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Prenatal co-exposure to manganese and depression and 24-months neurodevelopment

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ABSTRACT

Background: Normal prenatal neurodevelopment follows stages that are potentially influenced by both chemical and psychosocial environments. Exposure to elevated manganese during this critically vulnerable period has been found to be neurotoxic. Independently, maternal prenatal depression has been associated with subsequent neurodevelopmental decrements in children. The association between child neurodevelopment and prenatal co-exposure to manganese and maternal depression has not been sufficiently studied.
Methods: During pregnancy and at birth, we measured maternal blood and cord blood manganese levels respectively. Maternal depression was assessed in the 3rd trimester of pregnancy using the Edinburgh Depression Scale. Neurodevelopment was evaluated at 24 months of age with the Bayley Scales of Infant Development. A multivariate multiple regression model was used to analyze cognitive, language and motor scores simultaneously for 473 children from the PROGRESS birth cohort in Mexico City.
Results: Over 25% of our study participants reported having depressive symptoms. 3rd trimester blood manganese as well as depressive symptoms were independently negatively associated with all neurodevelopment scores in adjusted models. In stratified analyses, the negative association between manganese (maternal as well as cord blood) and 24-month language scores was stronger among women with depressive symptoms. Receptive language was mostly affected. Inverted U-shaped curves were seen for the association between with cord blood manganese and neurodevelopment scores.
Conclusions: Our findings are in line with previous studies of manganese and depression neurotoxicity. The prenatal period may be particularly sensitive to manganese and depression co-exposures and should be of interest for public health interventions to promote healthy emotional and nutritional pregnancies.

1. Background

The prenatal period is critical to neurodevelopment. During this time, the nervous system matures towards the achievement of the cognitive, motor and language functions. Independently, exposure to elevated manganese (Mn) and the presence of depression in pregnant women are factors that can influence the neurodevelopment of their offspring (Chung et al., 2015; Coetzee et al., 2016; Glover, 2014; Nulman et al., 2015).

Manganese (Mn) is an essential nutrient that contributes substantially to a variety of body functions including the

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breakdown of cholesterol, carbohydrates and proteins and also plays a key role in brain development and bone formation (Freeland-Graves and Turnlund, 1996). Mn is a core component of various metalloenzymes that ensure proper functioning of the central nervous system (Aschner and Aschner, 1991). The general population is exposed to Mn through food, water and air. Mn absorbed from ambient air might occur in areas with heavy traffic (Bueno-Brito et al., 2005). However, levels in ambient air are considered negligible when compared to the natural abundance of Mn in soil (Gulson et al., 2006). In food, its concentration is highest in string beans, nuts, legumes, seeds, tea, whole grains and green-leaf vegetables. Guidelines have been established for different exposure routes: the WHO establishes 0.15 $\mu g/m^3$ for air and 0.4 mg/L in water; the U.S. FDA establishes a limit of 0.05 mg/L in bottled drinking water and as for food the EPA has a reference dose of 0.14 mg/kg/day (ATSDR, 2012). According to the Food and Nutrition Board of the Institute of Medicine, 2 mg of Mn per day constitute an adequate intake for pregnant women, with the tolerable upper intake level of 11 mg (Food and Nutrition Board, 2001). Notwithstanding its protective effect against oxidative damage, in larger quantities Mn becomes an oxidizer itself (ATSDR, 2012) and is a known neurotoxicant. Mn accumulates in mitochondria-rich membranes and penetrates the blood-brain and placental barriers. Evidence of the neurotoxic effects of Mn is increasing, specifically with regard to cognition, memory, behavior and motor function (Claus Henn et al., 2012, 2010; Hernández-Bonilla et al., 2011; Menezes-Filho et al., 2011, 2009; Rodríguez-Barranco et al., 2013). Several studies have examined the neurodevelopmental effects of intrauterine Mn exposure, and results suggest that environmental exposure to Mn in utero may affect the psychomotor development of children at an early age (Gunier et al., 2015; Lin et al., 2013a; Mora et al., 2015a).

Perinatal depression has also been identified as a risk factor for inadequate infant neurodevelopment in the long term (Dossett, 2008). According to the World Health Organization, depression is a disease that alters the mood, thoughts, appetite, sleep, perception of self-esteem and overall lifestyle of individuals (WHO, 2016). Feeling sad, apathetic and hurt, those who suffer from this emotional disorder find it difficult to interact with the environment (Lara et al., 2006). Prenatal depression is differentiated by its adverse effects on the baby, whose neuronal development during this period is directly affected by context (Olhaberry et al., 2013).

