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Prenatal mercury exposure and birth outcomes

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ABSTRACT

Background: Results regarding the association between mercury exposure and anthropometry at birth, gestational length and placental weight are inconsistent, as is the role of seafood intake in these associations.

Objective: We assessed whether prenatal mercury exposure is associated with anthropometry at birth, placental weight and gestational length in a population with a relatively high exposure to mercury from seafood consumption.

Methods: Total mercury (T–Hg) was determined in cord blood from 1869 newborns with birth outcome measures, within the Spanish multicenter INMA cohort from 2004 to 2008. We adjusted cohort specific linear and Cox regression models to evaluate the association between T–Hg and birth anthropometry (weight, length, and head circumference), placental weight and gestational length. Non-spontaneous labor was taken to be censoring in the survival analysis. Final estimates were obtained using meta-analysis.

Results: Geometric mean T–Hg was 8.2 μg/L. A doubling of T–Hg was associated with a 7.7 g decrease in placental weight (95% CI: −13.6, −1.8) and marginally with head circumference (beta: −0.052 cm, 95% CI: −0.109, 0.005). T–Hg was also inversely related to weight and length, although with weaker estimates. Mercury exposure was not associated with the length of gestation. The inverse relation between T–Hg and growth was enhanced when the intake of different seafood groups was adjusted for in the models.

Conclusions: Prenatal mercury exposure may be associated with reduced placental and fetal growth. Confounding by fish intake should be considered when assessing these relationships.

Abbreviations: 4,4′-DDE, 4,4′-dichlorodiphenyldichloroethylene; AIC, Akaike's Information Criterion; AM, arithmetic mean; BL, birth length; BMI, body mass index; BW, birth weight; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; FGR, fetal growth restriction; GAM, generalized additive models; GL, gestational length; GM, geometric mean; HC, head circumference; HCB, hexachlorobenzene; INMA, Infancia y Medio Ambiente [Environment and Childhood]; LOD, limit of determination; Me, median; MeHg, methylmercury; OCs, organochlorine compounds; P, percentile; PCB, polychlorinated biphenyl; PUFAs, polyunsaturated fatty acids; PW, placental weight; SGA, small for gestational age; sv/wk, servings per week; T–Hg, total mercury

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1. Introduction

Mercury is a heavy metal released into the environment by both natural and anthropogenic sources. It has been estimated that the amount of mercury circulating in the ecosystem has tripled as a result of human activity (Selin, 2009). Mercury exposure negatively affects human health in all forms – elemental, inorganic, or organic – although the most predominant organic form, methylmercury (MeHg), is the one of most concern due to its known neurotoxicity (Grandjean and Landrigan, 2006; NRC (National Research Council), 2000).

Fetuses and children are more vulnerable to mercury exposure due to multiple factors: their developing organs and systems, their immature detoxification mechanisms, or their augmented absorption rates compared with adults (Ginsberg et al., 2004). Moreover, the placenta does not provide the fetus with an effective barrier against MeHg (Gundacker and Hengstschläger, 2012). Some studies have reported a detrimental effect of mercury exposure on newborn anthropometry or on the length of gestation; however, the results are inconclusive among populations with moderate chronic exposure (Karagas et al., 2012; NRC (National Research Council), 2000). The current evidence on the association between mercury exposure in humans and placental weight is even more limited (Drouillet-Pinard et al., 2010; Grandjean et al., 2001). The placenta is of special biological interest because of its intermediate role in the transfer of nutrients and contaminants to the fetus. Additionally, not only birthweight, but also the placental development (weight and shape) have been shown to predict health outcomes at later stages of life (Eriksson et al., 2010).

