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Maternal exposure to selenium and cadmium, fetal growth, and placental expression of steroidogenic and apoptotic genes

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ABSTRACT

Background: Cadmium (Cd) and selenium (Se) antagonistically influence redox balance and apoptotic signaling, with Cd potentially promoting and Se inhibiting oxidative stress and apoptosis. Alterations to placental redox and apoptotic functions by maternal exposure to Cd and Se during pregnancy may explain some of the Cd and Se associations with fetal development.

Objectives: Investigate associations between Cd and Se concentrations in maternal toenails with placental expression patterns of tumor necrosis factor (TNF) and steroidogenic genes involved in redox reactions and test associations with fetal growth.

Methods: In a sub-sample from the Rhode Island Child Health Study (n = 173), we investigated the relationships between: (1) maternal toenail Cd and Se concentrations and fetal growth using logistic regression, (2) Cd and Se interactions with factor scores from placental TNF and steroidogenic expression patterns (RNAseq) using linear models, and (3) TNF and steroidogenic expression factors with fetal growth via analysis of covariance.

Results: Se was associated with decreased odds of intrauterine growth restriction (IUGR) (OR = 0.27, p-value = 0.045). Cd was associated with increased odds of IUGR (OR = 1.95, p-value = 0.13) and small for gestational age (SGA) births (OR = 1.46, p-value = 0.11), though not statistically significant. Cd and Se concentrations were antagonistically associated with placental TNF and steroidogenic expression patterns, which also differed by birth size.

Conclusions: Se may act as an antagonist to Cd and as a modifiable protective factor in fetal growth restriction, and these data suggest these effects may be due to associated variations in the regulation of genes involved in placental redox balance and/or apoptotic signaling.

1. Introduction

Trace exposures to compounds or elements ubiquitous in the environment have received substantial recent attention for their potential detrimental influences on reproductive health and birth outcomes (Rahman et al., 2016). Cadmium (Cd), a common contaminant that is toxic at relatively low-levels, is well recognized as a human carcinogen and for its toxic effects on the kidneys, liver, and bones (Nair et al., 2013), and has been implicated as a developmental toxicant. Human exposure to Cd primarily occurs through the diet, though among smokers, cigarettes are the primary source of Cd exposure (Järup and Åkesson, 2009; Satarug and Moore, 2004). Selenium (Se), on the other hand, is an essential micronutrient that putatively elicits numerous health benefits including anti-carcinogenic and anti-inflammatory activities, positive effects on the immune and cardiovascular systems, an ability to mitigate the toxic effects of heavy metals, and critical anti-oxidative roles during pregnancy (Pieczyńska and Grajeta, 2015). However, Se also has a narrow window of sufficiency and may elicit toxic effects dependent on dose and interactions with other environmental exposures (Jablonska and Vinceti, 2015). Like Cd, the primary source of human Se exposure is via the diet, through the consumption of plants, or of animals that fed on Se-rich plants (Pieczyńska and Grajeta,

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2015; Mehdi et al., 2013).

At the cellular level, Cd can induce delayed apoptosis, apoptosis, or necrosis (Templeton and Liu, 2010; López et al., 2003), whereas Se can inhibit these signals (Zhou et al., 2009). Furthermore, Cd and Se appear to influence the generation and suppression of reactive oxygen species (ROS) in a diametrically opposed a manner (Zhou et al., 2009; El-Sharaky et al., 2007). Though Cd is not a redox-active metal, once it has been absorbed into a cell, it interferes with mitochondrial function, depletes and inhibits antioxidants, and displaces redox-active metals from metal-binding proteins, all of which can result in substantial shifts in cellular redox balance towards ROS generation and increased oxidative stress (Valko et al., 2016). Conversely, Se is a critical co-factor in redox homeostasis, interacting with many selenoproteins that neutralize reactive species and are involved in various anti-oxidative activities, hormone synthesis and reproduction (Mehdi et al., 2013). Se has also been shown to protect against Cd-induced oxidative stress and apoptosis (Zhou et al., 2009; El-Sharaky et al., 2007; Jihen and Imed, 2009; Karabulut-Bulan et al., 2016).

Animal models and in vitro studies have shown that Cd induces preeclampsia-like symptoms, restricts fetal growth (Wang et al., 2014, 2016a), may interfere with placental steroidogenesis (Kawai et al., 2002; Stasenko et al., 2010), inhibits trophoblast proliferation while promoting apoptosis (Wang et al., 2012; Erboga and Kanter, 2016), increases placental oxidative stress (Wang et al., 2012) and interferes with maternal-fetal nutrient transfer across the placenta (Wang et al., 2016a; Mikolić et al., 2015), demonstrating the placenta is a likely target tissue for Cd-associated reproductive toxicity. Indeed, excess ROS generation in the placenta has also been associated with altered placental function and negative pregnancy outcomes (Min et al., 2009; Scifres and Nelson, 2009; Vanderlelie et al., 2005). Furthermore, Cd may influence the distribution of Se across maternal, fetal and placental tissues, and vice versa (Al-Saleh et al., 2015; Kantola et al., 2004).

