result in adverse health outcomes such as early pregnancy, depression, reduced height, and obesity [9]. To increase adult height and slow early maturation, precocious puberty is treated with gonadotropin-releasing hormone (GnRH) analogs.

However, for cases diagnosed between the ages of six and eight, GnRH therapy is not always necessary because resulting conditions such as depression and reduced height are not as severe in older girls as they are in younger girls [9]. Regardless of the age range used to define precocious puberty, researchers agree that a better understanding of

the factors related to the early onset of pubertal changes is needed.

### Phthalates

Phthalates are a chemical family (dialkyl or alkyl esters of 1,2-benzene-dicarboxylic acid) found in a wide range of products such as food packaging and children's toys [6]. Because they are ubiquitous in the environment, human exposure can occur in various ways, such as inhalation of dust, ingestion of food, or dermal absorption from cosmetics.

Personal care products are a special source of concern for women. Di-ethyl (DEP), di-n-butyl (DBP) and butyl benzyl phthalate (BBzP) are each found in body lotions, gels, shampoos, and deodorants, ranging in levels from trace amounts to three percent of the product formulation [6]. Women of childbearing age were found to receive the highest exposure from these products.

Currently, no human data exist that quantify the proportion of exposure contributed by each route. However, a recent study shows that exposure to phthalates is widespread [10]. All seven of the urinary phthalate metabolites sought were detected in the reference population, with diethyl phthalate, dibutyl phthalate, and butyl benzyl phthalate having the highest levels. The metabolites of these esters were found in over 75% of subjects [10].

Studies of occupational exposure suggest an association between phthalates and reproductive health outcomes (decreased rates of pregnancy, increased rates of miscarriage and preeclampsia) [11]. Although occupational exposure affects a relatively small population, in the general population women are also exposed throughout every stage of their lives. At birth, the fetus and mother are exposed to phthalates in the medical equipment. As a child, many of the soft-squeeze toys contain phthalates. Once old enough, cosmetics become a major source of phthalates. Given the suggested health effects and the wide-spread exposure, more epidemiologic data are urgently needed, and in the meantime, perhaps precautionary policies.

While data in humans are limited, studies using laboratory animals show that di-(2-ethylhexyl) phthalate (DEHP) and its metabolite (MEHP) may cause female reproductive toxicity [11]. DEHP is primarily used as a plasticizer in soft polyvinyl chloride (PVC) plastic to add flexibility. The plasticizer is not bonded to the plastic so it is readily able to leach into the environment [12]. Exposure during the sensitive peri-pubertal period might disrupt hormonal activity and result in toxicity. Researchers attempting to understand the mechanisms of phthalate toxicity believe MEHP may affect different parts of the reproductive system, possibly promoting breast development while suppressing ovulation [11].

Phthalates have also been shown to cause toxicity in the male reproductive system. Unfortunately, very little data is available for trends in puberty for boys so it is still unknown if the age of pubertal changes has declined in males [8]. Lastly, phthalates have displayed weak estrogenic activity. As a result, exposure during critical periods of intrauterine development may disrupt reproductive systems [13].

In one of the few human studies, phthalates were investigated as a cause of precocious puberty in young Puerto Rican girls [3]. For decades, the epidemic of premature onset of puberty in Puerto Rico has generated various hypotheses. Food contamination from exogenous estrogens was first implicated, but no abnormal levels of suspect-

ed chemicals were detected in meat and dairy samples [1]. Recently, concern has focused on endocrine-disrupting chemicals (EDCs) that affect the normal function of the endocrine system. EDCs have been shown to disrupt reproductive outcomes in wildlife, especially in the Great Lakes region [14-16]. Known endocrine disruptors include phthalate esters, organochlorine pesticides, dioxins, and polychlorinated biphenyls (PCBs) [3]. Because of the ubiquitous presence of phthalates in the environment, Colon et al. compared the serum levels of phthalates in 41 girls with premature appearance of breast tissue to the serum levels of phthalate esters in 35 controls [3]. Phthalate esters were detected in 68% of the cases and 17% of the controls and controls were found to have significantly lower levels of phthalates than the cases. For DEHP, the average concentration was 70 ppb in the controls compared to 450 ppb in the cases.

Although the study was limited by a small population size and the possibility of contaminated serum samples, the association between phthalates and premature thelarche is biologically plausible. The phthalate metabolite MEHP activates the peroxisome proliferator-activated receptor (PPAR) pathway that induces the differentiation of fat cells and interacts with growth hormone signaling [11,17].

### Conclusion

The causes of most precocious puberty cases remain unknown. While many of the cases are attributed to excess weight gain or (paradoxically) improved nutrition, exposures to phthalates and other endocrine-disrupting chemicals have also been implicated as possible risk factors. The limited data show that the worldwide incidence of precocious puberty has increased and the age of pubertal changes has decreased over the past two decades.

Phthalates are found commonly throughout the environment and in many everyday products. Wildlife studies have already demonstrated the reproductive damage these chemicals can cause [14-15]. The sediment in the Great Lakes region shows the presence of phthalate esters [16]. Although phthalates do not bioaccumulate in the body like dioxins and other chemicals, their ubiquitous presence in nature and the size of the population exposed suggest that the potential impact of phthalate exposure could be very large.

Experimental toxicology studies show that phthalates disrupt the normal functions of the reproductive system. In addition, a recent study of young girls with a premature appearance of breast tissue revealed that the average levels of measurable phthalate esters and their metabolites were six times higher in cases than controls. Further studies are needed to investigate the association between precocious puberty and phthalates in various populations.

Precocious puberty is of particular concern in women because early timing of puberty is associated with the development of breast cancer [18]. This association may be due to the higher estrogen levels in women with early puberty or to environmental exposures during sensitive periods in a woman's reproductive development. The incidence of breast cancer has been steadily increasing over the past few decades among women 50-74 years of age, and chemicals in the environment are believed to have contributed to this increase [18]. Thus the problem of precocious puberty goes beyond issues of reproduction and childbearing to extend to chronic diseases in later life.

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Prepared by the Department of Environmental Health, Boston University School of Public Health under the direction of the International Joint Commission's Health Professionals Task Force. The Health Effects Review is a quarterly publication that summarizes the latest scientific literature on human health effects and environmental pollutants. This does not represent the official position of the International Joint Commission.

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