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Prenatal exposure to phthalate ester and pubertal development in a birth cohort in central Taiwan: A 12-year follow-up study

Pen-Hua Su [a,b,1], Chin-Kuo Chang [c,1], Ching-Yi Lin [d,e], Hsiao-Yen Chen [f], Pao-Chi Liao [g], Chao A. Hsiung [k], Hung-Che Chiang [h], Shu-Li Wang [f,i,j,*]

[a] Department of Pediatrics, Chung Shan Medical University Hospital, Taichung City, Taiwan
[b] School of Medicine, Chung Shan Medical University, Taichung City, Taiwan
[c] Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK
[d] Department of Obstetrics and Gynecology, School of Medicine, Chung Shan Medical University, Taichung City, Taiwan
[e] Department of Obstetrics and Gynecology, Chung Shan Medical University Hospital, Taichung City, Taiwan
[f] Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Miaoli County, Taiwan
[g] Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, Tainan City, Taiwan
[h] National Environmental Health Center, National Health Research Institutes, Miaoli County, Taiwan
[i] Department of Public Health, National Defence Medical Center, Taipei City, Taiwan
[j] Department of Public Health, College of Public Health, China Medical University, Taichung City, Taiwan
[k] Institute of Population Health Sciences, National Health Research Institutes, Miaoli, County, Taiwan

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ABSTRACT

Phthalate esters are widely used plasticizers that are present in many daily used products. Although some of their reproductive effects have been reported, pubertal development effects from prenatal exposure to phthalates awaits further investigations. A population based birth cohort was established ($N=437$ at baseline) with maternal exposure to phthalates assessed in urine collected at the third trimester of pregnancy in 2001 and 2002. Their 133 children with prenatal phthalates exposure were followed up for the outcomes of pubertal development by sequential physical examinations at eight and 11 years old in 2009 and 2012. Urinary concentrations of major phthalate metabolites (i.e., mono-2-ethylhexyl phthalate [MEHP], mono-(2-ethyl-5-hydroxyhexyl) phthalate [MEHHP], mono-(2-ethyl-5-oxohexyl) phthalate [MEOHP], mono-butyl phthalate [MBP], mono-benzyl phthalate [MBzP], mono-methyl phthalate [MMP], and mono-ethyl phthalate [MEP]) were determined using liquid chromatography linked to tandem mass spectrometry. The reproductive development measurements included bone age (for both genders), testicle size (for boys), uterus size, and ovarian volume (for girls). We reported results of 133 children with complete data by applying generalized estimating equations for the repeated continuous outcomes. After controlling for Tanner stage, we detected a significant association between reduced uterus size and increasing phthalate exposure in the 2nd tertile relative to the 1st tertile of creatinine-corrected MEHP ($B=-0.40$; 95% C.I.: -0.73, -0.07, relative to the 1st tertile) and total DEHP ($B=-0.39$, 95% C.I.: -0.66, -0.01 for the 2nd tertile and $B=0.34$, 95% C.I.: -0.67, -0.01 for the 3rd tertile, relative to the 1st tertile) with a linear trend among girls. MBzP was also found negatively associated with bone age/chronological age ratio ($B=-0.07$, 95% CI: -0.13, -0.01 for the 3rd tertile, relative to the 1st tertile) with a linear trend for girls. We found no evidence of an association between phthalate exposure and ovarian volume or testicle size. This analysis suggests phthalate exposure may affect specific pubertal development characteristics in human beings. Further studies with larger sample sizes and longer follow-up period are warranted.

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1. Introduction

Human exposures to phthalate esters are extensively ranging from house dust, food containers, toys, and medical devices, to the uses of some oral medications, and lotions or cosmetics for skin (Schettler, 2006; Wittassek et al., 2011). Di-ethyl-hexyl-phthalate (DEHP) is one of the most broadly used phthalate esters

* Corresponding author at: National Health Research Institutes, 35 Keyan Road, Zhunan Township, Miaoli County 35035, Taiwan. Fax: +886 37 587 406.
E-mail address: slwang@nhri.org.tw (S.-L. Wang).
[1] These authors share the first authorship.

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(phthalates) which is used as a plasticizer in many products used daily. It is easily released into the environment since it is loosely held within plastic polymers. The widespread use of phthalates makes them almost ubiquitous and, thus, the issues about their long-term effects on human health are of great concern.

Although most evidence was built on animal models, the adverse affects for phthalates on reproductive physiology and endocrine function has been suggested, but not yet conclusive (Kay et al., 2013; Martinez-Arguelles et al., 2013; Moyer and Hixon, 2012). In research focusing on the male reproductive system, investigators have observed some germ cell decrease, cryptorchidism, lower testosterone concentration, and malformations of the epididymis, vas deferens, seminal vesicles, and prostate gland in rats (Martino-Andrade and Chahoud, 2010; Noriega et al., 2009; Parks et al., 2000; Veeramachaneni and Klinefelter, 2014). For females, it has been suggested that phthalate exposures may modulate circulating hormone concentrations and cellular differentiation of estrogen sensitive tissues and disturb the reproductive system development, resulting in delayed puberty, adverse effects on ovarian function, steroidogenesis, structure of reproductive organs, oocyte development, ovulation, fertility, and progression of pregnancy in animal models (mostly rats) (Kay et al., 2013). Particularly, higher exposure to mono-2-ethylhexylphthalate (MEHP) was found to postpone estrous onset, cause premature ovarian senescence, and increase mammary hyperplasia in mice (Moyer and Hixon, 2012).

