Environmental Research 136 (2015) 27–34

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Maternal blood metal levels and fetal markers of metabolic function ☆

Jillian Ashley-Martin [a], Linda Dodds [a,*], Tye E. Arbuckle [b], Adrienne S. Ettinger [c], Gabriel D. Shapiro [d,e], Mandy Fisher [b], Shayne Taback [f], Maryse F. Bouchard [d], Patricia Monnier [g], Renee Dallaire [h], William D. Fraser [d,e]

[a] Perinatal Epidemiology Research Unit, Dalhousie University, Halifax, Nova Scotia, Canada
[b] Health Canada, Ottawa, Canada
[c] Yale University, New Haven, CT, USA
[d] University of Montreal, Montreal, Quebec, Canada
[e] CHU Sainte-Justine Research Centre, Montreal, Quebec, Canada
[f] University of Manitoba, Winnipeg, Manitoba, Canada
[g] McGill University, Montreal, Quebec, Canada
[h] Laval University, Quebec City, Quebec, Canada

ARTICLE INFO

Article history:
Received 10 September 2014
Received in revised form
15 October 2014
Accepted 17 October 2014
Available online 20 November 2014

Keywords:
Metals
Leptin
Adiponectin
Birth cohort
Cord blood

ABSTRACT

Exposure to metals commonly found in the environment has been hypothesized to be associated with measures of fetal growth but the epidemiological literature is limited. The Maternal–Infant Research on Environmental Chemicals (MIREC) study recruited 2001 women during the first trimester of pregnancy from 10 Canadian sites. Our objective was to assess the association between prenatal exposure to metals (lead, arsenic, cadmium, and mercury) and fetal metabolic function. Average maternal metal concentrations in 1st and 3rd trimester blood samples were used to represent prenatal metals exposure. Leptin and adiponectin were measured in 1363 cord blood samples and served as markers of fetal metabolic function. Polytomous logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between metals and both high ($\geq$90%) and low ($\leq$10%) fetal adiponectin and leptin levels. Leptin levels were significantly higher in female infants compared to males. A significant relationship between maternal blood cadmium and odds of high leptin was observed among males but not females in adjusted models. When adjusting for birth weight *z*-score, lead was associated with an increased odd of high leptin. No other significant associations were found at the top or bottom 10th percentile in either leptin or adiponectin models. This study supports the proposition that maternal levels of cadmium influence cord blood adipokine levels in a sex-dependent manner. Further investigation is required to confirm these findings and to determine how such findings at birth will translate into childhood anthropometric measures.

1. Introduction

Early pregnancy is a critical window of fetal development and exposure to environmental contaminants during this time period may adversely impact the pregnancy as well as neonatal, early childhood, and later life outcomes (Gluckman et al., 2008; Selevan et al., 2000). Previous studies have suggested that prenatal exposure to metals, such as lead, mercury, cadmium, and arsenic, may adversely affect fetal growth (Drouillet-Pinard et al., 2010; Gundacker et al., 2010; Kippler et al., 2012; Lin et al., 2011; Menai et al., 2012; Schell et al., 2009; Xie et al., 2013; Zhu et al., 2010). Maternal exposure to lead, mercury, and arsenic creates direct exposure to the developing fetus as these chemicals can pass through the placenta into fetal circulation (Barr et al., 2007; Klaasen, 2010; Needham et al., 2011). Cadmium, which does not directly enter fetal circulation, can promote potentially adverse effects on the fetus by accumulating in the placenta and altering normal placental processes and function (Barr et al., 2007; Roels et al., 1978). Studies in North American populations have demonstrated that exposure is ubiquitous with the majority of women having detectable concentrations of metals in their blood or urine (Health Canada, 2010; NHANES, 2013). Epidemiologic literature is suggestive of an inverse association between maternal exposure to certain metals, particularly lead, and infant growth (Gonzalez-

☆This study received ethical approval from Health Canada, St. Justine's Hospital (Montreal, QC), and the IWK Health Centre (Halifax, NS). All study participants provided informed consent.

* Correspondence to: Perinatal Epidemiology Research Unit, 7th Floor Women's Site, IWK Health Centre, 5980 University Avenue, PO Box 9700, Halifax, NS, Canada B3H 6R8.
E-mail address: l.dodds@dal.ca (L. Dodds).

http://dx.doi.org/10.1016/j.envres.2014.10.024

Cossio et al., 1997; Schell et al., 2009; Xie et al., 2013; Zhu et al., 2010), but longitudinal analyses in North American populations without relatively high levels of exposure is limited.

Metabolic function can be examined by measuring leptin and adiponectin levels in blood, two hormones produced by adipocytes that play critical roles in metabolic function (Karakosta and Chatzi, 2011; Trujillo and Scherer, 2005; Walsh et al., 2014). Elevated levels of both leptin and adiponectin in umbilical cord blood are correlated with high birth weight and may provide insight on future risk of childhood obesity (Karakosta and Chatzi, 2011; Mantzoros et al., 2009). In adults, elevated leptin levels are associated with increased adipose tissue mass, insulin resistance (Mantzoros et al., 2009), and, in pregnant women having large for gestational age infants (Retnakaran et al., 2012). In contrast, low adiponectin levels in adulthood have been implicated in insulin resistance, type 2 diabetes, and metabolic syndrome (Mazaki-Tovi et al., 2005; Trujillo and Scherer, 2005). Examining the relationship between maternal metal concentrations and biomarkers of fetal metabolic function may provide insight into the susceptibility of fetal metabolic development to exogenous *in utero* exposures. The objectives of the present study were to assess the relationship between maternal blood levels of lead, arsenic, cadmium, and mercury and umbilical cord blood levels of leptin and adiponectin among the cohort of mother–infants pairs enrolled in the Maternal–Infant Research on Environmental Chemicals (MIREC) study.

