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Sex specific influence on the relationship between maternal exposures to persistent chemicals and birth outcomes

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ABSTRACT

Prenatal exposure to persistent pollutants has been associated with adverse birth outcomes, although few studies have investigated the influence of the sex of the infant. Sex specific differences have been associated with neurobehavioural impacts from environmental exposures with limited and contrary findings in relation to persistent pollutants. This study investigated the relationships between maternal exposure to a range of metals, polychlorinated biphenyls and pesticides measured in biological samples and birth outcomes with a specific focus on the sex of the infant. Outcome measures used included birth weight, birth length and head circumference, proportion of optimal birth weight (POBW), proportion of optimal birth length, proportion of optimal head circumference (POHC) and ponderal index.

In general maternal urinary and blood metals, plasma polychlorinated biphenyl and pesticide concentrations were low. In adjusted regression models, a ln-unit increase in plasma β-hexachlorocyclohexane concentrations was associated with decreased birth weight (-76 g, 95% CI -149, -33), ponderal index (-0.048, 95% CI 0.102, 0.007) and proportion of optimal birth weight (-1.5%, 95% CI -3.6, 0.5) in the whole study population, with stronger associations observed for male infants. Maternal *p,p′*-dichlorodiphenyldichloroethylene concentrations were associated with reduced ponderal index in male infants ($\beta = -0.171$, 95% CI -0.269, -0.074). A ln-unit increase in plasma hexachlorobenzene concentrations was associated with a 5% increase in POBW in male infants (95% CI 0.67, 9.5). Increased urinary barium was associated with increased birth length and POBL and decreased ponderal index in boys. Conversely, urinary concentrations of caesium and rubidium were found to be associated with decreased foetal growth in female infants.

This study supports the growing body of evidence regarding the reductions in foetal growth associated with β-hexachlorocyclohexane and *p,p′*-Dichlorodiphenyldichloroethylene as well as reporting new relationships between metals exposures and birth outcomes. The finding that maternal exposure to barium, strontium, rubidium and caesium was associated with birth outcomes requires confirmation in larger studies. Similarly the apparent differences in susceptibility based on sex of the infant requires further investigation.

1. Introduction

There have been many studies investigating the relationship between persistent chemicals and their impacts on the developing foetus. Most commonly, maternal or placental concentrations of persistent chemicals, including metals and pesticides, have been used as a surrogate for prenatal exposure in studies examining birth outcomes. Given that reduced foetal growth is associated with decrements in neurological development in children (Franz et al., 2009) and also an increased risk of chronic disease in adults (Barker et al., 1989, 1993; Barker, 2007), understanding the relationship between environmental exposure and birth outcomes is of considerable public health importance.

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Prenatal exposure to the metals, especially cadmium and lead, has been associated with adverse birth outcomes. Higher maternal blood cadmium concentrations have been associated with decreases in crown-heel length and placental thickness (Al-Saleh et al., 2014) and birth weight (Salpietro et al., 2002). Maternal urinary cadmium concentrations have also been associated with decreases in birth weight and length (Shirai et al., 2010; Kippler et al., 2012), with inverse associations between maternal cadmium exposure and birth anthropometry reported in girls, but not boys (Kippler et al., 2012; Röllin et al., 2015). Even at low levels, maternal blood lead concentrations have been found to be associated with a small increased risk of reduced birth weight (Zhu et al., 2010; Taylor et al., 2015) and particularly in infant males (Nishioka et al., 2014). The relationship between mercury exposure and birth outcomes remains to be elucidated, with some studies reporting an inverse relationship between maternal concentrations and birth size (Ramón et al., 2009), whilst others reported no relationship (Bashmore et al., 2014). The potential for low level exposure to other metals to influence birth outcomes has received limited attention. Manganese is an essential element and non-linear associations between maternal blood manganese concentrations and birth weight have been reported, with decreased foetal growth at both lower and higher maternal concentrations (Zota et al., 2009; Chen et al., 2014).

Organochlorine pesticides have been used widely and measured in maternal blood as an indicator of prenatal exposure (Reid et al., 2013). Guo et al. (2014) reported that maternal serum Dichlorodiphenyltrichloroethane (DDT), β-hexachlorocyclohexane (β-HCH) and hexachlorobenzene (HCB) concentrations for 81 women were associated with a decrease in birth weight in offspring. Vafeiadi et al. (2014) showed a stronger association between maternal serum HCB concentrations and reduced birth weight in girls compared with boys. Prenatal exposure to HCB has also been associated with decreases in head circumference (Brucker-Davis et al., 2010), crown-heel length (Ribas-Fitó et al., 2002) and birth length (Lopez-Espinosa et al., 2011).

