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Prenatal exposure to dental amalgam in the Seychelles Child Development Nutrition Study: Associations with neurodevelopmental outcomes at 9 and 30 months

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ABSTRACT

Background: Dental amalgam is approximately 50% metallic mercury and releases mercury vapor into the oral cavity, where it is inhaled and absorbed. Maternal amalgams expose the developing fetus to mercury vapor. Mercury vapor can be toxic, but uncertainty remains whether prenatal amalgam exposure is associated with neurodevelopmental consequences in offspring.
Objective: To determine if prenatal mercury vapor exposure from maternal dental amalgam is associated with adverse effects to cognition and development in children.
Methods: We prospectively determined dental amalgam status in a cohort of 300 pregnant women recruited in 2001 in the Republic of Seychelles to study the risks and benefits of fish consumption. The primary exposure measure was maternal amalgam surfaces present during gestation. Maternal occlusal points were a secondary measure. Outcomes were the child's mental (MDI) and psychomotor (PDI) developmental indices of the Bayley Scales of Infant Development-II (BSID-II) administered at 9 and 30 months. Complete exposure, outcome, and covariate data were available on a subset of 242 mother–child pairs.
Results: The number of amalgam surfaces was not significantly ($p > 0.05$) associated with either PDI or MDI scores. Similarly, secondary analysis with occlusal points showed no effect on the PDI or MDI scores for boys and girls combined. However, secondary analysis of the 9-month MDI was suggestive of an adverse association present only in girls.
Conclusion: We found no evidence of an association between our primary exposure metric, amalgam surfaces, and neurodevelopmental endpoints. Secondary analyses using occlusal points supported these findings, but suggested the possibility of an adverse association with the MDI for girls at 9 months. Given the continued widespread use of dental amalgam, we believe additional prospective studies to clarify this issue are a priority.

1. Introduction

The safety of dental amalgam has been the subject of heated debate since its introduction into the practice of dentistry over a century and a half ago. Dental amalgam is approximately 50% metallic mercury by weight and when present in the oral cavity, exposes an individual to mercury vapor (Hg^0) released from the restoration's surface (WHO, 1991). For individuals not

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occupationally exposed to Hg^0, amalgam restorations are the primary source of exposure. Chronic exposure to elevated levels of Hg^0 is known to result in neurotoxicity consisting of various sensory, motor, cognitive and personality disturbances. Presently, the lowest level at which such associations occur is unknown. Reviews focused on low level Hg^0 exposure from dental amalgam restorations suggest that adverse health effects are unlikely to occur in adults (Brownawell et al., 2005; CETS, 1997; European Commission, 2004; Health Canada, 2008; WHO, 1997). However, the most recent extensive review of amalgam safety concluded that there was insufficient evidence to evaluate risk from *in utero* exposure to Hg^0 from maternal amalgam, and from co-exposure to Hg^0 and methylmercury (MeHg) (Brownawell et al., 2005). This gap in knowledge continues to be highlighted by numerous agencies (European Commission, 2004; FDA, 2009; Health Canada, 2008).

Against this backdrop, the presence and placement of dental amalgam restorations remain substantial in all age groups worldwide, including children and women of child-bearing age. There are clear benefits to the use of dental amalgams such as their low cost, durability, and ease of placement. In 2009, the FDA estimated nearly 900 million existing amalgam restorations were in place in the US (FDA, 2009). Moreover, current utilization of amalgam by US practitioners is still considerable, especially for restoration of posterior teeth (DeRouen et al., 2010; Makhija et al., 2011; Nascimento et al., 2010). Estimates suggest 50 million additional amalgam restorations were placed in the US in 2009 (about one third of restorations placed), with approximately 1.8 million amalgams placed in pregnant and lactating women (FDA, 2009). These amalgam restorations are in addition to the tens of millions of amalgams already in place in this potentially sensitive population.