Epidemiologic studies have observed increasing concentrations of placental, maternal or fetal Cd to be associated with various measures of restricted fetal growth or pregnancy complications (Al-Saleh et al., 2015, 2014; Kippler et al., 2013, 2012; Johnston et al., 2014; Laine et al., 2015; Llanos and Ronco, 2009; Wang et al., 2016b; Menai et al., 2012). Alternatively, many studies have found that maternal, fetal or placental Se concentrations positively correlate with fetal growth and successful pregnancies (Bogden et al., 2006; Klapec et al., 2008; Negi et al., 2012; Sun et al., 2014; Rayman et al., 2011, 2015, 2003). The adverse Cd-associated pregnancy and birth outcomes may be mitigated by concurrently higher levels of Se. While Cd-Se antagonism has been demonstrated at the cellular level with redox and apoptotic activity, only a handful of epidemiologic studies have investigated these responses, and these have produced mixed results. Laine et al. (2015) found that the odds of Cd-associated preeclampsia (PE) were higher among mothers with lower placental concentrations of Se (Laine et al., 2015), while Al-Saleh et al. (2015) observed no antagonism between Se and Cd on birth anthropomorphic measurements (Al-Saleh et al., 2015).

There is biological evidence that Cd and Se can influence steroid biosynthesis, redox balance, apoptotic signaling, fetal growth, and successful pregnancies. Yet there is much left to be unraveled about the mechanisms through which trace exposures to Cd and Se during pregnancy influence fetal growth and pregnancy outcomes in humans. Studies have shown that the tumor necrosis factor super family (TNF-SF) encompasses many potent pro-apoptotic cytokines and their receptors (Zelová and Hošek, 2013), in which some of them have been shown to be perturbed by Cd exposure (Kayama et al., 1995; Kim et al., 2002; Kumar et al., 2016). Cd has also been observed to perturb various steps in progesterone, testosterone, cortisol/cortisone, and estradiol/estrone synthesis (Wang et al., 2014; Kawai et al., 2002; Nagata et al., 2005; Pillai and Gupta, 2005; Pandya et al., 2012; Ronco et al., 2010), and the by-products of these activities present major sources of intracellular ROS, particularly those involved in electron transport at the mitochondrial membrane (Prasad et al., 2014). Based on these observations, we sought to test the hypothesis that maternal Cd and Se exposures during pregnancy might be associated with variations in the placental expression patterns of key genes involved in apoptotic signaling or ROS generation via steroidogenesis, and could be related to fetal growth. Cd and Se were measured in maternal toenails collected postpartum and which represent long-term exposure. In this study, we included all TNF-SF genes that were sufficiently detectable in our placental samples, which comprised of 19 TNF-SF receptors (*TNFRSF1A*, *TNFRSF1B*, *TNFRSF3*, *TNFRSF4*, *TNFRSF5*, *TNFRSF6*, *TNFRSF10A*, *TNFRSF10B*, *TNFRSF10C*, *TNFRSF10D*, *TNFRSF11A*, *TNFRSF12A*, *TNFRSF14*, *TNFRSF16*, *TNFRSF19*, *TNFRSF19L*, *TNFRSF21*, *TNFRSF25*, and *TNFRSF27*) and 2 TNF-SF ligands (*TNFSF10* and *TNFSF15*). Thorough descriptions of TNF-SF receptor-ligand interactions and their functions are reviewed (Zelová and Hošek, 2013). The TNF-SF genes included in our study, as well as their major structural similarities are highlighted in the supplemental materials (Supplemental Fig. 1A). Additionally, we investigated cytochrome P450 (*CYP11A1* and *CYP19A1*) and hydroxysteroid dehydrogenase (*HSD3B1*, *HSD3B7*, *HSD11B1*, *HSD11B2*, *HSD17B1*, and *HSD17B2*) genes involved in steroid biosynthesis. Moon et al (2014) provide a thorough description of this pathway in association with preeclampsia (Moon et al., 2014); we highlight the genes included in our study in the supplemental materials (Supplemental Fig. 1B).

2. Methods

2.1. Rhode Island Child Health Study

The Rhode Island Child Health Study (RICHS) is a hospital-based birth cohort of healthy mothers with singleton, viable, non-pathologic pregnancies born at ≥ 37 weeks gestation from the Women and Infants' Hospital in Providence, RI, USA (n = 840). Exclusion criteria comprised of maternal age less than 18 years, life threatening conditions, or infants with congenital/chromosomal abnormalities. This study aimed to investigate factors associated with very large and very small birth sizes. In accordance with the eligibility criteria, mothers of infants born large for gestational age (LGA) (≥ 90th BW percentile) and SGA (≤ 10th BW percentile) during normal working hours and up to two infants born adequate for gestational age (AGA) (between the 10th and 90th BW percentiles) of the same sex, gestational age (± 3 days), and maternal age (± 2 years) were approached; 63% of those approached agreed to participate. All protocols were approved by the institutional review boards at the Women and Infants' Hospital and Emory University and all participants provided written informed consent. Toenails for trace elements measurements (n = 242), and placental samples for gene expression profiling (n = 200), were collected after delivery. This study included the cross-section of mother-infant pairs for which both toenail trace elements and placental gene expression measurements were available (n = 173).

2.2. Medical records and questionnaire-based data

An interviewer administered questionnaire was used to collect self-reported sociodemographic, lifestyle, and medical history data, and a structured medical records review was employed to collect anthropometric and clinical data. Data on gestational weeks, infant sex, birth weight (grams) and intrauterine growth restriction (IUGR) status, which was determined *in utero* via ultrasound, were obtained via medical records abstraction. Size at birth was categorized as SGA, AGA, and LGA, calculated as sex-specific birthweight percentiles adjusted for gestational age via the revised Fenton growth chart (Fenton and Kim, 2013).

2.3. Toenail Cd and Se concentrations

Toenail clippings were collected from mothers approximately 2.8