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Synergism between exposure to mercury and use of iodine supplements on thyroid hormones in pregnant women

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ABSTRACT

Objective: To evaluate the association between mercury exposure and thyroid-stimulating hormone (TSH), total triiodothyronine (TT3) and free thyroxine (FT4) levels during pregnancy as well as to explore if there is any synergic action between mercury and intake of iodine from different sources.
Methods: The study population was 1407 pregnant women participating in the Spanish INMA birth cohort study. Total mercury concentrations were analyzed in cord blood. Thyroid hormones (THs) were measured in serum samples collected at 13.2 ± 1.5 weeks of gestation. The association between mercury and TH levels was evaluated with multivariate linear regression models. Effect modification caused by iodine intake from supplements and diet was also evaluated.
Results: The geometric means of TSH, TT3, FT4 and mercury were 1.1 μU/L, 2.4 nmol/L, 10.5 pmol/L and 7.7 μg/L, respectively. Mercury levels were marginally significantly associated with TT3 (β: −0.05; 95%CI: −0.10, 0.01), but were neither associated with TSH nor FT4. The inverse association between mercury and TT3 levels was stronger among the iodine supplement consumers (−0.08; 95%CI: −0.15, −0.02, interaction *p*-value=0.07). The association with FT4 followed the same pattern, albeit not significant.
Conclusion: Prenatal mercury exposure was inversely associated with TT3 levels among women who took iodine supplements during pregnancy. These results could be of public health concern, although further research is needed.

1. Introduction

Thyroid hormones (THs) are essential for cellular metabolism, growth, and development, especially for normal brain maturation (Porterfield and Hendrich, 1993). In fact, deficiencies in maternal THs may lead to neuropsychological disorders, especially during the first half of pregnancy, when the fetus is totally dependent on THs of maternal origin (Morreale de et al., 2004). Some epidemiological studies have observed an association between subclinical alterations of TH status during pregnancy and delays in child neuropsychological development later in life (Haddow et al.,

Abbreviations: CI, confidence interval; D1, deiodinase type I; D2, deiodinase type II; D3, deiodinase type 3; FT4, free thyroxine; GM, geometric mean; sd, standard deviation; TH, thyroid hormones; TSH, thyroid-stimulating hormone; TT3, total triiodothyronine

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1999; Julvez et al., 2013; Li et al., 2010; Pop et al., 2003, 1999).

A large number of environmental pollutants are known to interfere with TH equilibrium (Langer, 2008; Pearce and Braverman, 2009). Conversely, published data on mercury and thyroid function is limited and mostly focused on adults (Abdelouahab et al., 2008; Chen et al., 2013; Yorita Christensen, 2013) and only two studied pregnant populations. In a Canadian study ($n=147$) of pregnant women and their offspring (Takser et al., 2005), an inverse association between cord free thyroxine (FT4) and inorganic mercury was reported, however, such an association was not found in a larger study from the Faroe Islands (Steuerwald et al., 2000).

An adequate iodine intake during pregnancy is essential for the synthesis of maternal THs (Glinoer, 2007). It has been suggested that both deficient and excessive iodine intake can affect the occurrence of subclinical thyroid diseases (Laurberg et al., 2010). In fact, a previous study in pregnant women from the INMA study showed that iodine supplement intake of 200 daily grams or more in the first half of pregnancy was associated to maternal thyroid dysfunction, specifically increasing risk of levels of thyroid-stimulating hormone (TSH) above 3 μU/mL (adjusted odds ratio=2.5; 95% confidence interval=1.2–5.4) (Rebagliato et al., 2010).

Cord blood mercury concentrations in INMA cohort study were relatively high (the geometric mean of total mercury was 8.2 μg/L) (Ramon et al., 2011). However, the effect of the exposure to this metal on TH has yet to be explored.

The aim of this study is to evaluate the association between exposure to mercury and maternal TH levels (TSH, FT4, and total triiodothyronine [TT3]) in the INMA birth cohort study. We also propose to explore if there is any synergic action between mercury and the use of different sources of iodine intake during pregnancy.

2. Materials and methods

2.1. The study population

The study subjects were pregnant women participating in the INMA birth cohort. The INMA—INfancia y Medio Ambiente (Childhood and the Environment)—project is a multicenter cohort study which aims to investigate the effect of environmental exposures and diet during pregnancy on fetal and child development (http://www.proyectoinma.org/).

