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Hypertensive disorders of pregnancy and gestational diabetes mellitus among French Caribbean women chronically exposed to chlordecone

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ABSTRACT

Few studies have explored the consequences of environmental exposure to organochlorine pesticides for gestational hypertension (GH), preeclampsia (PE) and gestational diabetes mellitus (GDM). Chlordecone is a persistent organochlorine pesticide that was used intensively, and almost exclusively, in the French West Indies until 1993. We investigated the impact of prenatal exposure to chlordecone on the occurrence of GDM, GH and PE by studying 779 pregnant women enrolled in a prospective mother–child cohort (Timoun Study) in Guadeloupe between 2004 and 2007. Chlordecone exposure was determined by assaying maternal plasma and information about pregnancy complications was obtained from midwives, pediatricians and hospital medical records after delivery. The risks of GH (n = 65), PE (n = 31) and GDM (n = 71) were estimated by multiple logistic regression including potential confounders. Levels of chlordecone plasma concentration in the third (OR = 0.2; 95% confidence interval (CI): 0.1, 0.5) and fourth quartiles (OR = 0.3; 95% CI: 0.2, 0.7) were associated with a statistically significant decrease in the risk of GH. A log10 increase in chlordecone concentration was significantly associated with lower risk of GH (OR = 0.4; 95% CI: 0.2, 0.6). No significant associations were observed between the chlordecone exposure and the risk of PE or GDM. This study suggests an inverse association between chlordecone exposure during pregnancy and GH. Further studies are required to determine the underlying mechanism, or the potential unknown confounding factors, resulting in this association.

1. Introduction

Hypertensive disorders and diabetes mellitus are common problems a woman may experience during pregnancy (Olsen and Basso, 2005). These pregnancy complications are associated with significant short-term and long-term adverse health outcomes for both mothers and offspring.

Hypertensive disorders occur in 6% to 8% of pregnancies (National High Blood Pressure Education Program, 2000). They include gestational hypertension (GH) and preeclampsia (PE). Gestational hypertension describes women who develop hypertension after 20 weeks of gestation without proteinuria (Leeman and Fontaine, 2008). In most cases, it does not compromise the pregnancy but may be a precursor sign of later chronic hypertension or lead to worse perinatal outcomes if the woman progresses to severe GH (defined as a substantial increase in blood pressure). The causes of most cases of GH remain unknown. Preeclampsia is a pregnancy-specific syndrome characterized by increased blood pressure accompanied by proteinuria. Is a major cause of maternal mortality and morbidity, perinatal death, preterm birth, and intrauterine growth restriction (Sibai et al., 2005).

The prevalence of gestational diabetes mellitus (GDM) may range from 1% to 14% of all pregnancies, depending on the population studied and the diagnostic test employed (American Diabetes Association, 2004). Overweight or obesity and ethnicity are recognized risk factors (Zhang and Ning, 2011). Women with GDM are at increased risk of perinatal morbidity, impaired glucose tolerance and type 2 diabetes in the years after pregnancy. Children of women with GDM are also more likely to be obese and have impaired glucose tolerance and diabetes in childhood and early adulthood (Zhang and Ning, 2011).

Several studies have investigated risk factors for the occurrence of these pregnancy complications. However, few have examined the contribution of environmental risk factors such as pesticides, and in

Abbreviations: GH, gestational hypertension; PE, preeclampsia; GDM, gestational diabetes mellitus; OC, organochlorine; DDE, p,p′-dichlorodiphenyldichloroethylene; PCB, polychlorinated biphenyl; LOD, limit of detection; OR, odds ratio; CI, confidence interval.

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particular persistent organochlorine pesticides (OC). Recent reports from the Agricultural Health Study show an increased risk of self-reported GH, PE and GDM associated with residential or agricultural pesticide exposure during the first trimester of pregnancy (Saldana et al., 2007, 2009). In a recent population-based cohort in the Netherlands, no consistent associations between occupational exposure to chemicals, including pesticides, during pregnancy and hypertensive disorders were observed, but the frequency of exposure to chemicals in general and to pesticides in particular was very low (Nugteren et al., 2012). In a large cohort study of exposures of Norwegian farmers to immunomodulating substances, pesticide use was found to be associated with a moderate, but statistically significant, decrease in the risk of PE (Nordby et al., 2006).