Prenatal exposure to polychlorinated biphenyls (PCBs) has also been reported to be associated with decreased birth weight. Casas et al. (2015) undertook a pooled analysis of 9377 mother child pairs participating in 14 study populations from 11 European cohorts. They found a significant decline in birth weight with increasing cord blood PCB 153 concentrations, even at low levels, after adjustment for smoking and gestational weight gain. In Casas et al. (2015)'s meta-analysis, the PCB-smoking-sex interaction showed girls being more susceptible than boys, which is in contrast to previous studies by Hertz-Picciotto et al. (2005) and Tsukimori et al. (2012) which showed PCB concentrations and adverse birth outcomes were more significant in boys.

Sex differences in foetal growth rates have been reported, with maternal size observed to incur sex-modified timing effects on the rates of foetal growth and birth outcomes (Lampl et al., 2010). Whilst sex-specific differences have been observed in neurobehavioural health impacts associated with prenatal environmental exposures (e.g. Jedrychowski et al., 2009; Braun et al., 2009), the potential for the sex of a foetus to result in differential effects with respect to exposure and birth outcomes has remained largely unexplored, with few studies stratifying analyses by infant sex. In studies with adults, or indeed even children, it is challenging to separate the effects of gender (i.e. social and behavioural constructs that may influence exposure) from physiological differences between the sexes that result in differences in health effects following exposure (Clougherty, 2010). However for studies of birth outcomes, any differences arising between the sexes are presumably driven by biological differences during foetal development that influence the uptake, transport or impact of environmental exposures, although the mechanisms for this remain unclear.

This study provided an opportunity to explore the relationship between low level maternal exposure to a range of persistent substances and birth outcomes taking into account the possible associations with sex-differences, using data collected in the Australian Maternal Exposure to Toxic Substances (AMETS) study. Measures of foetal growth were used as outcomes. Concentrations of metals in maternal urine and whole blood and pesticides in maternal plasma have been previously reported (Callan et al., 2013; Hinwood et al., 2013, 2015; Reid et al., 2013) and were utilised in this study.

2. Materials and methods

2.1. Study design, population and recruitment

The Australian Maternal Exposure to Toxic Substances (AMETS) study was a cross sectional study of environmental exposure in non-smoking pregnant women recruited from across Western Australia (WA) aged 18 years and above between 2008 and 2011. Ethics approvals were obtained for this study from Edith Cowan University Human Research Ethics Committee, WA Country Health Service, St John of God Health Care (Subiaco and Bunbury), Joondalup Health Campus and King Edward Memorial Hospital. All participants provided written informed consent.

The design and methods of exposure assessment are reported elsewhere and briefly summarised here (Callan et al., 2013; Hinwood et al., 2013; Reid et al., 2013). Each participant was asked to provide a sample of blood and first morning void urine sample approximately 2 weeks prior to birth and complete a questionnaire on demographic and lifestyle factors that may be associated with environmental exposures. Following delivery participants were re-contacted and asked to complete a short questionnaire regarding their infant's birth outcomes including birth weight and length, head circumference, gestational age and the sex of the infant (Stasinska et al., 2014). Mothers obtained this information from the details recorded by the medical team in the baby book (recorded medical information following birth) given to mothers after delivery.

2.2. Analysis of metals, pesticides and PCBs in whole blood and plasma

Whole blood and urine samples were analysed for metals (Callan et al., 2013; Hinwood et al., 2013) and plasma samples for organochlorine pesticides (Reid et al., 2013). The following 25 metals were analysed in whole blood ($n = 165$) and urine ($n = 166$) aluminium, antimony, arsenic (total and inorganic), barium, bismuth, cadmium, caesium, chromium, cobalt, copper, gallium, lead, lithium, manganese, mercury, nickel, rubidium, selenium, strontium, thallium, thorium, tin, uranium, vanadium, zinc. Urinary creatinine was also measured using a discrete analyser (Labmedics/Thermo Fisher Aquakem 250) and used to adjust urinary metals concentrations.

Plasma samples ($n = 161$) were analysed for the following organochlorine pesticides: HCB, α-HCH, β-HCH, γ-HCH, δ-HCH, o,p'-DDD, p,p'-DDD, o,p'-DDT, p,p'-DDT, o,p'-DDE, p,p'-DDE, heptachlor, heptachlor epoxide, oxy-chlordane, *trans*-chlordane, *cis*-chlordane, *trans*-nonachlor, *cis*-nonachlor and mirex. The concentrations of most pesticides were below LOD in most samples, therefore only β HCH, HCB and p,p'-DDE, the three analytes that were detected in the majority of samples, were included in this analysis.