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The impact of prenatal perfluoroalkyl substances exposure on neonatal and child growth

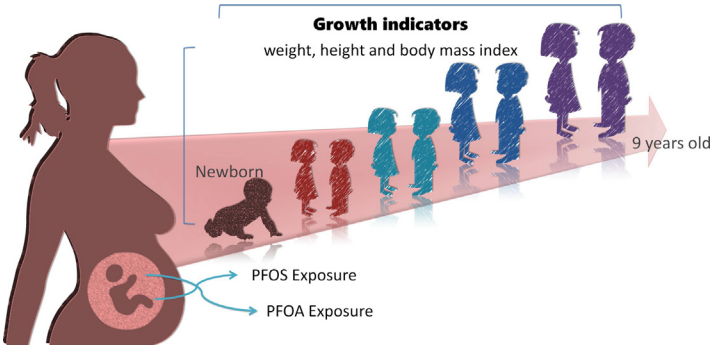
Mei-Huei Chen [a,b,c], Sharon Ng [d], Chia-Jung Hsieh [e], Ching-Chun Lin [f], Wu-Shiun Hsieh [c,g,*], Pau-Chung Chen [f,h,i,**]

[a] Institute of Population Health Sciences, National Health Research Institutes, Miaoli, Taiwan
[b] Department of Pediatrics, National Taiwan University Hospital Yun-Lin Branch, Yunlin County, Taiwan
[c] Department of Pediatrics, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan
[d] Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore
[e] Department of Public Health, Tzu Chi University, Hualian County, Taiwan
[f] Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan
[g] Department of Pediatrics, Cathy General Hospital, Taipei, Taiwan
[h] Department of Public Health, National Taiwan University College of Public Health, Taipei, Taiwan
[i] Department of Environmental and Occupational Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan

HIGHLIGHTS

- Negative association between prenatal PFOS exposure and fetal growth diminished as children grow up
- Gender susceptibility to prenatal PFOS was found as weight gain of girls and height gain for boys before puberty.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Perfluoroalkyl substances (PFASs) are wildly distributed environmental pollutants. Laboratory mice exposed prenatally to PFASs develop smaller birth weight but are more likely to become obese in adulthood. The evidences in human studies are still inconclusive.
Methods: The participants were 429 mother-infant pairs from Taiwan Birth Panel Study. These children were followed serially and growth data were collected through face to face interviews and records in Child Healthcare Handbooks until 108 months of age. The age-specific z-scores for weight (WAZ), length/height (LAZ/HAZ) and BMI (BMIAZ) were calculated. PFASs in umbilical cord blood were analyzed by ultra-high-performance liquid chromatography/tandem mass spectrometry.
Results: At birth, perfluorooctyl sulfonate (PFOS) levels were negatively associated with weight and height [per ln unit: adjusted β (95% confidence interval, CI) = −0.14 (−0.26, −0.01) for WAZ and −0.16 (−0.31, −0.02) for LAZ]. However, these adverse impacts diminished as children grow up. When stratified the analysis by gender,

Abbreviations: ETS, environmental tobacco smoke; LOQ, limit of quantitation; PFASs, perfluoroalkyl Substances; PFDeA, perfluorodecanoic acid; PFDoDA, perfluorododecanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctyl sulfonate; PFUnDA, perfluoroundecanoic acid; TBPS, Taiwan Birth Panel Study.

* Correspondence to: W.-S Hsieh, Department of Pediatrics, Cathy General Hospital, Taipei, Taiwan.
** Correspondence to: P.-C. Chen, Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, 17 Xuzhou Road, Taipei 10055, Taiwan.
E-mail addresses: hsiehws@ntu.edu.tw (W.-S. Hsieh), pchen@ntu.edu.tw (P.-C. Chen).

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the effects of prenatal PFOS exposure were more obvious for girls especially during the time span of 6 to 12 and 12 to 24 months of age [per ln unit: adjusted β (95% CI) = −0.25 (−0.47, −0.04) and −0.24 (−0.41, −0.04) for WAZ, respectively; per ln unit: adjusted β (95% CI) = −0.33 (−0.59, −0.08) and −0.25 (−0.45, −0.05) for BMIAZ, respectively]. Later in the period of 60 to 108 months of age, positive association between prenatal PFOS exposure and girls' BMI was observed [per ln unit: adjusted β (95% CI) = 0.34 (0.007, 0.68) for BMIAZ]. There was little evidence in these data for a consistent association of perfluorooctanoic acid (PFOA) with any of the indicators.
Conclusions: Our study had shown that higher prenatal PFOS exposure was associated with decreased fetal growth, but the effects were diminished as children grow up. Modest effect of gender specific manner was observed.

