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Blood metal levels and third trimester maternal plasma matrix metalloproteinases (MMPs)

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HIGHLIGHTS

- Prenatal metal exposure effects on plasma MMPs were tested in a pregnancy cohort.
- Metal type-, exposure trimester-, dose-related changes were observed in MMP levels.
- Hg, Cd, Pb, As and Mn exposures can influence maternal plasma MMP responses.

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ABSTRACT

While it is known that in utero exposure to environmental toxicants, namely heavy metals, can adversely affect the neonate, there remains a significant paucity of information on maternal biological changes specific to metal exposures during pregnancy. This study aims at identifying associations between maternal metal exposures and matrix metalloproteinases (MMPs) that are known to be engaged in pregnancy process. Third trimester maternal plasma (n = 1533) from a pregnancy cohort (Maternal-Infant Research on Environmental Chemicals Study, MIREC) were analyzed for MMP-1,-2,-7,-9 and -10 by affinity-based multiplex protein array analyses. Maternal metal concentrations (mercury, cadmium, lead, arsenic and manganese) in 1st and 3rd trimesters exhibited strong correlations ($p < 0.05$). Multivariate regression models were used to estimate odds ratio (OR) for the association between metal concentrations in quartiles and high (90%) and low (10%) maternal MMP levels. Significant ($p < 0.05$) metal exposure-related effects were observed with the different MMP isoform responses. MMP profiles were specific to the trimester at which the maternal blood metals were analyzed. Our findings suggest that the profiles of these MMP isoforms vary with the type of metal exposure, blood metal concentrations and the trimester at which metal levels were determined. These new findings on maternal metal-MMP relationships can guide future explorations on toxicity mechanisms relevant to metal exposure-mediated adverse birth outcomes.

1. Introduction

Maternal chemical burdens are shown to influence maternal and infant health (Stieb et al., 2012; Stillerman et al., 2008; Perera et al., 2007). Previous studies have revealed associations between factors such as maternal life style and adverse pregnancy outcomes (Wigle et al., 2008; Matthews et al., 1999; Jolly et al., 2000; Gelson and Johnson, 2010; Alsuwaida et al., 2011; Abu-Saad and Fraser, 2010; Dechanet et al., 2011). Adverse birth outcomes include preeclampsia, premature rupture of membranes (PROM), gestational diabetes, intrauterine growth restriction (IUGR), preterm birth (PTB), low birth weight (LBW), and small for gestational age infants (Godfrey et al., 1996; King, 2003; Hackshaw et al., 2011; Howe et al., 2012).

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Early life exposures to environmental metals can cause disease and disability in infants and across the entire lifespan (Shoeters et al., 2011; Wigle et al., 2007). Metals namely lead (Pb), mercury (Hg), cadmium (Cd), manganese (Mn) and arsenic (As) may act as endocrine disruptors (Caserta et al., 2013; Bellinger, 2005). Lead, mercury, and arsenic can cross the placental barrier and accumulate in amniotic fluid or fetal tissues (Vahter et al., 2002). Lead is associated with premature rupture of membrane (PROM)-related preterm delivery, LBW, PTB and IUGR (Andrews et al., 1994; Angell and Lavery, 1982; Falcon et al., 2003; Srivastava et al., 2001). Mercury is reported to alter neurological development and disrupt DNA replication among other effects (O'Reilly et al., 2010; Georgescu et al., 2011; Wigle, 2003). Arsenic, has been suggested to play a role in the risk of having LBW infants (Vahter et al., 2002; McDermott et al., 2014; Yang et al., 2003; Hopenhayn et al., 2003) and in maternal hypertension (Lee et al., 2003) and gestational diabetes (Ettinger et al., 2009; Saldana et al., 2007; Shapiro et al., 2015). Cadmium does not easily cross the placental barrier, but may affect placental function and thus fetal development (Iyengar and Rapp, 2001; Zhang et al., 2004a; b; Nishijo et al., 2004; Yang et al., 2006), and is implicated in preeclampsia (Semzcuk and Semczuk-Sikora, 2001; Dawson et al., 1999; Eisenmann and Miller, 1995; Kosanovic et al., 2002). Manganese is an essential element, yet deficiency and excess intake may result in adverse pregnancy outcomes such as IUGR, LBW and other effects (Eum et al., 2014; Marriott et al., 2007; McDermott et al., 2014; Mora et al., 2014; Sarwar et al., 2013; Wood, 2009). Some studies have indicated adverse birth effects at lower exposure levels than previously anticipated (Wigle et al., 2007; Vahter et al., 2002).