For OC exposure during pregnancy, an inverse association between exposure to p,p′-dichlorodiphenyldichloroethylene (DDE), the main metabolite of dichlorodiphenyl trichloroethane, or to PCBs and GH and PE was identified by a large birth cohort study including 2193 women (Savitz et al., 2013). In the general population, contradictory results have been found concerning the exposure to OC pesticides and hypertension risk (Goncharov et al., 2011; Ha et al., 2009; Valera et al., 2013a,b). We have been unable to find any study of the relationship between exposure to OC pesticides and GDM. Studies in the general population suggest that altered glucose metabolism, increased insulin resistance and reduced insulin production related to OC pesticide exposure may contribute to cause diabetes (Lee et al., 2006; Montgomery et al., 2008; Rylander et al., 2005).

The present study focuses on the population of Guadeloupe (French West Indies), which has been chronically exposed to chlordecone. Chlordecone is almost the only OC pesticide that was used, and extensively, in French West Indies to control banana root borers between the early 1970s and 1993. Chlordecone undergoes no significant biotic or abiotic degradation in the environment (Cabidoche et al., 2009; Faroon et al., 1995). As a consequence and despite chlordecone prohibition in 1993, permanently polluted soils and waterways have been, and are still nowadays, the major sources of human contamination in French West Indies, through the consumption of contaminated and locally produced foodstuffs (Dubuisson et al., 2007; Guldner et al., 2010).

Studies on animals have documented that pre-gestational or gestational exposure of rats and mice to chlordecone affects embryo implantation and both prenatal and postnatal development (Faroon et al., 1995). The mechanism of the toxic action of chlordecone is not completely understood but it has been suspected that its hormonal properties and/or its effect on neurotransmission may be involved (Faroon et al., 1995).

Experimental studies have documented the toxic effects of chlordecone exposure during gestation in animals, but there has been no epidemiological study to determine if chlordecone has similar consequences in humans at environmentally relevant exposure levels. The Timoun mother–child cohort study was established to investigate the consequences for pregnancy and child development of prenatal exposure to the widespread chlordecone pollution in the French West Indies. We recently reported an association between maternal exposure to chlordecone during pregnancy and an increased risk of preterm birth (Kadhel et al., 2014). Here, we report the relationships between maternal exposure to chlordecone and the risk of GH, PE and GDM.

2. Methods

2.1. Population and study design

The study population consisted of pregnant women enrolled in the Guadeloupean prospective epidemiological mother–child cohort study, Timoun, from November 2004 to December 2007. Women who had been living in Guadeloupe for at least 3 years were enrolled during the third-trimester prenatal visit to a Guadeloupe public hospital or dispensary. Of the 1068 women participants, we excluded women whose pregnancy ended in medical termination, fetal death or stillbirth ($n = 6$), women whose babies had major congenital malformations according to the EUROCAT definitions (EUROCAT, 2005) ($n = 36$), and women with missing data on pregnancy complications ($n = 34$) or on chlordecone exposure measurements ($n = 213$). The final analysis included 779 pregnant women. The study was approved by the Guadeloupean Ethics Committee for studies involving human subjects and each participant provided written informed consent.

2.2. Exposure assessment

The chlordecone concentration in maternal blood samples collected into EDTA tubes during labor was determined. After centrifugation, the resulting plasma samples were transferred to polypropylene Nunc® tubes and stored at −30 °C. Plasma samples were transferred, in dry ice, to the Center for Analytical Research and Technology (Liège, Belgium) for the determination of chlordecone concentrations by gas chromatography–electron capture detection. Preparation of samples and the quantification method were as previously described (Debier et al., 2003: Multigner et al., 2010), and details including quality control data are provided in Supplemental material. The limit of detection (LOD) of chlordecone was 0.06 μg/L. Samples from a subgroup of 358 women were also assayed for DDE and PCB 153 (Debier et al., 2003). The LOD for both compounds was 0.05 μg/L. Total cholesterol and triglyceride concentrations in plasma were determined by standard enzymatic procedures (DiaSys Diagnostic Systems GmbH, Holzheim, Germany) and total lipid concentrations were calculated as described elsewhere (Bernert et al., 2007)

