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Prenatal exposure to persistent organic pollutants and organophosphate pesticides, and markers of glucose metabolism at birth

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ABSTRACT

Background: Experimental evidence suggests that developmental exposure to persistent organic pollutants (POP) and to some non persistent pesticides may disrupt metabolic regulation of glucose metabolism and insulin secretion, and thereby contribute to the current epidemic of obesity and metabolic disorders. Quasi-experimental situations of undernutrition in utero have provided some information. However, the evidence in humans concerning the role of the prenatal environment in these disorders is contradictory, and little is known about long-term outcomes, such as type 2 diabetes, of prenatal exposure.

Objectives: Our aim was to evaluate the effects of prenatal exposure to POP and organophosphate pesticides on fetal markers of glucose metabolism in a sample of newborns from the Pelagie mother–child cohort in Brittany (France).

Methods: Dialkylphosphate (DAP) metabolites of organophosphate pesticides were measured in maternal urine collected at the beginning of pregnancy. Cord blood was assayed for polychlorinated biphenyl congener 153 (PCB153), p,p′-dichlorodiphenyl dichloroethene (DDE) and other POP. Insulin and adiponectin were determined in cord blood serum ($n=268$).

Results: A decrease in adiponectin and insulin levels was observed with increasing levels of DDE, but only in girls and not boys. Adiponectin levels were not related to the concentrations of other POP or DAP metabolites. Decreasing insulin levels were observed with increasing PCB153 concentrations. Insulin levels increased with DAP urinary levels. Additional adjustment for BMI *z*-score at birth modified some of these relations.

Abbreviations: BMI, body mass index; DAP, dialkylphosphate; DE, diethylphosphate metabolites; DEP, diethylphosphate; DETP, diethylthiophosphate; DEDTP, diethyldithiophosphate; DM, dimethylphosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate; DMDTP, dimethyldithiophosphate; DDE, dichlorodiphenyl dichloroethylene; DDT, dichlorodiphenyl trichloroethane; FC, free cholesterol; HCB, hexachlorobenzene; βHCH, beta-hexachlorocyclohexane; LOD, limit of detection; LOQ, limit of quantification; OP, organophosphate pesticides; PCB, polychlorinated biphenyls; PL, phospholipid; PON1, paraoxonase 1; POP, persistent organic pollutants; TC, total cholesterol; T2D, type 2 diabetes; TG, triglyceride

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Conclusions: Our observations bring support for a potential role of organophosphate pesticides and POP in alterations to glucose metabolism observable at birth.

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1. Introduction

The prevalence of obesity has increased steadily worldwide, including in France where its prevalence among adults in 2012 was 15% (Eschwege et al., 2015). The involvement of the perinatal environment in the pathogenesis of obesity and diabetes has been demonstrated by follow-up of the Dutch Hunger Winter: individuals who suffered undernutrition in utero and were subsequently born with a low birth weight were around six times more likely to develop type 2 diabetes (T2D) by age 64 than individuals with the highest birth weight (Bouret et al., 2015).

There is growing experimental evidence for a role of so-called "environmental obesogens" in this epidemic, especially when exposure occurs during developmental period. Maternal smoking has been implicated, and perinatal exposure to persistent organic pollutants (POP), phthalates, metals, pesticides, or chemicals with estrogenic or endocrine-disrupting properties may induce abnormalities in the metabolic regulation of glucose metabolism, insulin secretion and lipogenesis; these environmental exposures may thereby contribute to the increasing prevalence of metabolic disorders (Heindel and Vom Saal 2009; La Merrill and Birnbaum, 2011; Thayer et al., 2012; de Cock and van de Bor, 2014).

