Environmental Research 138 (2015) 271–278

Contents lists available at ScienceDirect

Environmental Research

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

Perinatal exposure to chlordecone, thyroid hormone status and neurodevelopment in infants: The Timoun cohort study in Guadeloupe (French West Indies)

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ARTICLE INFO

Article history:
Received 8 December 2014
Received in revised form
22 January 2015
Accepted 20 February 2015
Available online 3 March 2015

Keywords:
Chlordecone
Prenatal
Breast Feeding
Thyroid Hormone
Children

ABSTRACT

Background: Perinatal exposure to endocrine-disrupting chemicals may affect thyroid hormones homeostasis and impair brain development. Chlordecone, an organochlorine insecticide widely used in the French West Indies has known estrogenic and progestin properties, but no data is available, human or animal, on its action on thyroid hormone system.
Objectives: Our aim was to evaluate the impact of perinatal exposure to chlordecone on the thyroid hormone system of a sample of infants from the Timoun mother–child cohort in Guadeloupe and their further neurodevelopment.
Methods: Chlordecone was measured in cord blood and breast milk samples. Thyroid stimulating hormone (TSH), free tri-iodothyronine (FT3), free thyroxine (FT4) were determined in child blood at 3 months ($n=111$). Toddlers were further assessed at 18 months using an adapted version of the Ages and Stages Questionnaire (ASQ).
Results: Cord chlordecone was associated with an increase in TSH in boys, whereas postnatal exposure was associated with a decrease in FT3 overall, and in FT4 among girls. Higher TSH level at 3 months was positively associated with the ASQ score of fine motor development at 18 months among boys, but TSH did not modify the association between prenatal chlordecone exposure and poorer ASQ fine motor score.
Conclusions: Perinatal exposure to chlordecone may affect TSH and thyroid hormone levels at 3 months, differently according to the sex of the infant. This disruption however did not appear to intervene in the pathway between prenatal chlordecone exposure and fine motor child development.

1. Introduction

Adequate maternal thyroid function in early pregnancy and adequate fetal thyroid function are essential for optimal fetal development, and subtle changes in circulating levels of thyroid hormone may have permanent effect on child development (Zoeller et al., 2002).

Thyroid disruption resulting from exposure to environmental synthetic chemicals has been documented in wildlife and

Abbreviations: ASQ, Ages and Stages Questionnaire; BMI, Body Mass Index; DDE, dichlorodiphenyl dichloroethylene; DDT, dichlorodiphenyl trichloroethane; FT3, free tri-iodothyronine; FT4, free thyroxine; GAM, generalized additive model; HCB, hexachlorobenzene; IQ, Intelligence Quotient; LOD, limit of detection; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated biphenyls; TSH, Thyroid stimulating hormone

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http://dx.doi.org/10.1016/j.envres.2015.02.021
0013-9351/

experimental animals (Brucker-Davis, 1998). The picture is not as clear in humans but there is concern that exposure of pregnant women and infants to endocrine-disrupting chemicals such as polychlorinated biphenyls (PCBs), dichlorodiphenyl trichloroethane (DDT) and its metabolite dichlorodiphenyl dichloroethylene (DDE), hexachlorobenzene and its metabolite pentachlorophenol, polybrominated diphenyl ethers (PBDEs), and nonylphenol may affect thyroid hormones homeostasis and impair growth and brain development (Boas et al., 2012).

Several epidemiological studies have evaluated in particular the impact of prenatal PCBs exposure on child thyroid function, mainly at birth, relying on measures of exposure to PCBs during pregnancy and measures of thyroid hormone levels in cord blood or shortly after birth (prick tests). Some have found decreasing levels of free tri-iodothyronine (FT3) and free thyroxine (FT4) (Maervoet et al., 2007) or total T4 (Herbstman et al., 2008) or increase in thyroid stimulating hormone (TSH) (Alvarez-Pedrerol et al., 2008a; Chevrier et al., 2007) in relation with prenatal PCB exposure but most have found no association (Dallaire et al., 2008, 2009; Longnecker et al., 2000; Lopez-Espinosa et al., 2010; Ribas-Fitó et al., 2003; Steuerwald et al., 2000; Takser et al., 2005; Wang et al., 2005; Wilhelm et al., 2008). These contradictory findings may be partly due to the high variability of thyroid hormone levels at birth due to determinants such as gestational age, mode of delivery or neonatal health that are often not taken into account (Boas et al., 2012). When thyroid function has been evaluated among older children including toddlers, results regarding consequences of perinatal exposure to PCBs are more consistent. Increase in TSH level or decrease in T3 (free or total) or total T4 have been observed in most studies (Alvarez-Pedrerol et al., 2008b; Darnerud et al., 2010; Herbstman et al., 2008; Koopman-Esseboom et al., 1994; Osius et al., 1999), except in Matsuura et al., (2001) and Dallaire et al., (2009).