Research performed during outpatient consultations at the National Institute of Perinatology indicated that as many as 21.7% of pregnant women in Mexico may experience probable depression episodes (Ortega et al., 2001). Another study revealed a 23.3% prevalence of depression among pregnant users of primary healthcare services at Family Medicine Unit 171 of the Mexican Social Security Institute (*Instituto Mexicano del Seguro Social, IMSS*) (Delgado-Quiñones et al., 2015). A recent study in the US estimated that the prevalence of minor depression was higher among pregnant women (16.6%) compared to non-pregnant women (11.4%) (adjusted PR = 1.5, [95% confidence interval (CI): 1.2, 1.9]). Studies have found that depression occurs particularly during weeks 6 to 10 and in the third trimester of pregnancy, when the body prepares for labor and delivery (Carter and Kostara, 2005).

Depression can affect the central nervous system through anomalous levels of aminergic neurotransmitters (e.g., serotonin, norepinephrine and dopamine) acting upon the neurons of the central nervous system (Escobar Izquierdo et al., 2009). Mn is essential to the proper functioning of the hypothalamus, a region of the brain containing a large number of neurons. One of the primary functions of the hypothalamus is to link the nervous and endocrine systems by secreting neurohormones through the pituitary gland. The molecular mechanisms by which Mn affects hypothalamic processes are not fully understood, therefore determining exactly which mechanisms are at play in the interaction between Mn and depression and consequently child neurodevelopment is not completely clear (Tellerias and Paris, 2008). However, both could be acting on the same dopamine pathway and epidemiologic evidence is scarce.

Because both Mn and depression are common exposures in pregnancy, we explored their joint associations with children's neurodevelopment at 24 months of age. We hypothesized that depression could be an effect modifier of the association between Mn and neurodevelopment.

2. Methods

2.1. Study population

The Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) birth cohort recruited women during their prenatal visit at four IMSS clinics in Mexico City, between 2007 and 2011 and followed them since their 2nd trimester. Inclusion criteria have been previously described in more detail (Braun et al., 2014). Briefly, women had to be healthy, at least 18 years old, between 12 and 24 weeks pregnant, and plan to live in Mexico City. All protocols were approved by the institutional review boards of the Icahn School of Medicine at Mount Sinai, the Harvard T.H. Chan School of Public Health, the National Institute of Public Health Mexico, the National Institute of Perinatology Mexico, and the Mexican Social Security System. Upon consent, women visited our research centers during their 2nd and 3rd trimesters, we collected samples and data at birth and 760 mother-infant pairs visited our research centers at 6, 12, 18 and 24 months postpartum. Our study analyzed data from 541 dyads for which a neurodevelopmental assessment was administered to the child at the 24 month visit. We excluded from analyses children who were born at $\leq$32 weeks and/or weighed $\leq$1,500 g (n = 4).

2.2. Child neurodevelopment

Neurodevelopment was assessed at 24 months of age using the Bayley Scales of Infant and Toddler Development 3rd edition (Albers and Grieve, 2006). Trained psychologists blind to the prenatal Mn and depression levels evaluated the cognitive, language and motor development of children.

2.3. Maternal gestational depression

The Edinburgh Depression Scale (EDS) was administered during the 3rd trimester of pregnancy. The questionnaire consists of ten polytomous (four-option) response items exploring last-week symptoms of a major depression episode. Each question is rated on a scale of 0 to 3 points. Studies have found that a cut-off of 12 indicates a probable depressive disorder (Evans et al., 2001; Murray and Cox, 1990). The scale was applied in a Chilean cohort (Hispanic population, closer to our study population) and found that a cut-off between 12 and 13 had an 87.4% correct classification of cases and non-cases (Alvarado et al., 2012). For our main analyses we had a conservative approach and used a dichotomous variable with a cutoff of $\geq$13 for depressive symptoms. We also explored using quartiles of the EDS for a secondary analysis.

2.4. Prenatal manganese

Mn was measured in maternal venous blood samples in the 3rd trimester (between the 30th and 34th week) of pregnancy, from here on referred to as BMn and during birth in umbilical cord blood (CMn). Royal blue trace metal Vacutainer tubes (Becton-Dickinson and Company, Franklin Lakes, New Jersey) containing EDTA were

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