Environmental Research 160 (2018) 97–106

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Prenatal exposure to mercury and longitudinally assessed fetal growth: Relation and effect modifiers

Ferran Ballester[a,b,c,1,*], Carmen Iñiguez[b,c,1], Mario Murcia[c,b], Mònica Guxens[c,d,e,f], Mikel Basterretxea[g,h], Marisa Rebagliato[b,c,i], Jesús Vioque[c,j], Aitana Lertxundi[c,k], Ana Fernandez-Somoano[c,l], Adonina Tardon[c], Jordi Sunyer[c,d,e], Sabrina Llop[b,c]

[a] Nursing School, Universitat de València, Valencia, Spain
[b] FISABIO–Universitat Jaume I–Universitat de València Joint Research Unit of Epidemiology and Environmental Health, Valencia, Spain
[c] Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Spain
[d] Universitat Pompeu Fabra, Barcelona, Spain
[e] ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
[f] Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre–Sophia Children's Hospital, Rotterdam, The Netherlands
[g] Public Health Division of Gipuzkoa, San Sebastián, Spain
[h] Health Research Institute (BIODONOSTIA), San Sebastián, Spain
[i] Medicine Department, Universitat Jaume I, Castelló de la Plana, Spain
[j] Universidad Miguel Hernández, San Juan de Alicante, Spain
[k] Universidad del País Vasco, Spain
[l] IUOPA, Departamento de Medicina, Universidad de Oviedo, Spain

ARTICLE INFO

Keywords:
Pregnancy
Mercury
Fetal growth
Seafood consumption
Polychlorinated biphenyl 153

ABSTRACT

Background: Prenatal mercury exposure has been related to reductions in anthropometry at birth. Levels of mercury have been reported as being relatively elevated in the Spanish population.
Objective: To investigate the relation between prenatal exposure to mercury and fetal growth.
Methods: Study subjects were pregnant women and their newborns (n:1867) participating in a population-based birth cohort study set up in four Spanish regions from the INMA Project. Biparietal diameter (BPD), femur length (FL), abdominal circumference (AC), and estimated fetal weight (EFW) were measured by ultrasounds at 12, 20, and 34 weeks of gestation. Size at and growth between these points were assessed by standard deviation (SD) scores adjusted for constitutional characteristics. Total mercury (T-Hg) was determined in cord blood. Associations were investigated by linear regression models, adjusted by sociodemographic, environmental, nutritional – including four seafood groups – and lifestyle-related variables in each sub-cohort. Final estimates were obtained using meta-analysis. Effect modification by sex, seafood intake and polychlorinated biphenyl (PCB) congener 153 concentration was assessed.
Results: Geometric mean of cord blood T-Hg was 8.2 μg/L. All the estimates of the association between prenatal Hg and growth from 0 to 12 weeks showed reductions in SD-scores, which were only statistically significant for BPD. A doubling of cord blood T-Hg was associated with a 0.58% reduction in size of BPD at week 12 (95% confidence interval -CI-: − 1.10, − 0.07). Size at week 34 showed estimates suggestive of a small reduction in EFW, i.e., a doubling of T-Hg levels was associated with a reduction of 0.38% (95% CI: − 0.91, 0.15). An interaction between PCB153 and T-Hg was found, with statistically significant negative associations of T-Hg with AC and EFW in late pregnancy among participants with PCB153 below the median.
Conclusions: Exposure to mercury during pregnancy was associated with early reductions in BPD. Moreover, an