Heavy metal exposures are associated with oxidative stress and inflammatory pathways (Dagouassat et al., 2012; Sivanesan et al., 2007; Valko et al., 2005) which may be relevant to PTB and LBW (Buhimschi et al., 2010; Conde-Agudelo et al., 2011; Ferguson et al., 2015). A family of zinc-dependent proteinases involved in the degradation of extracellular matrix during normal and pathological tissue remodelling that are known as matrix metalloproteinases (MMPs) play a critical role in embryo implantation, placentation, cervical dilation and fetal-maternal membrane lysis (Tu et al., 1998), and are associated with inflammatory conditions (Zhou et al., 2000; Dagouassat et al., 2012; Conde-Agudelo et al., 2011). Both arsenic and mercury, at high levels, have been shown to affect MMP activity (Jacob-Ferreira et al., 2009; Liang et al., 2012). There is a paucity of information on the mechanistic basis for environmental metal exposure-mediated adverse pregnancy outcomes (Dagouassat et al., 2012; Kumarathasan et al., 2014). An understanding of how pre- and peri-natal metal exposures affect maternal biological pathways and pregnancy outcomes including long term effects is critical for risk estimation.

In this study, the objective was to investigate the relationships between maternal prenatal (first and third trimester) blood metal concentrations and maternal third trimester circulating MMPs, key enzymes in the process of pregnancy, to gain information towards the understanding of environmental chemical exposure-mediated adverse pregnancy outcomes. For this purpose, we have employed participants from the Maternal-Infant Research on Environmental Chemicals (MIREC) study.

2. Materials and methods

2.1. Study design

Details on the MIREC study have been reported by Arbuckle et al. (2013). To summarize, 2001 women were recruited from 10 Canadian sites from 2008 to 2011 during their first trimester of pregnancy. From the 2001 women, 18 withdrew and the 1983 remaining subjects gave birth to 1959 infants. Of this subset, 426 women were excluded for multiple births, missing metal biomonitoring data and anthropometric measurements, or unknown sex of the baby, resulting in a final sample size of 1533 mother-infant pairs.

2.2. Ethics

The research protocol, questionnaires, consent forms and recruitment posters and pamphlets were reviewed and approved by human studies research ethics committees, including the Research Ethics Board at Health Canada, the ethics committee at the coordinating center at St-Justine's Hospital in Montreal and more than ten academic and hospital ethics committees across Canada. All participants signed informed consent forms.

2.3. Metal exposure

Whole blood samples collected during the first and third trimesters were analyzed for As, Cd, Hg, Mn and Pb using inductively coupled plasma mass spectrometry (PerkinElmer ELAN ICP-MS DRC II). These analyses were performed by the Laboratoire de Toxicologie, Institut National de Santé Publique du Québec (INSPQ) (Québec, QC, Canada), accredited by the Standards Council of Canada.

2.4. Plasma sample preparation and MMP biomarker analyses

Plasma samples were derived from the 3rd trimester maternal blood samples ($n = 1533$) which were stabilized with preservatives EDTA and PMSF following a procedure described by Kumarathasan et al. (2014). These plasma samples were treated with DETPA, BHT and an antiprotease (Halt™ protease inhibitor) cocktail (Thermo Fisher Scientific, Canada), vortexed, and frozen at −80 °C for storage (Kumarathasan et al., 2014).

Aliquots of plasma samples were analyzed for MMP-1, MMP-2, MMP-7, MMP-9, and MMP-10 by affinity (antibody)-based multiplex liquid suspension (fluorescence-coded magnetic beads) protein array analyses using Milliplex Map kits (Millipore, Canada). Briefly, plasma was treated with the corresponding MMP capture antibody-coated magnetic beads and was incubated for 2 h. Beads were then washed and reacted with biotinylated-detection antibodies followed by incubation with streptavidin-phycoerythrin, re-washed, re-suspended in sheath fluid (Bio-Rad, Canada) and analyzed by Bioplex 100 using Bioplex Manager (version 6.0) software (Bio-Rad, Canada).

2.5. Statistical analysis

Data were extracted from questionnaires and hospital charts to test whether maternal characteristics and infant sex influenced maternal plasma MMPs. Initially, descriptive statistics was conducted using frequency distributions and chi-square tests of significance for the difference between the low ($\leq$10th percentile), moderate (>10−<90th percentiles), and elevated ($\geq$90th percentile) MMP categories by maternal and birth characteristics [maternal age at delivery, maternal education, household income, smoking status prior to pregnancy, pre-pregnancy body mass index (BMI) according to WHO guidelines (World Health Organization, 2006), premature rupture of membranes, baby sex and parity)]. In addition, the geometric mean (GM) and standard deviation (SD) of the metal concentrations were determined according to MMP categories. All samples with metal concentrations below the level of detection (LOD) were imputed as one half of the LOD. The LOD values for plasma MMP-1, -2, -7, -9 and -10, were 3, 200, 97, 2 and