1. Introduction

Perfluoroalkyl substances (PFASs) have been widely used in a variety of consumer and industrial applications since the production of 1950 (Lau et al., 2007). However, their environmental and biological accumulations highlight the concern of adverse health effect on living beings. High dose or repeat exposure of PFASs cause a range of problems in laboratory animals, including liver damage, developmental delay, immunosuppression, imbalance of thyroid hormone, and tumor formation. Limited human epidemiological study revealed that low dose intrauterine exposures still cause growth and neurodevelopment impairment (Roth and Wilks, 2014; Bach et al., 2015). In addition to oral ingestion of contaminated food and water and inhalation of household dust, fetus and infant are exposed additionally through placental transfer and breastfeeding (Fei et al., 2007; Fromme et al., 2009; Haug et al., 2010). The elimination half-life for several years is even worrisome for developing children (Olsen et al., 2007; Bartell et al., 2010).

Laboratory mice exposed prenatally to perfluorooctanoic acid (PFOA) and perfluorooctyl sulfonate (PFOS), the most well-known eight-carbon chemicals, develop more slowly and suffer a higher rate of neonatal mortality than non-exposed mice (Lau et al., 2003; Luebker et al., 2005; Wolf et al., 2010). While they reach adulthood, these exposed mice were more likely to become obese (Betts, 2007; Hines et al., 2009). Increased insulin and leptin levels in postpubertal female offspring following low dose in utero PFOA was reported in a CD-1 mouse model (Hines et al., 2009). Systemic review in human studies conclude the adverse impact of PFOS and PFOA on birth outcomes (Johnson et al., 2014; Bach et al., 2015), while the evidence of research related to long-term growth is unclear. In a cohort study, negative association between maternal PFOS and PFOA concentration and children's weight was only noted until infancy (age of one year) but not in later childhood (age of 7 years) (Andersen et al., 2010; Anderson et al., 2013). Furthermore, British girls with higher prenatal exposure to PFOS were found to be smaller at birth but larger at 20 months-old (Maisonet et al., 2012). A positive association between in utero PFOA exposure and the prevalence of overweight at 20 years of age was reported (Halldorsson et al., 2012). More studies are warranted to exam the hypothesis that early life exposure to certain endocrine disruptors, even at low concentrations, may leads to growth restriction at birth but obesity in later adulthood.

Our previous study, based on Taiwan Birth Panel Study (TBPS), had showed that PFOS levels in cord blood plasma are negatively associated with gestational age, birth weight, preterm birth, and small for gestational age (Chen et al., 2012). Thus, we further collected the growth indicators of participants until 9 years of age, before the onset of puberty, to explore the long-term growth effect of in utero PFASs exposure.

2. Methods

2.1. Study population

The study subjects were from the Taiwan Birth Panel Study (TBPS) (Hsieh et al., 2011), a longitudinal birth cohort study that was conducted at one medical center in Taipei and one local hospital and two clinics in New Taipei from April 2004 to January 2005. Mothers were interviewed by trained interviewers using a structured prenatal questionnaire during the postpartum hospital stay. Cord blood was collected at birth and stored at −80 °C until required for laboratory analysis. At birth, 429 mother-infant pairs with complete records of birth weight, and mother had reported as non-smoker constituted the study cohort. These children were followed with health examination and standardized questionnaires at age of 4, 6, 12, 24, 60, 84 and 108 months. These children are all classified as prepuberty according to the Tanner stages examined at 108 months of age.

The Institutional Review Board of National Taiwan University Hospital approved the study, and informed consent was obtained from the parents prior to enrollment in the study and at each step of follow-up.

2.2. Exposure assessment

We analyzed plasma samples of cord blood for PFOA and PFOS using a Waters ACQUITY UPLC system (Waters Corporation, Milford, MA, USA) coupled with a Waters Quattro Premier XE triple quadrupole mass spectrometer. The detail of the analytic method was described elsewhere (Lien et al., 2011). All laboratory analyses were conducted by investigators who were unaware of the characteristics of the study subjects. The detection rates of PFOA and PFOS were 82% and 100%, and their limits of quantitation (LOQ) were 1.58 and 0.22 ng/mL, respectively. For PFOA levels less than the limit of detection, we assigned values equal to one-half of the quantitation limit.

2.3. Outcome variables

The child growth indicators examined in this study included body weight (kilograms), body length/height (centimeters), and body mass index. The body mass index (BMI) was calculated as the body weight divided by the height squared.

Data at birth were extracted from medical records which were measured by trained nurses. All of the other growth data were obtained from face to face interviews at 4, 6, 12, 24, 60, 84 and 108 months and the Child Healthcare Handbooks. The Child Healthcare Handbooks was published and designed by the Health Promotion Administration, Ministry of Health and Welfare of Taiwan to record information on child-rearing, vaccinations, and health check-ups. In total 9 times of free health examination were provided for each children: four times from birth to 1 year of age, twice between 1 and 2 years of age, once between 2 and 3, 3 and 4, 4 and 7 years of age, respectively. The body weight and length/height weight of the child will be measured and recorded at each visit.

The age-specific z-scores for weight (WAZ), length/height (LAZ/HAZ), BMI (BMIAZ) were calculated by World Health Organization (WHO) Anthroplus software (http://www.who.int/growthref/tools/en/). The outliers were excluded in the analysis following the instruction of the WHO.

2.4. Potential confounders

The levels of cotinine in umbilical cord blood were measured to represent in utero environmental tobacco smoke (ETS) exposure (Hsieh