Abbreviations: 4,4′-DDE, 4,4′-dichlorodiphenyldichloroethylene; AC, abdominal circumference; AIC, Akaike's Information Criterion; AM, arithmetic mean; BL, birth length; BPD, biparietal diameter; BMI, body mass index; BW, birth weight; CI, confidence interval; CRL, crown-rump length measurement; DHA, docosahexaenoic acid; EFW, estimated fetal weight; ETS, environmental tobacco smoke; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; FGR, fetal growth restriction; FL, femur length; GAM, Generalized additive models; GM, geometric mean; GSTM1, glutathione S-transferase M1; GSTT1, glutathione S-transferase T1; I^2, I-squared statistic; HC, head circumference; HCB, hexachlorobenzene; Hg, mercury; INMA, Infancia y Medio Ambiente [Environment and Childhood]; LMP, last menstrual period; LOD, limit of determination; LSPPV, Public Health Laboratory in Alava; Me, median; MeHg, methylmercury; NO_2, nitrogen dioxide; OCs, organochlorine compounds; P, percentile; PCB, polychlorinated biphenyl; PUFAs, Polyunsaturated fatty acids; SGA, small for gestational age; SD, standard deviation; sv/wk, servings per week; T-Hg, total mercury

* Corresponding author at: FISABIO–Universitat Jaume I–Universitat de València Joint Research Unit of Epidemiology and Environmental Health, Av. Catalunya 21, 46020 Valencia, Spain.
E-mail address: ballester_fer@gva.es (F. Ballester).
[1] Both authors contributed equally to the development of the manuscript.

http://dx.doi.org/10.1016/j.envres.2017.09.018
Received 22 December 2016; Received in revised form 6 July 2017; Accepted 16 September 2017

antagonism with PCB 153 was observed with noteworthy reductions late in pregnancy in AC and EFW in the group with lower PCB153.

1. Introduction

Fetuses and children are especially vulnerable to the adverse effects of environmental toxicants because, in comparison to adults, their organs and systems are still developing, their detoxification mechanisms are not yet fully mature, and they have higher absorption rates (Selevan et al., 2000). Altered fetal growth and low birth weight have been associated with an increased risk of multiple diseases later in life, including hypertension, obesity, cardiovascular diseases, and diabetes (Gluckman et al., 2008; Guallar et al., 2002;Zheng et al., 2016). Fetal exposures to environmental contaminants, even at low doses, can result in reduced fetal growth or functional changes that may affect the relative development of various organs, leading to persistent alterations in physiologic and metabolic homeostatic set points (Gluckman et al., 2008; Barouki et al., 2012).

Mercury (Hg) is a heavy metal of global concern owing to its ubiquity and persistence in the environment and, more especially, because of its negative effects on human health (UNEP, 2013). The main perturbing impact is the proven developmental neurotoxicity of methylmercury (MeHg), its most prevalent organic form (Grandjean and Landrigan, 2006). The potential impact of moderate chronic exposure to MeHg on fetal growth is uncertain (Karagas et al., 2012), but evidence suggests an effect, especially from some studies within the upper range of current levels of exposure (Lee et al., 2010; Ramon et al., 2009; Dallaire et al., 2013; Tang et al., 2016). In their review Karagas et al. (2012) concluded that this exposure might affect fetal growth but more research was needed.

To date most of the studies have assessed this relation using anthropometric measures at birth as a proxy for fetal growth (Karagas et al., 2012; Taylor et al., 2016). However, by using these measures a distinction cannot be drawn between small but healthy fetuses and those with restricted growth during the fetal period. The use of longitudinally measured fetal biometry could be useful to examine these changes. This approach would also allow the identification of the periods when effects could occur as well as the fetal body segments affected. These facts could be of interest regarding postnatal growth and health later in life (Karagas et al., 2012; Gluckman et al., 2008; Zheng et al., 2016). To our knowledge only one study has assessed the relation between prenatal Hg exposure and ultrasound fetal measurements in two periods of pregnancy (Drouillet-Pinard et al., 2010), i.e., in the French EDEN cohort study, a negative association was reported between hair Hg in 691 pregnant women and fetal biparietal diameter at 20–24 weeks of gestation.

