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Prenatal di(2-ethylhexyl) phthalate exposure and disruption of adrenal androgens and glucocorticoids levels in cord blood: The Hokkaido Study

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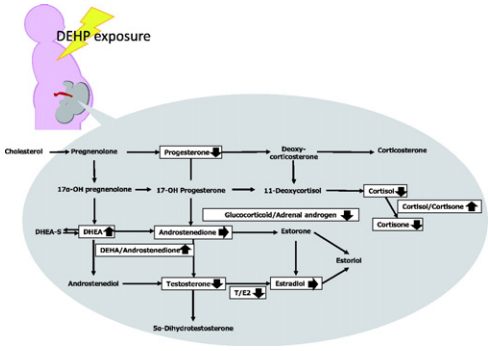
HIGHLIGHTS

- Epidemiological studies of DEHP exposure on adrenal androgen and glucocorticoid disruption are limited.
- Associations between maternal blood MEHP level and fetal adrenal androgen and glucocorticoids in cord blood were examined.
- Prenatal DEHP exposure was associated with changes in adrenal androgen and glucocorticoid levels at birth.
- Even relatively low level of DEHP that humans are exposed has altered steroid hormone profiles of fetus at birth.

GRAPHICAL ABSTRACT



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ABSTRACT

Di(2-ethylhexyl) phthalate (DEHP) is known for its endocrine disrupting properties. We previously demonstrated that prenatal DEHP exposure is associated with decreased progesterone levels and testosterone/estradiol ratio in the cord blood. However, evidence of the effects of prenatal DEHP exposure on adrenal androgen and glucocorticoids in infants is scarce. Thus, the objectives of this study were to investigate the association between prenatal DEHP exposure and adrenal androgen and glucocorticoids, and to discuss its effects on steroid hormone profiles in infants. This is part of a birth cohort study: The Hokkaido Study on Environment and Children's Health,

Abbreviations: CI, confidence interval; CYP11A1, cytochrome P450 family 11 subfamily A member 1; CYP11B1, cytochrome P450 family 11 subfamily B member 1; CYP17A1, cytochrome P450 family 17 subfamily A member 1; CYP19A1, cytochrome P450 family 19 subfamily A member 1; CYP21A2, cytochrome P450 family 21 subfamily A member 2; CV, coefficient of variation; DBP, dibuthyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; HSD11B2, hydroxysteroid 11-beta dehydrogenase 2; HSD17B1, hydroxysteroid 17-beta dehydrogenase 1; HSD3B1, hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1; IQR, interquartile range; LSM, least square means; MEHP, mono(2-ethylhexyl) phthalate; PFOS, perfluorooctane sulfonate; MBP, Monobutyl phthalate; PPAR, peroxisome proliferator-activated receptor; SULT2A1, DHEA sulfotransferase family 2A member 1; T/E2, testosterone/estradiol.

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Adrenal androgen
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Prenatal exposure
Fetal blood

Sapporo Cohort. Among the 514 participants, 202 mother-infant pairs with available data on maternal mono(2-ethylhexyl) phthalate (MEHP), adrenal androgen (dehydroepiandrostenedione [DHEA] and androstenedione) and glucocorticoid (cortisol and cortisone) cord blood levels were included in this study. After adjusting for potential confounders, a linear regression analysis showed that maternal MEHP levels were associated with reduced cortisol and cortisone levels and glucocorticoid/adrenal androgen ratio, whereas increased DHEA levels and DHEA/androstenedione ratio. In a quartile model, when comparing the adjusted least square means in the 4th quartile of MEHP with those in the 1st quartile, cortisol and cortisone levels and glucocorticoid/adrenal androgen ratio decreased, whereas DHEA/androstenedione and cortisol/cortisone ratios increased. Significant *p*-value trends for cortisol and cortisone levels, cortisol/cortisone ratio, and glucocorticoid/adrenal androgen ratio were observed. In combination with the previous results of reduced progesterone levels and testosterone/estradiol ratio, prenatal exposure to DEHP altered the steroid hormone profiles of infants. Further studies investigating the long-term effects of DEHP exposure on growth, neurodevelopment, and gonad and reproductive function are required.

1. Introduction

Phthalate diesters (phthalates) have been used as plasticizers for various plastic products, including toys, food containers, furniture, personal care products, medical devices, and housing materials. According to a report from the Japan Plasticizer Industry Association and Ministry of Economy, Trade and Industry in 2012, di(2-ethylhexyl) phthalate (DEHP) constitutes >50% of the phthalates used in production in Japan. Phthalates are not chemically bonded to polyvinyl chloride in plastic products; thus, they can leach into the air, dust, foodstuffs, and other materials. Consequently, humans are constantly exposed to phthalates, and biomonitoring studies have demonstrated the widespread exposure of the general population to these chemicals (Ait Bamai et al., 2015; Fromme et al., 2007; Jensen et al., 2015; Koch et al., 2004; Wittassek et al., 2007).