In human beings, although exceptionally lower exposure levels of phthalates than in animal studies were mostly found, epidemiologic studies revealed some evidence for de-feminization, thelarche, early secondary breast development, delayed pubarche among girls in puberty (Frederiksen et al., 2012), premature breast development among girls (Colon et al., 2000), later pubic hair development among girls (Wolff et al., 2014), and progression of breast cancer (Kay et al., 2013), but its associations with precocious puberty, endometriosis, leiomyomas, fibromatosis, and early pregnancy loss were still inconclusive (Hart et al., 2014; Roy et al., 2009). Recent studies also revealed that the prenatal exposure to phthalates was related to decreased penile size (Bustamante-Montes et al., 2013) and anogenital distance (Bustamante-Montes et al., 2013; Suzuki et al., 2012; Swan et al., 2005), which is a sensitive indicator for the chemicals interfering with sex hormones in newborn baby boys. However, limitations of the epidemiologic studies in the literature include methodological disadvantages (cross-sectional or retrospective study design), lower exposure levels in the community, various phthalate metabolites for exposure measurements in different studies (Wolff et al., 2014), and small sample sizes (Kay et al., 2013; Martinez-Arguelles et al., 2013), consequently leading to inconsistent results.

Up to now, only a few studies have been published focusing on prenatal phthalate exposures and adverse reproductive health consequences in human beings (Bustamante-Montes et al., 2013; Hart et al., 2014; Huang et al., 2009; Swan et al., 2005). A well established birth cohort from the general population, consisting of mothers and their children with the assessments of maternal/children's urine for environmental exposures to chemicals and long periods of follow up for health consequences, has been maintained in central Taiwan (Lin et al., 2011b). Based on this cohort, results about the effects of maternal phthalates to cord sex hormones at birth were reported, indicating that free testosterone and testosterone/estradiol levels in cord serum of female newborns were negatively associated to MEHP and 5OH-MEHP identified in maternal urine (Lin et al., 2011a). Taking advantage of a prospective study design with long-term follow up and repeated measurements on the same group of participants at the age of eight and 11 years old, which is close to puberty especially in girls, we performed analyses particularly on the effects of phthalate metabolites on major landmarks of puberty development. To our best knowledge, this is the first long-term follow-up study of a birth cohort to examine the hypothesis that prenatal phthalate exposure is related to reproductive growth in early adolescence.

2. Methods

2.1. Study setting and participants

The process of participant recruitment has been thoroughly described elsewhere (Lin et al., 2011a, 2011b; Su et al., 2012b). In brief, the current analysis was based on a birth cohort consisting of pregnant women, aged 25–35 years old in central Taiwan during December 2000 and November 2001, and then regularly followed up every two and half years until August 2012 for consecutive examinations of physical consequences. In total, 610 pregnant women were approached and 437 of them (around 70%) planned to delivery their babies at the hospital and agreed to be interviewed by a baseline questionnaire.

2.2. Baseline data collection

As it was described in our previously published article, information about demographic and perinatal characteristics for participants at pregnancy and after child birth was obtained in baseline records with a standard instrument, covering maternal age, parity, parent's education level, medical history, dietary and smoking habits, and history of child's breast feeding (Su et al., 2012b). Maternal urine samples were collected with a glass beaker in the third trimester of pregnancy (28–36 weeks). The children were traced for the assessments of their puberty development landmarks at eight and 11 years old in 2009 and 2012. This study was approved by the ethics review committee of the National Health Research Institutes in Taiwan (Code: EC0980405, EC1010505) and parental and children written informed consent was obtained for each participant.

2.3. Phthalate metabolite and creatinine measurements

Mothers' urine samples collected in their third trimester of pregnancy were first transferred into amber glass bottles to be stored at −20 °C for quantification analyses on phthalate metabolites and creatinine. Urinary concentrations of phthalate metabolites (i.e., mono-2-ethylhexyl phthalate [MEHP], mono-(2-ethyl-5-hydroxyhexyl) phthalate [MEHHP], mono-(2-ethyl-5-oxohexyl) phthalate [MEOHP], mono-butyl phthalate [MBP], mono-benzyl phthalate [MBzP], monomethyl phthalate [MMP], and mono-ethyl phthalate [MEP]) were determined with liquid chromatography linked to tandem mass spectrometry(LC–MS/MS) (Koch et al., 2003; Preuss et al., 2005). All metabolite concentrations were expressed as μg/L. Total DEHP levels indicated the sum of MEHP, MEHHP, and MEOHP levels. Variability in urinary output was compensated for by adjusting phthalate metabolite concentration divided by the urinary creatinine level, expressed as micrograms per grams of creatinine (μg/g creatinine). Urinary creatinine levels were measured at the Kaohsiung Medical University Chung-Ho Memorial Hospital, using spectrophotometric methods, with picric acid as the reactive and the reader set at 520 nm.

2.4. Evaluation of puberty development at eight and 11 years old

Successive physical examinations and clinical assessments on detailed reproductive development were carried out by a pediatric specialist in reproductive development (P-H Su) every two and half years in the follow up, within which puberty landmarks at

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