2.3. Pregnancy complications

Information about the medical history of the pregnancy was collected from midwives, pediatricians and hospital medical records after delivery. Participants were considered to have GH if they developed systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg after 20 weeks of gestation without proteinuria and if they were previously normotensive. PE was defined as GH associated with proteinuria ≥ 0.3 g/L in a 24-hour urine sample (National High Blood Pressure Education Program, 2000). Women who were diagnosed with both GH and PE were assigned to the PE group. Women assigned to the GH group had GH alone. If hypertension was reported before pregnancy and/or it was detected before 20 weeks of gestation, the women were considered to have chronic hypertension and were included in the control group. Women were considered to have GDM if they had two or more abnormal glucose tolerance test results between 24 and 28 weeks of gestation (Carpenter and Coustan, 1982) and if they were previously normoglycemic. Pregnant women were systematically screened between 24 and 28 weeks of gestation with a fasting oral glucose tolerance test, in which venous blood was sampled 1 h after oral loading with 100 g glucose (American Diabetes Association, 2004). Normal results were a blood glucose < 95 mg/dL at baseline, <180 mg/dL at 1 h, <155 mg/dL at 2 h and <140 mg/dL at 3 h. If diabetes was reported before pregnancy or an abnormal glucose test result was observed at the first prenatal visit (usually between 5 and 10 weeks of gestation), the women were considered to have a preexisting diabetes mellitus (this group included those with pre-gestational diabetes mellitus) and were included in the control group.

2.4. Statistical analysis

The odds ratio (OR) and 95% confidence intervals (CIs) for the association between outcomes and chlordecone were estimated using multiple logistic regression. Polytomous logistic regression was used to estimate simultaneously the risks of non-ordered hypertensive disorders of pregnancy (GH, PE) *versus* a common control group (without GH and without PE).

Regression models included the following potential confounders chosen *a priori* as being likely to interfere with the association between chlordecone exposure and outcome variables (see Table 1 and Supplemental material, Table S1): maternal place of birth (Guadeloupe/Martinique, other Caribbean islands, Europe), place of enrolment (University hospital, local hospital, and local antenatal care unit), maternal age (≤25, 26–31, 32–37, and ≥38 years), pre-pregnancy body mass index (BMI; in kg/m^2; underweight or normal: <25, overweight: 25–<30, obese: ≥30) and average weekly weight gain during pregnancy categorized according to the median (in g/week) (<340, ≥340). Because a substantial fraction of chlordecone is transported by lipids, all analyses were further adjusted for the total lipid concentration in maternal plasma (in g/L). Analyses were performed using chlordecone as a categorical variable (in quartiles, in μg/L) and as a log10-transformed continuous variable.

When chlordecone was analyzed as a categorical variable, exposure levels equal to or below the LOD were included in the first (lowest) quartile. In sensitivity analyses, we handled missing values for chlordecone (N = 213) using multiple imputation techniques (Little and Rubin, 1986; Rubin, 2008) implemented in the R mi package (Yu-Sung et al., 2011). For the imputation procedure, we included the following predictors of exposure categories: case status, maternal place

Table 1
Hypertensive disorders during pregnancy and gestational diabetes mellitus according to maternal characteristics and chlordecone exposure in the Timoun Cohort Study (N = 779).[a]

