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Placental concentrations of essential, toxic, and understudied metals and relationships with birth outcomes in Chattanooga, TN

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A R T I C L E I N F O

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A B S T R A C T

Background: Comprehensive examinations of placental metal concentrations and correlations with infant parameters are under-investigated. Chattanooga, Tennessee's consistently high incidence of low birth weight and potential for metal exposure provides an ideal opportunity to investigate potential correlations.
Objectives: To investigate the associations between a wide variety of metals in placental tissue and multiple infant parameters.
Methods: A total of 31 elements were screened via ICP-MS in 374 individual placental samples. Of those, 14 were quantifiable in > 86% of the samples. We examined correlations between metal concentrations and infant parameters (birth weight, gestational age, birth weight centile, placental weight, birth length and head circumference). We fit multivariable regression models to estimate the covariate-adjusted associations of birth weight with ln-transformed concentrations of each of the 14 metals and used generalized additive models to examine nonlinear relationships.
Results: Some of the strongest relationships with infant parameters came from several lesser-studied metals. Placental rhodium concentrations were negatively correlated with almost all infant parameters. In the fully adjusted regression model, birth weight was significantly associated with several metals. On an IQR (25th to the 75th percentile) basis, estimated changes in birthweight were: for cobalt (82.5 g, IQR = 6.05 µg/kg, $p = 0.006$), iron (−51.5 g, IQR = 171800 µg/kg, $p = 0.030$), manganese (−27.2 g, IQR = 152.1 µg/kg, $p = 0.017$), lead (−72.7 g, IQR = 16.55 µg/kg, $p = 0.004$) and rhodium (−1365.5 g, IQR = 0.33 µg/kg, $p < 0.001$). Finally, a generalized additive model showed significant nonlinear relationships between birth weight and concentrations of Co and Rh.
Conclusions: Our comprehensive examination of placental metals illustrate many strong associations between lesser-studied metals and infant parameters. These data, in combination with our correlations of well-studied metals, illustrate a need to consider *in utero* exposure to a broad array of metals when considering fetal development.

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1. Introduction

Singleton, full-term infants are classified as low birth weight (LBW) if weighing less than 2500 g and very low birth weight (VLBW) if weighing less than 1500 g. Birth weight is well known to correlate with infant mortality and myriad adult health indicators. Infants born on the lower end of the normal birth weight range also have an increased risk of adult chronic diseases, such as heart disease and type 2 diabetes (Barker et al., 1989; Yajnik et al., 1995). Hamilton County, TN, has a persistently high LBW rate. According to the Hamilton County Health Department (Fagerstedt et al., 2015), 27 of the 28 zip code areas in Hamilton County have an incidence of LBW infants that is consistently 50% higher than the national average. Race alone does not explain these observations. For example, white Hamilton County (HC) infants are consistently born LBW at a greater incidence than white United States (US) infants; similarly, black HC infants are consistently born LBW at a greater incidence than white or black US infants (Hamilton County Health Department, 2015). While many factors are known to contribute to LBW (e.g., diet, smoking, access to health care, poverty) (Krans and Davis, 2014; Lagiou et al., 2004; Magee et al., 2004; Miller and Korenman, 1994), environmental pollution is another potential causative factor. Indeed, the potential for metal and metalloid intrauterine exposure must be understood for proper mitigation of LBW/VLBW.

Prior to environmental regulations, metal foundry sand was commonly used as fill dirt for Chattanooga area home construction which ultimately resulted in a large portion of Chattanooga residential soils being named a Superfund Site (EPA, 2018). Foundry sand is often contaminated with multiple metals. For example, the EPA conducted a risk assessment of foundry sand from multiple types of metal smelting (Aluminum, Iron, Steel (EPA, 2014)). That risk assessment focused on an array of metals and metalloids: Antimony (Sb), Arsenic (As), Beryllium (Be), Cadmium (Cd), Chromium (Cr), Cobalt (Co), Copper (Cu), Iron (Fe), Lead (Pb), Manganese (Mn) and Nickel (Ni), as these were the most commonly associated with all types of metal smelting. Because Hamilton County has a high incidence of LBW and because the majority resides in Chattanooga among widespread legacy foundry sand, exposure to co-occurring metals needs to be considered as potential contributors to LBW in Hamilton County, TN.