Exposure to Hg has been reported as relatively elevated in the Spanish population, including vulnerable groups such as pregnant women, fetuses and children, compared with other populations in Europe and globally (Ramon et al., 2011; Esteban et al., 2015; Sheehan et al., 2014). These elevated levels have been related to seafood consumption (Ramon et al., 2011; Castaño et al., 2015), the main source of MeHg exposure in human populations. Fish is an important source of beneficial nutrients, like high-quality proteins, vitamins, minerals and, especially, n-3 long-chain PUFA. Fish intake during pregnancy has been associated with increased birth size (Leventakou et al., 2014; Brantsæter et al., 2012). But fish can also be a source of toxicants other than Hg, such as polychlorinated biphenyls (PCBs) (Llop et al., 2010), which have been shown to be related to decreased birth weight (Govarts et al., 2012; Lopez-Espinosa et al., 2016). Accordingly, when analyzing the influence of prenatal Hg exposure on fetal growth, it is important to make adequate adjustments for fish intake as well as related nutrients and other toxicants (Choi et al., 2008, 2014; Dallaire et al., 2013). Moreover, other environmental exposures (i.e., air pollution) related with fetal growth in our study population should also be taken into account (Iñiguez et al., 2016).

Within the Spanish INMA (Environment and Childhood) multicenter birth cohort study, besides reporting elevated cord blood total Hg (T-Hg) levels (Ramon et al., 2011), we have recently assessed the association with birth outcomes (Murcia et al., 2016). There, an association of T-Hg levels with a decrease in placental weight, as well as with head circumference, was reported. In this work we aim to investigate the relation between prenatal exposure to T-Hg and longitudinally measured fetal biometry in the INMA Project.

2. Materials and methods

2.1. Study design and sample

The INMA Project is a mother-and-child cohort study established in 2003 in different areas of Spain following a common protocol (Guxens et al., 2012). This study was based on the sub-cohorts sited in Asturias, Gipuzkoa, Sabadell, and Valencia. The Hospital Ethics Committees of each area approved the research protocol.

Fig. 1 shows the population participating in the different analyses of this study. A total of 2644 eligible women (aged 16 years or more, enrollment at 10–13 weeks of gestation, with a singleton pregnancy, non-assisted conception, delivery scheduled at the reference hospital, and no communication impairment) were recruited in the first trimester of pregnancy and gave their written informed consent prior to inclusion

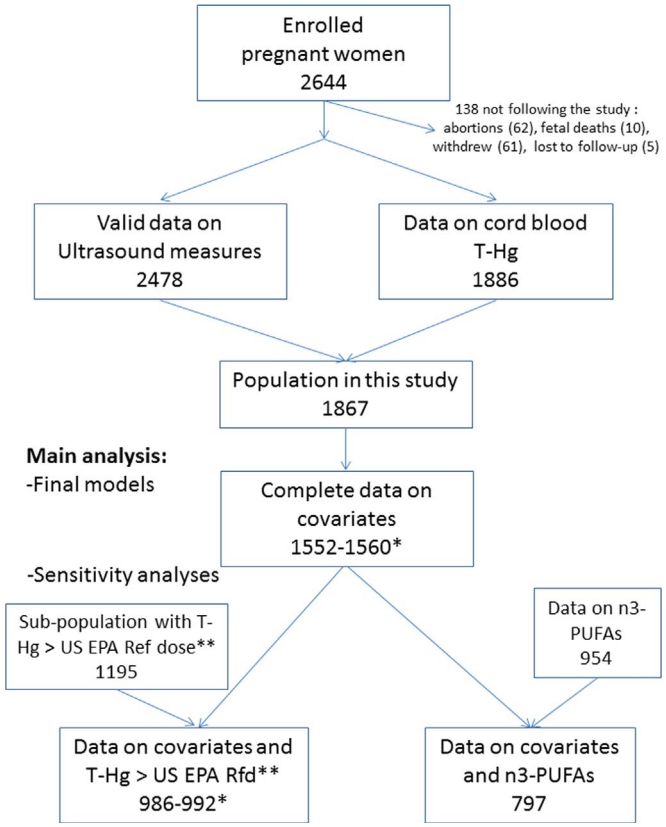

Fig. 1. Flow chart of the population at study. Footnotes: * Depending on different outcomes. ** sub-population with T-Hg concentrations above the current US Environmental Protection Agency reference dose (6.4 μg/L of T-Hg equivalent to 5.8 μg/L of MeHg).