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Prenatal exposure to endocrine disrupting chemicals and risk of being born small for gestational age: Pooled analysis of seven European birth cohorts

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ABSTRACT

Background and aims: There is evidence that endocrine disrupting chemicals (EDCs) have developmental effects at environmental concentrations. We investigated whether some EDCs are associated with the adverse birth outcome Small for Gestational Age (SGA).

Methods: We used PCB 153, *p,p'*-DDE, HCB, PFOS and PFOA measured in maternal, cord blood or breast milk samples of 5446 mother-child pairs (subset of 693 for the perfluorinated compounds) from seven European birth cohorts (1997–2012). SGA infants were those with birth weight below the 10th percentile for the norms defined by gestational age, country and infant's sex. We modelled the association between measured or estimated cord serum EDC concentrations and SGA using multiple logistic regression analyses. We explored effect modification by child's sex and maternal smoking during pregnancy.

Results: Among the 5446 newborns, 570 (10.5%) were SGA. An interquartile range (IQR) increase in PCB 153 was associated with a modestly increased risk of SGA (odds ratio (OR) of 1.05 [95% CI: 1.04–1.07]) that was stronger in girls (OR of 1.09 [95% CI: 1.04–1.14]) than in boys (OR of 1.03 [95% CI: 1.03–1.04]) (*p*-interaction = 0.025). For HCB, we found a modestly increased odds of SGA in girls (OR of 1.04 [95% CI: 1.01–1.07] per IQR increase), and an inverse association in boys (OR of 0.90 [95% CI: 0.85–0.95]) (*p*-interaction = 0.0003). Assessment of the HCB-sex-smoking interaction suggested that the increased odds of SGA associated with HCB exposure was only in girls of smoking mothers (OR of 1.18 [95% CI: 1.11–1.25]) (*p*-interaction = 0.055). Higher concentrations of PFOA were associated with greater risk of SGA (OR of 1.64 [95% CI: 0.97–2.76]). Elevated

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PFOS levels were associated with increased odds of SGA in newborns of mothers who smoked during pregnancy (OR of 1.63 [95% CI: 1.02–2.59]), while an inverse association was found in those of non-smoking mothers (OR of 0.66 [95% CI: 0.61–0.72]) (*p*-interaction = 0.0004). No significant associations were found for *p,p'*-DDE.
Conclusions: Prenatal environmental exposure to organochlorine and perfluorinated compounds with endocrine disrupting properties may contribute to the prevalence of SGA. We found indication of effect modification by child's sex and smoking during pregnancy. The direction of the associations differed by chemical and these effect modifiers, suggesting diverse mechanisms of action and biological pathways.

1. Introduction

A suboptimal intra-uterine environment can affect fetal growth and contribute to the risk of developing adult diseases (Barker, 1998). The fetus depends on an accurate hormone balance for its development (Diamanti-Kandarakis et al., 2009). Concern has risen since several endocrine disrupting chemicals (EDCs), particularly those with estrogenic activity, are suspected of disrupting the programming of endocrine signaling pathways during development (Newbold, 2011). Maternal exposure to EDCs has been associated with fetal growth (de Cock and van de Bor, 2014; Tang-Peronard et al., 2011). During gestation, fetuses are exposed to the accumulated maternal body burden of persistent organic pollutants with endocrine properties, including: polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (*p,p'*-DDE), hexachlorobenzene (HCB), perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). Despite regulatory measures and due to their long half-lives, these compounds are still ubiquitous in the environment and detected in a variety of human tissues and fluids (Malisch and Kotz, 2014). The human elimination half-lives of PCB 153, *p,p'*-DDE, HCB, PFOS and PFOA are > 10 years (Ritter et al., 2011), ~5 years (Ferreira et al., 2011), ~6 years (To-Figueras et al., 2000), ~5 years (Olsen et al., 2007), and 3.5 years (Olsen et al., 2007), respectively. Due to their high lipophilicity (organochlorine compounds) or amphoteric properties (perfluorinated compounds) these compounds are transported via the placenta to the fetus and can also reach the infant through maternal milk (Stefanidou et al., 2009; WHO/UNEP, 2013).