Details of protocol and study population in INMA project were reported previously (Guxens et al., 2012). Briefly, for this study, women were recruited at the beginning of their pregnancy (November 2003–February 2008) in three regions of Spain: Valencia ($N=855$), Sabadell ($N=657$), and Gipuzkoa ($N=638$). A total sample of 2021 women (92.0% in Valencia, 94.7% in Sabadell and 95.8% in Gipuzkoa) were followed up until delivery. Among them, those women who reported having been diagnosed with thyroid pathology ($n=87$), regardless of whether or not they continued in treatment, were excluded as was a woman from Gipuzkoa with an outlier value in TT3 (15.2 nmol/L). Only women with data available on cord mercury concentrations, maternal THs, as well as questionnaire information were included in this study. We were unable to collect cord blood samples from all participants in the study. This is the main reason for the differences between included ($n=1407$) and excluded ($n=614$) participants.

Characteristics of the areas at study have been described previously (Guxens et al., 2012). Briefly, the Valencia area at study has been sub-divided in four different zones as function of the population density and main uses of land: the urban area is the part of the city of Valencia included in the project, the metropolitan are composed by towns near the city within the ring road, the semi-urban are composed by towns where agriculture and a certain amount of industrial activity are combined with residential areas, and the rural area with villages with a low population density. The Sabadell area is exclusively urban composed by the medium size city of Sabadell (Catalonia). The area of Gipuzkoa (Basque Country) included 25 municipalities and is divided in three narrow valleys that have a high grade of unevenness. Metallurgy is the principal industrial activity in the area.

Women participating in the study signed an informed consent form and the Ethics Committees of the centres involved in the study approved the research protocol.

2.2. Mercury analysis

Whole cord blood samples were collected by using venipuncture of cord vessels before the placenta was delivered. Samples were processed, separated into aliquots of 1 mL, and then frozen to −80 °C until analysis. One aliquot was used to analyze total mercury by thermal decomposition, amalgamation, and atomic absorption spectrometry by using a single purpose AMA-254 advanced mercury analyzer (LECO Corporation, St. Joseph, Michigan). The limit of determination was 2 μg/L. More details of analytical procedure can be found in Ramon et al. (2011). We have categorized the variable mercury into quartiles (1st: <4.8, 2nd: 4.8–7.8, 3rd: 7.9–13.0, 4th: >13 μg/L).

2.3. Thyroid hormone analysis

We measured TSH, TT3, FT4 as biomarkers of thyroid function in maternal serum samples taken at 13.1 ± 1.5 (mean ± standard deviation [sd]) weeks of gestation by means of a solid-phase, time-resolved sandwich fluoroimmunoassay (AutoDELFIA, Perkin Elmer Life and Analytical Sciences, WallacOy, Turku, Finland) using a lanthanide metal europium label. Measurements were performed at the Public Health Laboratory of Bilbao (Spain). Between-assay coefficients of variance were 3.0%, 3.1%, and 2.6% for TSH, 7.2%, 5.5%, and 5.2% for TT3, and 6.1%, 4.1%, and 4.0% for FT4 at low, medium, and high concentrations, respectively.

2.4. Other variables

At the end of the first trimester of pregnancy (12.9 ± 1.7 weeks of gestation), women filled in a questionnaire on socio-demographic, environmental, dietary and lifestyle characteristics, as well as iodine supplement information. The maternal covariates used in this study were maternal age (years), country of birth (Spain, South America, other), level of education (up to primary, secondary, university studies), working situation (unemployed, employed), smoking at the beginning of pregnancy (no, yes), parity (0, 1, >1 children), season of samples collection (winter, spring, summer, autumn), caffeine intake (0, >0–1, >1 mg/day), alcohol intake (0, >0–2 servings/week), and social class, defined according to the most privileged occupation during pregnancy of the mother or the father using a widely used Spanish adaptation of the international ISCO88 coding system. Class I included managerial jobs, senior technical staff, and commercial managers; class II included skilled non-manual workers; and class III included manual workers.

Information on brand names, dose and timing of consumption of specific potassium iodide supplements, or vitamin/mineral preparations containing iodine was obtained with a reference time window from 3 months before conception until the date of the interview. The iodine content per daily dose was obtained from the composition referred to in the reference manual or in the product label information. We defined supplement consumers as those women who were taking supplements at the time of TH