	All	No GH, no PE	GH	PE	No GDM	GDM
	n = 779	n = 683	n = 65	n = 31	n = 708	n = 71
Maternal place of birth						
Guadeloupe/Martinique	606 (77.8)	532 (77.9)	50 (76.9)	24 (77.4)	549 (77.5)	57 (80.3)
Other Caribbean islands	79 (10.1)	66 (9.7)	10 (15.4)	3 (9.7)	70 (9.9)	9 (12.7)
Europe	94 (12.1)	85 (12.4)	5 (7.7)	4 (12.9)	89 (12.6)	5 (7.0)
Place of enrolment						
University hospital	539 (69.2)	463 (67.8)	50 (76.9)	26 (83.9)	485 (68.5)	54 (76.1)
Local hospital	172 (22.1)	160 (23.4)	9 (13.8)	3 (9.7)	160 (22.6)	12 (16.9)
Local antenatal care units	68 (8.7)	60 (8.9)	6 (9.2)	2 (6.4)	63 (8.9)	5 (7.0)
Maternal age (years)						
≤25	231 (29.6)	214 (31.3)	11 (16.9)	6 (19.3)	224 (31.6)	7 (9.9)
26–31	192 (24.6)	169 (24.7)	12 (18.5)	11 (35.5)	176 (24.9)	16 (22.5)
32–37	144 (18.5)	122 (17.9)	18 (27.7)	4 (12.9)	130 (18.4)	14 (18.5)
≥38	212 (27.2)	178 (26.1)	24 (36.9)	10 (32.3)	178 (25.1)	34 (27.2)
Marital status [b]						
Single	193 (25.4)	163 (24.5)	22 (33.8)	8 (26.7)	174 (25.2)	19 (27.9)
Living with partner	410 (54.0)	365 (55.0)	31 (47.7)	14 (48.7)	370 (53.6)	40 (58.8)
Single living with family	156 (20.6)	136 (20.5)	12 (18.5)	8 (26.7)	147 (21.3)	9 (13.2)
Educational level (years of education)						
Low (<5)	420 (53.9)	358 (52.4)	44 (67.7)	18 (58.1)	376 (53.1)	44 (62)
Medium (5–12)	166 (21.3)	147 (21.5)	9 (13.8)	10 (32.3)	152 (21.5)	14 (19.7)
High (>12)	193 (24.8)	178 (26.1)	12 (18.5)	3 (9.7)	180 (25.4)	13 (18.3)
Parity						
0	289 (37.1)	255 (37.3)	20 (30.8)	14 (45.2)	270 (38.1)	19 (26.8)
1	234 (30.0)	208 (30.5)	22 (33.8)	4 (12.9)	213 (30.1)	21 (29.6)
≥2	256 (32.9)	220 (32.2)	23 (35.4)	13 (41.9)	225 (31.8)	31 (43.6)
Pre-pregnancy BMI (kg/m2)						
<25	471 (60.5)	448 (65.6)	11 (16.9)	12 (38.7)	443 (62.6)	28 (39.4)
25–<30	168 (21.6)	146 (21.4)	14 (21.5)	8 (25.8)	149 (21.0)	19 (26.8)
<30	140 (17.9)	89 (13.0)	40 (61.5)	11 (35.5)	116 (16.4)	24 (33.8)
Weight gain during pregnancy (g/week)						
<340	397 (51.0)	352 (51.5)	33 (50.8)	12 (38.7)	361 (51.0)	36 (50.7)
≥340	382 (49.0)	331 (48.5)	32 (49.2)	19 (61.3)	347 (49.0)	35 (49.3)
Multiple birth						
No	765 (98.2)	671 (98.2)	65 (100.0)	29 (93.6)	695 (98.2)	70 (98.6)
Yes	14 (1.8)	12 (1.8)	0 (0.0)	2 (6.4)	13 (1.8)	2 (1.4)
Smoking during pregnancy						
No	733 (94.1)	640 (93.7)	63 (96.9)	30 (96.8)	664 (93.8)	69 (97.2)
Yes	46 (5.9)	43 (6.3)	2 (3.1)	1 (3.2)	44 (6.2)	2 (2.8)
Alcohol use during pregnancy [c]						
No	729 (97.3)	639 (97.4)	60 (96.8)	30 (96.8)	666 (97.1)	63 (100)
Yes	20 (2.7)	17 (2.6)	2 (3.2)	1 (3.2)	20 (2.9)	0 (0)
Maternal serum lipids (g/L)	6.8 (1.8)	6.9 (1.8)	6.6 (1.4)	7.1 (1.9)	6.9 (1.8)	6.7 (1.6)
Chlordecone (μg/L)						
<0.17	193 (24.8)	158 (23.1)	28 (43.1)	7 (22.6)	173 (24.4)	20 (28.2)
0.17–0.38	203 (26.1)	176 (25.8)	19 (29.2)	8 (25.8)	178 (25.1)	25 (35.2)
0.39–0.80	186 (23.9)	170 (24.9)	7 (10.8)	9 (29.0)	176 (24.9)	10 (14.1)
>0.80	197 (25.3)	179 (26.2)	11 (16.9)	7 (22.6)	181 (25.6)	16 (22.5)

GH, gestational hypertension; PE, preeclampsia; GDM, gestational diabetes mellitus.
[a] n (%) except for maternal serum lipids: mean (standard deviation).
[b] Missing data: 20 for All; 19 for no GH, no PE; 1 for PE; 17 for no GDM; 3 for GDM.
[c] Missing data: 30 for All; 27 for no GH, no PE; 3 for GH; 22 for no GDM; 8 for GDM.

of birth, place of enrolment, education level, parity, maternal age, marital status, pre-pregnancy BMI, and weight gain during pregnancy. A total of five imputed datasets were generated and the main analyses were repeated. Final estimators of associations were then combined using the SAS Proc MIANALYZE procedure.