Mercury vapor readily crosses the placental barrier and an increased number of maternal amalgams has been associated with elevated levels of mercury in the placenta (Ask et al., 2002), amniotic fluid (Luglie et al., 2005), cord blood (Palkovicova et al., 2008), the kidney and liver of the fetus (Drasch et al., 1994), and the kidney and cerebral cortex of older infants (Drasch et al., 1994). Despite concerns, there remains a paucity of scientific data to adequately assess whether there are health risks to the developing human fetus from prenatal exposure to Hg^0 from maternal dental amalgams. We recently reported an adverse association of maternal amalgams present during gestation on Seychellois boys' performance at 66 months of age on the Letter-Word Identification subtest of the Woodcock–Johnson Tests of Achievement (Watson et al., 2011). Uncertainties associated with the retrospective nature of the exposure assessment and inconsistencies in the findings, however, limited our ability to draw firm conclusions.

Besides Hg^0, exposure to MeHg is common and occurs principally through fish consumption (WHO, 1991). Experimental studies in animals have suggested that co-exposure to Hg^0 and MeHg resulted in more adverse findings than either exposure alone (Fredriksson et al., 1996). These findings led us to hypothesize that a study of the Seychelles Child Development Nutrition Study (SCDNS) might be more likely to identify adverse Hg^0 associations if any were present. Consequently, we prospectively studied mothers and children enrolled in the SCDNS. The original aim of this longitudinal cohort study was to examine potential confounding effects of beneficial nutrients associated with maternal fish consumption against possible adverse effects of prenatal MeHg exposure.

2. Methods

2.1. Subjects

The SCDNS Cohort is a well-characterized group of mother–infant pairs residing in the Republic of Seychelles (Bonham et al., 2008; Davidson et al., 2008; Strain et al., 2008). The study is prospective, double-blind, and longitudinal. Enrollment, inclusion, and exclusion criteria were reported previously (Davidson et al., 2008). Data on amalgam, covariates and at least one outcome were available on 242 mothers. The study was reviewed and approved by the institutional review boards of the University of Rochester, Rochester, NY, and the Ministry of Health, Republic of Seychelles.

2.2. Determination of maternal dental amalgam status (Hg^0 exposure)

The total number of amalgam surfaces present in the mother during gestation was the primary metric of Hg^0 exposure. We determined this by examining the mothers shortly before or just after the birth of her child, and reviewing the historic dental records maintained by the national dental service. The total amalgam surfaces metric has been widely used in numerous studies (Bellinger et al., 2006, 2007; DeRouen et al., 2006; Factor-Litvak et al., 2003; Luglie et al., 2005; Kingman et al., 1998, 2005; Maserejian et al., 2008; Pesch et al., 2002) and includes all surfaces of amalgam available for release of Hg^0. The first author independently examined approximately 5% of subjects for amalgam status reliability and there was 100% agreement.

We also determined a secondary metric, an occlusal point score (Watson et al., 2011). Several studies have demonstrated significantly enhanced release of Hg^0 from amalgams during brushing and chewing, which likely results from perturbation of the occlusal surface of the amalgam restoration (Abraham et al., 1984; Gay et al., 1979; Sallsten et al., 1996; Vimy and Lorscheider, 1985). To further refine occlusal exposure, we estimated the area of each occlusal surface by assigning a score of 1 point for small size occlusal amalgams such as pits, 2 points for medium size such as on premolars, and 3 points for large size on molars, based on a modification of the 'amalgam points' scoring system developed by Olstad and colleagues (1987).

2.3. Metrics of other environmental toxicant exposures

Prenatal MeHg exposure was determined by assessing the average concentration of total mercury (THg) in the longest available segment of maternal hair representing growth during gestation. Infant brain THg levels have been shown to correlate well with maternal hair THg (Cernichiari et al., 2007). Exposures to lead and PCBs have been shown to be low in children and mothers in Seychelles (Davidson et al., 1998) and were not assessed in this cohort.

2.4. Developmental assessment

The primary developmental endpoints were the Mental Developmental Index (MDI) and psychomotor developmental index (PDI) of the Bayley Scales of Infant Development II (BSID-II). The BSID-II was administered at ages 9 and 30 months by specially trained evaluators. Reliabilities for BSID-II testing were high as reported previously (Davidson et al., 2008).

2.5. Maternal nutrition

Total omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs) were measured as total lipids (including phospholipids) in maternal serum samples taken at 28 weeks and at delivery as described previously (Strain et al., 2008).