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Prenatal exposure to glycol ethers and sex steroid hormones at birth

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ABSTRACT

Background: Glycol ethers (GEs) are oxygenated solvents widely found in occupational and consumer water-based products. Some of them are well-known reproductive and developmental toxicants.
Objectives: To study the variations in circulating sex steroid hormones, measured in cord blood, according to biomarkers of prenatal GE exposure.
Methods: The study population comes from the PELAGIE mother–child cohort, which enrolled pregnant women from Brittany (France, 2002–2006). Maternal urine samples were collected from a random subcohort (n = 338) before 19 weeks' gestation, from which we measured 8 alkoxycarboxylic metabolites of GEs. We subsequently measured 13 sex steroid hormones and sex hormone-binding globulin (SHBG) in cord blood samples. Linear regressions adjusted for potential confounders were used, and nonlinear dose-response associations were investigated.
Results: The detection rates of GE metabolites ranged from 4% to 98%; only the 5 most detected (> 20%) metabolites were investigated further. Phenoxyacetic acid (detection rate > 95%) was associated with lower levels of SHBG and various steroids (17-alpha-hydroxy-Pregnenolone, delta-5-androstenediol, and dehydroepiandrosterone) among boys and higher SHBG and 16-alpha-hydroxy-dehydroepiandrosterone levels among girls. The two other highly detected metabolites, methoxyetoxyacetic acid and butoxyacetic acid, were associated with variations in estradiol. Butoxyacetic acid was associated with higher delta-5-androstenediol levels while detectable levels of methoxyacetic acid were associated with lower levels of this hormone.
Conclusion: Our study suggests that prenatal exposure to GE may affect endocrine response patterns, estimated by determining blood levels of sex steroid hormones in newborns. These results raise questions about the potential role of these changes in the pathways between prenatal GE exposure and previously reported adverse developmental outcomes, including impaired neurocognitive performance.

1. Introduction

Glycol ethers (GEs) are oxygenated solvents. Their low volatility and high miscibility in water and oil have led to their wide use in occupational and domestic products, such as water-based paints, cleaning agents, cosmetics, and drugs. There are > 30 different GEs, derived

Abbreviations: 1PG2ME, 2-Methoxypropanol; 2-MPA, 2-methoxyproprionic acid; 16-DHEA, 16-hydroxy-DHEA; 17-Preg, 17-hydroxy-pregnenolone; 17-Pro, 17-hydroxy-progesterone; BAA, 2-butoxyacetic acid; D4, Androstenedione; D5, Androstenediol; DEGDME, diethylene glycol dimethyl ether; DEGME, diethylene glycol methylether; DHEA, Dehydroepiandrosterone; DHT, Dihydrotestosterone; E1, Estrone; E2, Estradiol; EAA, Ethoxyacetic acid; EEAA, Ethoxyethoxyacetic acid; EGBE, ethylene glycol butylether; EGDEE, Ethylene glycol diethylether; EGDME, Ethylene glycol dimethylether; EGEE, Ethylene glycol ethylether; EGME, Ethylene glycol methyl ether; EGPhE, Ethylene glycol phenyl ether; fT, Free testosterone; GE, Glycol ether; HCl, Hydrochloric acid; HNO_3, Nitric acid; LOD, Limit of detection; MAA, Methoxyacetic acid; MEAA, Methoxyethoxyacetic acid; PAA, n-propoxyacetic acid; PGME, Propylene glycol methyl ether; PhAA, Phenoxyacetic acid; Preg, Pregnenolone; Pro, Progesterone; SHBG, Sex hormone binding protein; T, Testosterone; TEGDME, Triethylene glycol dimethylether; TEGME, Triethylene glycol methylether; WG, Week of gestation

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from ethylene glycol (E series) or propylene glycol (P series). GEs of the E series and minor isomers of GEs of the P series containing a primary alcohol function are rapidly metabolized into alkoxycarboxylic acids, which are thought to be responsible for reproductive and developmental toxicity. Alkoxycarboxylic acids are eliminated by urine and used as biomarkers of exposure (Labat et al., 2008). Animal studies have shown that several GEs have pronounced adverse effects on sperm production and fetal development (Inserm, 1999, 2006; Multigner et al., 2005). In humans, exposure to GEs has been associated with longer time to pregnancy, higher risk of spontaneous abortion and birth defects, lower semen quality, and menstrual cycle disorders (Chen et al., 2002; Eskenazi et al., 1995; Garlantézec et al., 2013; Hsieh et al., 2005; Multigner et al., 2007; Ratcliffe et al., 1989; Samuels et al., 1995; Veulemans et al., 1993; Welch et al., 1988).

At the cellular level, GE toxicity appears to be associated with interference with energy-releasing pathways, DNA synthesis, chromatin condensation, and apoptosis (Dayan and Hales 2014; Inserm, 1999, 2006; Wade et al. 2008). Additional studies have revealed that GE toxicity may be explained by an original mode of endocrine disruption through hormone sensitization. GEs, notably ethylene glycol phenyl ether (EGPhE) and the GE metabolite methoxyacetic acid (MAA), derived mainly from ethylene glycol methyl ether (EGME), do not compete with steroid hormones for binding to nuclear receptors and do not elicit genomic response (Jansen et al., 2004; Morohoshi et al., 2005). As reported for MAA, however, they do dramatically enhance the natural ligand-mediated transcriptional effect of nuclear receptors, including α and β estrogen, progesterone, and androgen receptors (Jansen et al., 2004).