Not all these environmental exposures have been the object of studies in humans. In a large meta-analysis of low-level prenatal exposure to POP among 12 European birth cohorts, exposure to polychlorinated biphenyl congener 153 (PCB153) was found to be linearly associated with lower birth weight, whereas no association was found with *p,p′*-dichlorodiphenyl dichloroethene (DDE), the main metabolite of dichlorodiphenyl trichloroethane (DDT) (Govarts et al., 2012; Casas et al., 2015). Recent reviews of studies investigating the consequences of such exposure on child growth have had difficulties in identifying even the general direction of the associations (de Cock and van de Bor, 2014; Tang-Péronard et al., 2011). The recent pooled analysis of infant growth in seven European cohorts concluded that prenatal exposure to DDE was associated with increased infant growth (weight-for-age *z*-score) whereas postnatal PCB153 was associated with decreased growth (Iszatt et al., 2015). A US National Toxicology Program Workshop convened in January 2011 evaluated that the evidence was sufficient to conclude that there is an association between the risk of T2D and certain POP, more specifically *trans*-nonachlor, DDT/DDE, dioxins/dioxin-like chemicals, some polychlorinated biphenyls (PCB) and Agent Orange, but not sufficient to establish causality (Thayer et al., 2012; Taylor et al., 2013; Lee et al., 2014). Possible associations were observed for other POP but with fewer relevant studies; no formal meta-analysis has been conducted and most of the studies reviewed were cross-sectional or prospective studies starting at adult ages.

A small number of epidemiological studies have suggested an association between prenatal exposure to organophosphate pesticides (OP) and poor fetal growth outcomes in interaction with maternal or fetal genetic susceptibility (low activity of the paraoxonase PON1 enzyme) (Berkowitz et al., 2004; Wolff et al., 2007; Harley et al., 2011). However, there is still no consensus about the consequences of OP exposure for fetal growth (Mink et al., 2012). No human data is available for child growth, obesity or the risk of T2D following prenatal exposure to OP, although evidence from animal studies suggests that there may be effects (Thayer et al., 2012; Slotkin, 2011).

Longitudinal epidemiological studies of potential links between prenatal exposure to environmental agents and long-term body weight and type 2 diabetes outcomes are logistically difficult. The analysis of the concentration of fetal markers at birth is an alternative approach to assessing the impact of environmental agents on glucose metabolism. High cord insulin levels, related at birth with low gestational age, are associated with the persistence of hyperinsulinemia in early childhood, which is a reliable marker of insulin resistance (Wang et al., 2014).

Adiponectin is produced by adipose tissue and modulates insulin sensitivity and inflammation in adults (Kadowaki and Yamauchi, 2005). In adults (Li et al., 2009), children and adolescents (Cruz et al., 2004; Gilardini et al., 2006; Shaibi et al., 2007), adiponectin concentrations are low in subjects with high body mass index (BMI), metabolic syndrome or type 2 diabetes. A number of studies of healthy newborns have reported positive relationships between cord levels of adiponectin and birth weight or birth length (Sivan et al., 2003; Chan et al., 2004; Kotani et al., 2004; Tsai et al., 2004; Mantzoros et al., 2004), or have found low levels of adiponectin in low birth weight, preterm or small-for-gestational age newborns (Martos-Moreno et al., 2009; Mazaki-Tovi et al., 2011); however, others found no association between adiponectin and birth weight (Lindsay et al., 2003; Bozzola et al., 2010). Adiponectin levels at birth are moderately correlated with values at older ages (Hibino et al., 2009; Volberg et al., 2013). However, little is known about the predictive value of adiponectin levels at birth for obesity-related outcomes at later ages. A positive association has been found between the adiponectin level at birth and central adiposity at age 3 (Mantzoros et al., 2009) or BMI gain from birth to 3 years (Nakano et al., 2012); by contrast, adiponectin at birth has also been found to be inversely associated with weight gain in the first 6 months (Mantzoros et al., 2009), or with BMI and weight gain at one year (Mazaki-Tovi et al., 2011).

Our aim was to determine prenatal exposure to organophosphate pesticides, organochlorine pesticides and PCB by assaying maternal and fetal fluids, and assess the associations with two markers of glucose metabolism at birth. In the absence of a measure of glucose at birth, we selected adiponectin, in addition to insulin, despite the fact that its predictive value at birth for obesity-related outcomes at later ages is not well established. Its concentration is positively correlated with insulin sensitivity (Finucane et al., 2009) and it is considered as a reliable marker of insulin resistance in humans.

This study was based on the mother–child PELAGIE cohort set up in the general population of the Brittany region.

2. Methods

2.1. Population and data collection

The PELAGIE cohort included 3421 pregnant women from Brittany from 2002 to February 2006. Gynecologists, obstetricians, and ultrasonographers recruited women during consultations in early pregnancy (before the 19th week of gestation), and obtained written informed consent. Women completed a questionnaire at home concerning family, social and demographic characteristics, diet, and lifestyle. Women were asked to return the questionnaire by mail, along with a first-morning-void urine sample that they

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