Diet, and primarily fish and seafood intake, is the main source of MeHg exposure in the general population (NRC (National Research Council), 2000; Ramon et al., 2011). Some studies have evaluated the net effect of fish intake on fetal growth and the length of gestation (Grandjean et al., 2001; Halldorsson et al., 2007; Leventakou et al., 2014; Lucas et al., 2004; Olsen et al., 2006), with discrepant findings. Discrepancies could be related to differences in the frequency of consumption, the fish species that are most commonly consumed, and their origin. Fish intake provides beneficial nutrients such as selenium, iron, or iodine; moreover, fish intake is recommended to achieve a balanced diet, since it is a good source of protein, low in saturated fats, and is the main source of n-3 fatty acids, critical to prevent deficiencies in brain development and cardiovascular disorders (Choi et al., 2008; WHO (World Health Organization), 2008). However, seafood intake is also a via of exposure not only to environmental pollutants such as mercury or polychlorinated biphenyls (PCBs), but also to other known contaminants such as hexachlorobenzene, dioxins and dibenzofurans, brominated diphenyl ethers, cadmium, or lead (Domingo et al., 2007). Differences in fish choices may affect the balance between their possible benefits and risks, and are therefore a key factor in confounding assessment, so that the potentially adverse effects linked to mercury exposure may be outweighed by the beneficial effects of fish intake, or strengthened by other contaminants (Choi et al., 2008; Ramon et al., 2009; WHO (World Health Organization), 2008; Domingo et al., 2007).

In the Spanish multicenter mother-and-child cohort study INMA (Infancia y Medio Ambiente [Environment and Childhood]) we previously reported high cord blood total mercury (T–Hg) concentrations, with a geometric mean of 8.2 μg/L, and strongly associated with fish intake (Ramon et al., 2011). We also found that T–Hg was associated with birth weight in the Valencia sub-cohort (Ramon et al., 2009) and that the intake of different fish groups was confounding this association. The objective of the present study is to assess the association between cord blood T–Hg levels and anthropometric measures at birth in the 4 INMA sub-cohorts with available T–Hg determination in cord blood, while also expanding the set of response variables by including head circumference, placental weight, and gestational length. We additionally assessed the possible heterogeneity among geographical areas and the confounding role of fish intake.

2. Materials and methods

2.1. Study population and data collection

INMA (www.proyectoinma.org) is a mother and child cohort study conducted in various Spanish regions to evaluate the effect of environmental contaminants, and the role of diet, on fetal and infant growth and development (Guxens et al., 2012). During the first trimester of pregnancy, 2644 women were enrolled at their first routine specialized prenatal care visit in their reference primary health care centers or public hospitals in the sub-cohorts of Valencia, Sabadell, Asturias, and Gipuzkoa, following a common protocol (participation rate: 56%). Recruitment took place by consecutive sampling of those women who met the inclusion criteria: $\geq$16 years, singleton pregnancy, non-assisted conception, delivery scheduled at the reference hospital, and no communication handicap. After excluding women who had induced or spontaneous abortions (62), fetal deaths (10), withdrew from the study (61), or were lost to follow-up (5), a total of 2506 (95%) children were born between May 2004 and August 2008. The study sample comprised 1869 newborns with T–Hg determination and information on anthropometric outcomes and/or gestational length. Among the 637 deliveries excluded from the present study, there was no available cord blood sample in 543 of them, 49 samples were excluded due to problems related to their preservation, 28 samples did not include an analytical determination for other reasons (not enough blood, coagulation, etc.), and no information about reproductive outcomes was available for the remaining 17 births. Details about the study protocol, the follow-up of the cohort, and the availability of mercury samples are provided elsewhere (Guxens et al., 2012; Ramon et al., 2011).

2.2. Mercury exposure

Whole blood samples were collected using venipuncture of cord vessels before the placenta was delivered. Samples were processed, separated into aliquots and frozen at −80 °C until analysis in the Public Health Laboratory of Alava (Basque Country, Spain). One aliquot of 1 mL was used to analyze T–Hg by thermal decomposition, amalgamation, and atomic absorption spectrometry using a single-purpose LECO AMA-254 analyzer. Analyses were replicated for each sample and the limit of determination (LOD) of the procedure was 2.0 μg/L. For measurements below the LOD, taking into account its low frequency ($<5\%$), we used the $\mathrm{LOD}/\sqrt{2}$ approach.

2.3. Birth outcomes

Gestational age was defined on the basis of the self-reported last menstrual period. An early crown–rump length measurement was used to correct gestational age when both approximations differed by 7 days or more (12%). Women for whom this difference exceeded 3 weeks (0.7%) were removed from the study to avoid possible bias. Preterm births were those with a gestational age below 37 weeks.

Birth weight was measured by the midwife attending the birth, whereas birth length and head circumference (HC) were measured by a nurse when the newborn arrived at the hospital ward within the first 12 h of life. Placental weight was available in 3 cohorts (Gipuzkoa, Sabadell and Valencia); placentas were weighed