DEHP is a potential endocrine-disrupting chemical, and multiple adverse effects on human health due to DEHP exposure in early life were found. Phthalate exposure has been reported to shorten the anogenital distance of infants (Bornehag et al., 2015; Swan et al., 2005; Swan et al., 2015). The associations between phthalates exposure and neurodevelopment and childhood obesity were also investigated (Ejaredar et al., 2015; Kim and Park, 2014). The underlying mechanisms of their effects were not clearly understood; however, disruption of steroidogenesis could be one of the contributing factors because steroid hormones play an important role in homeostasis. Sex steroid hormones including testosterone, progesterone, and estradiol, have effects predominantly in the gonads; and dehydroepiandrosterone (DHEA) and androstenedione, which are weak adrenal steroid precursors, are activated to form androgens and estrogens that have important roles in sex differentiation and maturation (Labrie et al., 2001). Glucocorticoids, including cortisol, and cortisone are synthesized within the adrenal cortex, and are involved in a wide range of physiological processes. Glucocorticoids are essential for regulating and/or modulating homeostasis in metabolism, growth, neurodevelopment, and the immune system (Braun et al., 2013; Reynolds, 2010). As a whole, steroid hormones in early life play important roles in reproductive growth and neurodevelopment for later life (Hollier et al., 2014; Quinn et al., 2016).

In previous experimental studies in rat, Chinese rare minnow, and zebrafish, DEHP and/or its primary metabolite, mono (2-ethylhexyl) phthalate (MEHP), were reported to upregulate and/or downregulate several enzymes in the steroidogenesis pathway (Akingbemi et al., 2001; Akingbemi et al., 2004; Lehmann et al., 2004; Sekaran and Jagadeesan, 2015; Thompson et al., 2005; Zhu et al., 2016a; Zhu et al., 2016b). Exposure to DEHP could modify steroidogenesis and disrupt both hypothalamic-pituitary-gonad and hypothalamic-pituitary-adrenal axes. One animal study demonstrates that dibythol phthalate initiated a rapid and dynamic change in gene expression unique to the fetal testis while in the adrenal was unaffected (Thompson et al., 2005). However, there are fundamental regulation differences of steroidogenesis in the fetal testis between rodent and human (Scott et al., 2009). In addition to species differences, exposure timing, duration, and dosage variations between studies are not relevant for the human exposure scenario. Thus, results from animal studies are limited in predicting the impact of phthalates exposure on adrenal steroid production in human.

Despite the importance of DEHP properties on steroidogenesis, epidemiological studies on DEHP exposure, especially during early life, and its effects on adrenal androgen and glucocorticoid modulation are limited. In birth cohort studies in Mexico, the DHEA sulfate (DHEA-S) levels were increased and decreased following prenatal phthalate exposure in pubescent boys and girls, respectively (Ferguson et al., 2014; Watkins et al., 2014). In a Danish cohort, urinary phthalate metabolites in children were measured every 6 months from the baseline (aged 5.9 years) to pubertal age; girls with levels of monobutyl phthalate (MBP) and DEHP metabolites that were above the geometric group mean had lower levels of DHEA-S and androstenedione, whereas boys with higher MBP levels had lower DHEA-S levels (Mouritsen et al., 2013). Currently, only one study has investigated the effects of phthalate exposure on androstenedione and glucocorticoid levels in amniotic fluid, and the authors did not identify a significant association between phthalate and steroid hormone levels, including glucocorticoids (Jensen et al., 2015).

We recently demonstrated that prenatal DEHP exposure resulted in reduced progesterone levels and a reduced testosterone/estradiol (T/E2) ratio in cord blood (Araki et al., 2014). The aims of this study were to examine the effects of prenatal DEHP exposure on adrenal androgens (DHEA and androstenedione) and glucocorticoids (cortisol and cortisone), and to discuss its effects on the steroid hormone profile of infants, including adrenal androgens and glucocorticoids, and sex hormones (progesterone, testosterone, and estradiol) as reported by Araki et al. (2014).

2. Methods

2.1. Participants

This study was based on the Sapporo Cohort of the Hokkaido Study on Environment and Children's Health. Details of this study, regarding the population, data collection, sampling of the biological specimens, and contents of the questionnaire, have been previously described (Kishi et al., 2013; Kishi et al., 2011). Briefly, native Japanese women at an obstetrics and gynecology hospital in Sapporo (Hokkaido, Japan), who lived in Sapporo City or surrounding areas, were enrolled in the study at 23–35 weeks of gestation between July 2002 and October 2005. Among the 1796 pregnant women approached, 25% were excluded as they were enrolled in the Japanese Cord Blood Bank or planned to deliver the baby at another hospital. Eventually, 514 pregnant women