When chlordecone was analyzed as a continuous variable, we imputed values of chlordecone plasma concentrations below the LOD (12.4%) using the likelihood method (Jin et al., 2011), under the assumption that chlordecone concentration is log-normally distributed. When examining relations between outcomes and exposures considered as continuous variables, simple substitution methods replacing values < LOD by 0, LOD/2, LOD or others, may lead to biased estimations when the percentage of non-detects is >15% (Baccarelli et al., 2005; Whitcomb and Schisterman, 2008); consequently, the use of distribution-based multiple imputation is recommended (EPA US, 2000). These methods have been shown to be able to produce unbiased estimations, even when the percentage of detected values is high (50% to 70%). Five datasets with imputed concentrations below the LOD were generated and analyzed, and the five estimations of associations were then combined using the SAS Proc MIANALYZE procedure. To identify the linear and/or non-linear components of the relationship between chlordecone exposure and pregnancy outcomes, we examined spline functions (with three knots at the quartiles of the distribution), using the SAS macro developed by Desquilbet and Mariotti (2010).

SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina) and R version 2.12.2 (http://www.r-project.org/) were used for analyses; all tests were two-sided, and P values < 0.05 were considered statistically significant.

3. Results

The mean age of the 779 women included in the analysis was 31 years (range 12.4 to 49.6); 77.8% were born in Guadeloupe or Martinique, 69.2% were enrolled at the Guadeloupe university hospital, and 40% were classified as overweight or obese before pregnancy. Overall, 8.3% of all women had GH and 4% PE. GDM was diagnosed in 9.1% of the women. Women with GH or GDM were more likely to be enrolled at the university hospital, to have been born on the other Caribbean islands, and to be older and obese (Table 1). Women with PE were more likely to be nulliparous, to have multi-fetal pregnancies and to have a greater weight gain during pregnancy. The proportion of women who smoked during their pregnancy was lower among those with either GH, PE or GDM. Chlordecone plasma concentration levels were above the LOD for 87.6% of the women and the median concentration was 0.4 μg/L (interquartile interval: 0.2–0.8).

Two hundred and eighty nine (27%) of the 1068 women eligible for inclusion in the cohort were excluded, in most cases because of missing chlordecone exposure data (N = 213). Excluded women were more likely than included women to have been born in the French West Indies or other Caribbean islands, to have a lower educational level and to have been enrolled at a local hospital. The frequencies of GH, PE and GDM among excluded women were 8.6%, 5.7% and 10.7%, respectively (see Supplemental material, Table S2).

Crude and adjusted ORs for hypertensive disorders during pregnancy in relation to exposure to chlordecone are given in Table 2. After adjustment for confounders, a negative association between chlordecone exposure and GH was detected: the decrease in OR was statistically significant for the third quartile (OR = 0.2; 95% confidence interval (CI): 0.1, 0.5) and fourth quartile (OR = 0.3; 95% CI: 0.2, 0.6) of chlordecone plasma concentrations. When considering chlordecone as a continuous variable, chlordecone concentration was significantly associated with a lower risk of GH (OR = 0.4; 95% CI: 0.2, 0.6). The study of the relationship between log-chlordecone blood concentrations and GH risk using splines revealed a significant decreasing linear component (P < 0.01), the non-linear component not being significant (P = 0.37) (see Supplemental material, Figure S1). In contrast, we found no significant association between chlordecone exposure during pregnancy and PE (Table 2).

There was no statistically significant association between chlordecone exposure during pregnancy and risk of GDM in both crude and adjusted models, although a decreasing trend in risk with increasing plasma chlordecone concentration was observed (Table 3).

The comparison of the associations obtained when considering complete cases (N = 779) (Tables 2 and 3) or all subjects with missing chlordecone values imputed (N = 992) (Supplemental material, Table S3) shows that imputation attenuated the slope of decreased risk of GH, but the decreasing trend in risk remained statistically significant. For PE and GDM, the results were less sensitive to the inclusion of imputed values for missing chlordecone measurements.