We recently showed that prenatal exposure to GEs, in particular to EGPhE, is associated with impaired neurocognitive abilities in 6-year-old children (Beranger et al., 2016). Fetal development, especially that of the brain, takes place under the influence of an ever-changing hormonal milieu that includes endogenous fetal gonadal and adrenal hormones, placental and maternal hormones, and exogenous substances with hormonal activity that can cross the placental barrier (Gore et al., 2014). Moreover, because pregnancy is accompanied by dramatic increases in estrogen and progesterone, environmental chemicals acting as hormone sensitizers may promote adverse developmental outcomes (Tabb & Blumberg, 2006).

Although animal and human studies have reported reproductive and developmental toxicity associated with some GEs, less is known about circulating levels of sex steroid hormones, which nonetheless play a central role in reproductive function and during the developmental period of life. To our knowledge, no previous work has studied the relation between in utero *exposure* to hormone sensitizers such as GEs and hormone levels in cord blood. We therefore consider our work to be an exploratory study aimed at studying the association between GE exposure during pregnancy, measured by urinary biomarkers, and circulating levels of sex steroid hormones in cord blood of newborns enrolled in a prospective mother-child cohort.

2. Material and methods

2.1. Study population

The study population comes from the PELAGIE mother-child cohort, which enrolled 3421 pregnant women from 3 districts of Brittany (northwestern France) between 2002 and 2006. Women were recruited before 19 weeks of gestation (WG) by gynecologists, obstetricians, or ultrasonographers at visits for prenatal care and were followed up through the end of pregnancy. They were asked to complete a questionnaire at home about sociodemographic characteristics, lifestyle, and reproductive history. They sent the completed questionnaire to our laboratory, together with a first-morning-void urine sample in a 10-mL test tube (95 × 16 mm polypropylene, with wing plug) including a stabilizer (hydrochloric acid [HCl] or nitric acid [HNO3]). On arrival at the laboratory, the urine samples were frozen at −20 °C. At birth, staff pediatricians of the maternity wards completed forms reporting medical data about the pregnancy and the newborn's health (n = 3399 [99%]). A cord blood sample was collected from 2138 (62%) women and immediately centrifuged before storage at −20 °C in our laboratory.

For cost reasons, a random sample of 609 (18%) births was selected from the entire cohort (n = 3421) for GE measurements from the maternal urine samples. Among them, cord blood samples were available for 361 (59%). In addition, we excluded newborns from multiple pregnancies (n = 3) or with a major congenital anomaly (n = 6) or gestational age < 35 weeks (n = 2) and thus had a final study population of n = 350 newborns (Appendix Fig. A.1).

2.2. Ethics approval

All participants provided informed written consent and the appropriate ethics committees approved the study (ethics board for human participation in research study on health, CCTIRS and the national commission on informatics and liberty, CNIL).

2.3. Exposure assessment

GE urinary alkoxycarboxylic metabolites were measured by gas chromatography coupled to mass spectrometry, and detection was performed in negative ionization mode with methane in full-scan acquisition between 85 and 152 m/z at the Toxicology and Genopathy Laboratory at the CHRU (Centre Hospitalier Regional Universitaire) of Lille. The GE metabolites simultaneously analyzed were 8 alkoxycarboxylic metabolites related to the GEs used most often in Europe at the time of urine collection: MAA, mainly derived from EGME; methoxyethoxyacetic acid (MEAA), mainly derived from di and tri-ethylene glycol methyl ethers (DEGME and TEGME, respectively); ethoxyacetic acid (EAA), mainly derived from ethylene glycol ethyl ether (EGME); ethoxyethoxyacetic acid (EEAA), mainly derived from di and tri-ethylene glycol ethyl ethers (DEGEE and TEGEE, respectively); butoxyacetic acid (BAA), mainly derived from ethylene glycol butyl ether (EGBE); phenoxyacetic acid (PhAA), derived from EGPhE; n-propoxyacetic acid (PAA), derived from ethylene glycol n-propyl ether (EGnPE); and methoxy propionic acid (MPA), derived from the minor beta isomer of propylene glycol methyl ether (PGME). The method is linear (r^2 = 0.99) from 0.05 to 2.0 mg/L for all of the alkoxycarboxylic acids, yields coefficients of variation < 10% at 0.10 mg/L, and had a limit of detection (LOD) of 0.05 mg/L (Labat et al., 2008). We explored whether GE metabolite levels were affected by sampling characteristics including creatinine level (continuous), gestational age at sampling (continuous), transportation time at room temperature (0, 1, or at least 2 days), duration of storage at −20 °C (continuous), and the type of stabilizer (HCl or HNO_3). Because the BAA detection rate decreased with the number of days at room temperature when HCl was used as stabilizer (Cordier et al., 2012), we excluded the samples so stabilized when studying this metabolite.

2.4. Hormone measurements

Cord blood assays took place at the Mondor Biomedical Research Institute (IMRB, Inserm U955 – University Paris Est Créteil, UPEC, France). Twelve sex steroid hormones were measured by gas chromatography coupled to mass spectrometry after extraction and derivatization as described by Giton et al. (Giton et al., 2015): delta-4-androstenedione (D4), delta-5-androstenediol (D5), dehydroepiandrosterone (DHEA), 16-alpha-hydroxy-DHEA (16-DHEA), dihydrotestoterone (DHT), estrone (E1), estradiol (E2), pregnenolone (Preg), 17-alpha-hydroxy-pregnenolone (17-Preg), progesterone (Pro), 17-alpha-hydroxy progesterone (17-Pro), and total testosterone (T). In addition, sex-hormone binding protein (SHBG) was measured by an

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