2. Material and methods

2.1. Study design

Details of the MIREC study have been previously reported (Arbuckle, et al., 2013). Briefly, 2001 women were recruited from 10 Canadian sites during their first trimester and consented to provide urine and blood samples. Women were eligible for inclusion if they were <14 weeks gestation at the time of recruitment, ≥ 18 years of age, able to communicate in French or English, and planning on delivering at a local hospital. Women with known fetal or chromosomal anomalies in the current pregnancy and women with serious medical complications were excluded from the study (Arbuckle et al., 2013). Of the 2001 women recruited into the MIREC study, 18 withdrew and asked that all their data and biospecimens be destroyed. Of the remaining 1983 subjects, 1363 had infants with a cord blood sample. For this analysis, 103 were excluded for: multiple birth, pre-term birth, cord blood samples unsuitable for analysis, missing metal data or unknown infant sex, resulting in an analytical sample size of 1260.

2.2. Metal exposure

Chemical analysis of blood samples were carried out at the Laboratoire de Toxicologie, Institut National de Santé Publique du Québec (INSPQ) (Québec, QC, Canada), accredited by the Standards Council of Canada. Lead, arsenic, mercury, and cadmium were measured in maternal whole blood collected during the 1st and 3rd trimesters using inductively coupled plasma mass spectrometry (PerkinElmer ELAN ICP-MS DRC II). Metal concentrations from the two time points were averaged to create an estimate of gestational exposure. In the case where the value for one time point was missing, the other value was used. All samples below the level of detection (LOD) were imputed as one half the level of detection. We also conducted an analysis to determine whether samples collected in the third trimester would have a different influence on results compared to the first trimester measurements.

2.3. Fetal markers of metabolic function

Leptin and adiponectin were measured in plasma from 1363 stored umbilical cord blood samples by ELISA using kits from Meso Scale Discovery (MSD) (Rockville, MD, USA) at Mt. Sinai Laboratory (Toronto, ON, Canada). Repeated analysis was performed on all samples with a coefficient of variation (CV) greater than 15%. The inter- and intra-assay CVs, respectively, were 11.8% and 9.3% for leptin and 8% and 9% for adiponectin. All samples were above the limit of detection.

2.4. Covariates

Data on covariates were extracted from questionnaires and hospital charts by trained research staff. We examined the following variables as potential confounders: maternal age at delivery (≤ 24, 25–29, 30–34, ≥ 35 years), pre-pregnancy body mass index (BMI) according to WHO guidelines (World Health Organization, 2006), parity (nulliparous, parous), maternal education (high school diploma or less, some college or trade school, undergraduate university degree, graduate university degree), household income ($\leq 30,000, 30,001–50,000, 50,001–100,000, $\geq 100,000$), ethnicity (Caucasian/non-Caucasian), and maternal smoking (never or quit before pregnancy, quit when pregnancy confirmed, current smoker).

2.5. Statistical analysis

Umbilical cord blood levels of leptin and adiponectin were categorized into the 10th and 90th percentiles, as the previous literature has shown that both low and high levels of both of these biomarkers are associated with potentially adverse outcomes (Mantzoros et al., 2009; Trujillo and Scherer, 2005; Walsh et al., 2014). Due to differing leptin levels between male and female infants, the binary leptin variables were derived using sex specific cut-off points: 10th percentile (males 1.8, females 3.5 ng/mL) and 90th percentile (males 31.2, females 54.6 ng/mL). Adiponectin levels did not vary by sex, thus, sex-specific cut-offs were not necessary.

Descriptive statistics for maternal demographics, weight-related characteristics, and pregnancy characteristics were calculated according to levels of leptin and adiponectin using frequency distributions and chi-square tests of significance for the difference between the low ($\leq$ 10%ile), moderate ($>10–<90%$) and elevated ($\geq$ 90%ile) leptin and adiponectin groups.

The geometric means (GM) and standard deviations (SD) of the metals according to the outcome categories of leptin and adiponectin were determined. Separate models were developed for leptin and adiponectin using polytomous regression to examine the odds of both high ($\geq$ 90%) and low ($\leq$ 10%) levels of the markers of metabolic function. Polytomous logistic regression is an extension of simple logistic regression that facilitates analysis of multinomial outcomes (Ananth and Kleinbaum, 1997). The cut-off points in the present study were selected to capture infants with elevated and suppressed adipokine values. But, in recognition of the fact that the choice of these cut-off points was somewhat arbitrary, we conducted a sensitivity analysis to examine the outcome categories at the 25th and 75th percentiles.

Next, metals were categorized in quartiles and, since no metal had more than 25% below the LOD, all levels below LOD were included in the lowest quartile for each metal. Due to the lack of linearity in quartile association estimates, we did not examine the chemical exposures as continuous variables. In the multivariate models, we included variables that were selected *a priori* (maternal age) or significantly associated with the adipokines at a p-value <0.1 in order to facilitate identification of a common set