In the subgroup of 358 women for whom DDE and PCB 153 concentrations were assayed, Spearman's rank correlation coefficients were 0.02 (P = 0.75) between chlordecone and DDE, and −0.02 (P = 0.76) between chlordecone and PCB 153. There is thus no evidence suggesting that DDE and PCB 153 are confounders in these associations.

4. Discussion

This study conducted in a population of pregnant women chronically exposed to chlordecone suggests an inverse association between chlordecone exposure during pregnancy and GH risk. Conversely, we found no statistically significant association between chlordecone exposure and PE or GDM.

These results were obtained by studying a population chronically exposed to chlordecone through the consumption of contaminated locally produced foodstuffs such as root vegetables. In the French West Indies, DDT has not been extensively used in agriculture or for disease vector control. In addition, this territory has had only very limited industrial activities involving significant use or emission of PCBs. Consequently, exposure to these chemical pollutants is likely to be the consequence of the universal atmospheric transport from remote areas and background

Table 2
Associations between chlordecone exposure and hypertensive disorders during pregnancy in the Timoun Cohort Study (n = 779).

	Gestational hypertension n = 65			Preeclampsia n = 31		
	n [a]	Crude OR (95% CI)	Adjusted OR (95% CI)	n [a]	Crude OR (95% CI)	Adjusted OR (95% CI)
Chlordecone (μg/L)						
<0.17	28	1.0	1.0 (reference)	7	1.0	1.0 (reference)
0.17–0.38	19	0.6 (0.3, 1.1)	0.5 (0.3, 1.1)	8	1.1 (0.4, 2.9)	1.1 (0.3, 2.8)
0.39–0.80	7	0.2 (0.1, 0.5)	0.2 (0.1, 0.5)	9	1.2 (0.4, 3.3)	1.2 (0.4, 3.4)
>0.80	11	0.3 (0.2, 0.7)	0.3 (0.1, 0.6)	7	0.9 (0.3, 2.6)	1.0 (0.3, 3.1)
Log10 chlordecone	65	0.4	0.4 (0.2, 0.6)	31	0.9	0.9 (0.4, 1.7)

OR, odds ratio; CI, confidence interval.
The odds ratios reported in this table were adjusted to maternal place of birth, place of enrolment, maternal age, pre-pregnancy body mass index, maternal weight gain during pregnancy and total lipids in maternal plasma.
[a] Number of cases in the model.

Table 3
Associations between chlordecone exposure and gestational diabetes mellitus in the Timoun Cohort Study (n = 779).

	Gestational diabetes mellitus n = 71		
	n [a]	Crude OR (95% CI)	Adjusted OR (95% CI)
Chlordecone (μg/L)			
<0.17	20	1.0	1.0 (reference)
0.17–0.38	25	1.2 (0.7, 2.3)	1.1 (0.6, 2.2)
0.39–0.80	10	0.5 (0.2, 1.1)	0.5 (0.2, 1.1)
>0.80	16	0.8 (0.4, 1.5)	0.7 (0.3, 1.5)
Log10 chlordecone	71	0.7	0.7 (0.5, 1.1)

OR, odds ratio; CI, confidence interval.
The odds ratios reported were adjusted to maternal place of birth, place of enrolment, maternal age, pre-pregnancy body mass index, maternal weight gain during pregnancy and total lipids in maternal serum.
[a] Number of cases in the model.

contamination of the food chain. The poor correlation we found between chlordecone plasma concentration and other OCs chemicals may be explained by the different sources of exposure.

Chlordecone has not been measured in populations other than those in the French West Indies (Boucher et al., 2013; Dallaire et al., 2012; Guldner et al., 2010; Kadhel et al., 2014; Multigner et al., 2010) and Hopewell (Virginia, USA) (Cannon et al., 1978; Cohn et al., 1978). A chlordecone poisoning episode in Hopewell affected plant workers during the mid-1970s. This led to a very high exposure, resulting in blood concentrations one hundred to one thousand times greater than those currently observed among the French West Indian population. Chlordecone exposure was also measured among adult residents of Hopewell during the mid-1970s and the serum concentrations in subjects with detectable values (at this time the LOD was around 1.5 μg/L) were between 5 and 32 μg/L (Cannon et al., 1978), a range similar to those currently observed in French West Indies population.