Up to date, most epidemiological studies have investigated associations between EDCs and birth weight or other continuous measures like birth length, head circumference, gestational age, and most of them reported significant inverse associations, i.e. lower birth weight, birth length and head circumference for increased EDC concentrations, including HCB (Eggesbo et al., 2009), PCBs (Govarts et al., 2012) and perfluorinated compounds (Bach et al., 2015; Johnson et al., 2014). However, there is much variation in studies reporting on these associations with several studies observing no significant association (Berkowitz et al., 1996; Gladen et al., 2003; Khanjani and Sim, 2006; Longnecker et al., 2005; Wolff et al., 2007). Moreover, although birth weight is accurately measured, its interpretation is not always obvious (EURO-PERISTAT, 2013). Investigating infants born small for gestational age (SGA) has advantages since it is a clinical outcome, and therefore has clear implications for public health (Lee et al., 2013). Only a few studies, have looked at the association of EDCs and SGA (Basterrechea et al., 2014; Eggesbo et al., 2009; Lauritzen et al., 2017; Longnecker et al., 2005; Manzano-Salgado et al., 2017). Longnecker et al. (Longnecker et al., 2005) found a significant positive association of PCBs with SGA while no significant association was found for birth weight. The HUMIS cohort found a positive association close to significance of HCB with SGA (Eggesbo et al., 2009), while Basterrechea et al. (Basterrechea et al., 2014) found no significant association for HCB. In a recent Scandinavian study, prenatal exposure to PFOA, PCB 153 and HCB were significantly associated with higher odds for SGA (Lauritzen et al., 2017). Manzano-Salgado et al. (Manzano-Salgado et al., 2017) found no significant associations between some perfluorinated compounds and SGA, whereas PFOS exposure was associated with low birth weight in boys.

In the present study, we harmonized and pooled data from seven European birth cohorts with organochlorine measures and four of them with measures of the perfluorinated compounds, providing a large study sample to investigate the association between the selected EDCs and SGA. This allowed us to examine the hypothesis that EDCs influence fetal growth.

2. Methods

2.1. Description of cohorts

Within the EU-FP7 OBELIX project, five European birth cohorts were available for our pooled analysis: FLEHS I and II (FLemish Environment and Health Study), HUMIS (HUman Milk Study), LINC (LInking EDCs in maternal Nutrition to Child health) and PCB cohort of Flanders, Norway, The Netherlands and Slovakia respectively. We invited two additional cohorts, INMA (INfancia y Medio Ambiente; Environment and Childhood) (Spain) and PELAGIE (Endocrine disruptors: longitudinal study on pathologies of pregnancy, infertility and childhood) (France), resulting in seven European birth cohorts. Cohort participants were sampled from the general population and included births from 1997 to 2012. The INMA cohort was considered as two populations based upon the matrix (one available per child) used for the EDC measurements (maternal or cord serum). This makes a total of 8 study populations. Our study population sample was restricted to live-born singleton births, with available exposure levels and information on at least one birth outcome. In total, we used EDC measurements from 5446 women. Table 1 lists cohort characteristics, while Supplemental Material, Table S1 contains cohorts' descriptions and references. Each cohort study was approved by the national ethical committee. Mothers provided written informed consent prior to participation.

2.2. Exposure assessment

All cohorts provided concentrations from the selected exposure markers if available. PCB 153 was selected as a marker of overall exposure to PCBs (used in many industrial applications), since it is the most abundant congener (Hagmar et al., 2006) and highly correlated with most of the congeners, *p,p'*-DDE because it is the most persistent metabolite of the widely used insecticide DDT (Agency for Toxic Substances and Disease Registry (ATSDR), 2002), and HCB, another organochlorine pesticide widely used as fungicide. PFOS and PFOA were included as markers for exposure to the perfluorinated compounds which are used as fluorosurfactants in consumer products such as teflon, stain-resisting fabrics and fire-fighting foams. Information on chemical-analytical methods and their limits of detection/quantification (LODs/LOQs) together with the lipid analysis method of the sampled matrices is given in the Supplemental Material, p.6–7 and Table S2. Concentrations below the LOD/LOQ were replaced with LOD/LOQ divided by $\sqrt{2}$ (Hornung and Reed, 1990). Cohorts with ≥50% of samples below the LOD/LOQ for an exposure biomarker were excluded from the analysis of that exposure biomarker.

Since cord serum levels are considered the best proxy of organochlorine exposure during fetal life (Korrick et al., 2000), we estimated the equivalent concentrations in cord serum from the concentrations measured in maternal serum or breast milk.