Chlordecone (Kepone) is an organochlorine insecticide that was principally used for control of the banana root borer in Asia, Latin America, and Africa (ATSDR, 1995) and in Eastern Europe for control of the potato beetle. It was initially manufactured in the US but production and use were banned there in 1976. Subsequently it was produced in Brazil by a French company and intensively used in banana fields in the French West Indies from 1981 to 1993. Its persistence in the environment has resulted in a widespread contamination of soils, water sources and foodstuff (Dubuisson et al., 2007) leading to contamination of populations. Chlordecone is neurotoxic, spermatotoxic, potentially carcinogenic in humans and possesses well defined estrogenic activity (Cannon et al., 1978; Hammond et al., 1979; Multigner et al., 2010). To our knowledge no data is available, human or animal, on its thyroid effects and/or its action on thyroid hormone system.

A longitudinal mother-child study (the TIMOUN cohort) has been set up in Guadeloupe (French West Indies) to investigate the impact of perinatal environmental exposure to chlordecone on child development. In previous reports we have shown impairments of fine motor function at 18 months of age, specifically among boys (Boucher et al., 2013). Here we propose to study the association between chlordecone and thyroid hormone levels at 3 months, and the potential mediation of thyroid dysfunction, if any, on impairment of later child neurodevelopment.

2. Methods

2.1. Population and data collection

The TIMOUN mother-child cohort included women in the second trimester of pregnancy that planned to give birth in the University Hospital of Pointe-à-Pitre and the General Hospital of Basse-Terre (accounting for 70% of all deliveries in Guadeloupe) from December 2004 to December 2007. A detailed informed consent was obtained from 1068 pregnant women. The research procedures were approved by the Guadeloupean Ethics Committee for biomedical studies involving human subjects. A prenatal maternal face-to-face interview was conducted at enrollment by trained midwives to assess obstetrical, medical, personal, and socioeconomic characteristics. Maternal diseases, adverse delivery incidents as well as newborn anthropometric parameters and health information were collected at the end of pregnancy from medical records. Cord blood samples were obtained.

A subgroup of infants was examined at 3 months of age. Exclusion criteria included maternal conditions such as history of diabetes, gestational diabetes mellitus, hypertension, epilepsy, human immunodeficiency virus infection, and long-term corticotherapy ($n=263$). Exclusion criteria for newborns ($n=230$) were not singleton, preterm, small for gestational age, APGAR <7 at 5 min, severe respiratory distress, severe icterus, severe hypoglycemia and materno-fetal infection. For the remaining 575 participants, 365 could not be contacted because of incorrect address or refusal to participate, and 62 had incomplete data. This left 148 children for this analysis. Maternal interviews were conducted at that time (3 months after birth) to assess potential confounders and breast feeding status.

Table 1
Sociodemographic and medical characteristics of mothers and infants ($n=111$).

Characteristics	% or mean ± SD
Maternal	
Age (years)	30.7 ± 6.8
Birthplace (% French West Indies)	80.2
Education (% ≥ 12 years)	48.6
Marital status [a]	
Alone	25.9
With a partner	54.6
Alone with family members	19.4
Parity	1.1 ± 1.2
Maternal BMI (kg/m²) (% ≥ 25)	26.1
Maternal weight gain during pregnancy (g/week) [a]	367 ± 229
Smoking during pregnancy (% yes)	9.0
Alcohol drinking during pregnancy (% yes) [a]	3.6
Fish consumption during pregnancy (g/day) [a]	130 ± 153
Infant	
Age at (weeks)	13.5 ± 1.2
Sex (% male)	52.2
Gestational age (weeks)	39.1 ± 1.1
Birth weight (g)	3258 ± 383
Birth weight *z*-score	0.1 ± 0.9
Breast-fed at 3 months (% yes)	67.6

SD: Standard Deviation; BMI: Body Mass Index.

[a] Missing values for marital status ($n=3$), maternal weight gain during pregnancy ($n=2$), alcohol drinking during pregnancy ($n=1$), fish consumption during pregnancy ($n=5$).

2.2. Exposure assessment

2.2.1. Prenatal exposure to chlordecone and other organochlorine compounds

Cord blood sample were collected, processed and frozen at -30° until shipment on dry ice to Liege University (CART) for analysis. Chlordecone, PCB153 chosen as the representative of the whole mixture of PCBs, and *p,p′*-DDE were measured by gas chromatography–electron capture detection. Preparation of samples and the quantification method were as previously described (Multigner et al., 2010). The limit of detection (LOD) was 0.06 µg/L for chlordecone, and 0.05 µg/L for PCB-153 and *p,p′*-DDE.