Very few studies have been conducted in this domain. The major epidemiological studies that investigated the effects of pesticides on pregnancy-related hypertensive disorders and GDM examined the consequences of occupational or residential exposure to these agents. In these studies, pesticide exposure was frequently nonspecific, or the pesticides belonged to chemical families with particular properties, different from chlordecone (Nordby et al., 2006; Nugteren et al., 2012; Saldana et al., 2007, 2009; Willis et al., 1993). A recent report described the relationship between serum levels of persistent OC measured during the third trimester of pregnancy and the development of GH and PE, among 2193 women included in a large birth cohort study in the United States (Savitz et al., 2013). The authors found an inverse association between exposure to DDE or PCBs, and GH and PE, and the association was stronger for PE. Other studies on the risk of hypertension were conducted in the general population exposed to OC pesticides, and report conflicting results (Goncharov et al., 2011; Ha et al., 2009; Valera et al., 2013a,b). These studies represent a pathophysiological context different than hypertensive disorders of pregnancy. Thus, the body of evidence relevant to the association between OC pesticides and hypertensive disorders of pregnancy is limited, and therefore our findings should be interpreted with caution.

There are several modes of action of chlordecone that could explain the inverse association with the risk of GH. Animal studies have shown that chlordecone exposure affects centrally regulated functions through noradrenaline-mediated effects (Chen et al., 1985; Tilson et al., 1987). Additional studies in rats have shown that chlordecone induces hypothermia mediated by alterations in alpha-adrenergic nervous system (Cook et al., 1987, 1988a,b; Swanson and Woolley, 1982). Both the regulation of central body temperature and the control of vascular tone regulating blood pressure are under the influence of adrenergic mechanisms in the sympathetic arm of the autonomic nervous system. Unfortunately, blood pressure measurements were not reported in any of the studies cited above. It has not been established whether or not chlordecone acts on the regulation of blood pressure in the same way and direction as on the central temperature. Another possible mode of action is related to the endocrine disrupting properties of chlordecone with progestagenic-like characteristics. Chlordecone stimulates the synthesis of the progesterone receptor in rat uterine tissues *in vivo* (Hammond et al., 1979), and can inhibit the binding of the progestin agonist R5020 to the form A of the progesterone receptor *in vitro* (Vonier et al., 1996). Progesterone also has hypotensive properties (Rylance et al., 1985) and the progesterone receptor in vascular smooth muscle cells has been identified as a target (Falkenstein et al., 1996). These observations raise the possibility that the observed inverse association between exposure to chlordecone and risk of GH may be due to the sympathomimetic and/or progestin properties of chlordecone.

However, the possibility of reverse causation cannot be excluded: GH may affect the chlordecone concentration in blood. Indeed, during pregnancy there is a physiological increase in plasma volume (Letsky, 2008), and this could lead to a dilution of chlordecone in the plasma of pregnant women. Nevertheless, GH does not cause specific changes in plasma volume compared to normotensive pregnant women (Silver et al., 1998), and the mechanisms through which blood pressure may influence the chlordecone concentration in blood, if any, are unclear.

The possible influence of other, unknown, determinants that may be associated with both plasma chlordecone concentrations and GH should also be considered. Savitz et al. (2013) raised the possibility that renal dysfunction and/or hypertriglyceridemic dyslipidemia may distort the association observed between DDE or PCB exposure and GH or PE. However, this is not fully coherent with the fact that we found no significant association between chlordecone exposure during pregnancy and PE: both renal impairment and dyslipidemia are more likely in cases of PE than GH (Franz and Wendler, 1992; Gallos et al., 2013; Wang et al., 2013).

The main strengths of this study lie in its design, a population-based cohort study, and the exposure and outcome measurements. Chlordecone exposure was determined with maternal plasma samples, providing an accurate reflection of the load of this compound in the body (Cohn et al., 1978; Guzelian, 1982). Its half-life in blood is around 6 months (Cohn et al., 1978), so a single measure at the end of pregnancy can be considered to be reasonably representative of exposure throughout the pregnancy. Co-exposures to other OC compounds were also considered (DDE and PCB153). Data for pregnancy complications were collected from obstetricians participating in the cohort study, which enhances their reliability. Also, the known risk factors for GH, PE or GDM were found. The small numbers in some of the groups may however have limited our capacity to uncover associations with PE in particular.

5. Conclusion

This study suggests a possible inverse association between chlordecone exposure during pregnancy and GH but no relationship with PE or GDM. Additional studies are necessary to explore the mechanisms involved, and in parallel to identify putative unknown confounding factors that may affect this association.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2014.03.024.

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