The placenta is a temporary organ that provides for the exchange of nutrients and wastes between fetus and mother. Along with this vital exchange, there is the potential for the passage of deleterious compounds from mother to fetus for intrauterine exposure. As such, placentae can serve as a non-invasive, long-term (gestational length) sample that can be studied for transplacental toxicant transfer (Iyengar and Rapp, 2001). Several studies have addressed these questions of placental transfer by evaluating the ratio of metal concentration between fetal and maternal blood supply. The higher the ratio, the greater the passage of the metal through the placenta. Sakamoto (2010) found Cd had the lowest correlation coefficient of maternal and fetal blood supplies. Other metals measured had increased passage through the placenta (Se < Pb < As), with the greatest correlation between maternal and fetal blood samples being mercury. Similarly, Rudge et al. (2009) saw strong correlations between lead, cobalt, arsenic and selenium between maternal and fetal blood samples, while cadmium, manganese, copper and zinc have a decreased pathway through the placenta, suggesting tighter regulation.

Correlations of placental metal concentrations with birth weight are well documented. Osada (2002) quantified essential elements that are required for proper growth (magnesium (Mg), manganese, iron (Fe), copper (Cu), zinc (Zn), and selenium (Se)) and elements that are non-essential (rubidium (Rb), strontium (Sr), cadmium (Cd), cesium (Cs)) in placenta tissue of 30 appropriate for gestational age (AGA) infants and 21 intrauterine growth restricted (IUGR) infants in Japan. Se and Mg were significantly greater in the AGA infants compared to the IUGR infants. Zadrozna (2009) reported significantly greater placental concentrations of Zn and Cu in normal pregnancies compared to pregnancies complicated by IUGR. Both of these metals also had a significant, positive correlation with birth weight. In the same study however, Se was greater in placenta from IUGR cases compared to a control group. Llanos and Ronco (2009) reported lower birth weight as Cd, Pb, and As concentrations increased in the placenta. Ronco et al. (2009) also found that Cd exposure directly caused reduced birth weight in rats and depressed the transfer of Zn (a beneficial metal) across the placenta. Greater Pb concentrations were reported in placentae from associated with IUGR infants (Llanos and Ronco, 2009). In addition, lead (Pb) has been found to readily pass through the placenta and previous work has shown that cord blood Pb concentrations were negatively correlated with birth weight, length and head circumference (Osman et al., 2000).

Several metals, including rhodium (Rh), barium (Ba), and aluminum (Al) are under reported in placenta tissue. Rh has been detected globally in urban environments, surface water, river sediment, freshwater isopods, well-water and many other environmental matrices (Gómez et al., 2001; Ravindra et al., 2004). To date, there are no published data on Rh in placental tissue. Sharma and Mishra (2006) studied the effects of Al on pregnant rats and showed that oral exposure to Al resulted in uptake to fetal and maternal brain tissues, as well as placental tissues. Subsequently, birth weight, placental weight and fetal growth were all significantly reduced compared to the control group. Al and Ba were detected in amniotic fluid (16–19 weeks gestation), at an average of 93.4 and 22.4 μg/L, respectively (Hall et al., 1983). Ba has also been detected in stillborn babies, which indicates passage through the placental barrier (IPCS, 1990), as well as reduced birth weight in rats given an oral dose of Ba (ATSDR, 2007).

To that end, the present study quantified and compared concentrations of 14 elements against birth weight (male and female births separately) as well as gestational age, birth weight centile (BWC), placental weight, birth length, and head circumference. In the absence of complete information about the effects of these 14 metals on birth outcomes, we consider this a hypothesis generating study.

2. Methods

Placental collection was conducted at Erlanger Hospital (Baroness campus), Chattanooga, TN from singleton births of HIV and hepatitis negative mothers over 18 years of age. Infants born at or greater than 34 weeks, with no major morphological or chromosomal abnormalities, were included in the sample population. Over the study period, 690 women were asked to participate in the study. From those requests, 665 placentae were successfully collected across a large spectrum of pregnancies. When processing samples for elemental analysis, samples from normal weight births were a random subset of a larger population (n = 292). Because low birth weight samples were the minority of the births, all LBW placentae above the gestational date cutoff were processed (n = 82). Maternal and infant data were collected from questionnaire interviews and medical records. All specimen and data collection methods were approved by the UT College of Medicine Institutional Review Board (#05–031, FWA# 2301). As samples became available, consent was sought out and obtained within the day, or in the case of a night delivery, first thing the following morning. In the rare case the consent was not obtained or refused to be given, the samples were discarded. Post-delivery, placentae were refrigerated in a plastic container. Placentae were collected no more than 12 h after delivery. After umbilical cord and amniotic sac were removed with ceramic scissors, the placenta was weighed, cut in half and placed in a sterile plastic bag and frozen at −20 °C until processing (as illustrated in Fig. 1). The placental half was thawed and both fetal and maternal membranes (decidua basalis and chorionic plate, respectively) were removed, which allowed for sampling of the syncytiotrophoblast layers to be maximized, the area of fetal/maternal exchange (Sun et al., 1997). Because the spatial distribution of metals through the placenta is not