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Persistent organochlorines and hypertensive disorders of pregnancy

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ABSTRACT

Although there is indirect evidence to suggest that persistent organochlorines might increase risk of hypertensive disorders of pregnancy, there are no epidemiologic studies directly addressing this question. In this cohort study, sampled from the Collaborative Perinatal Project, 1933 women had complete data on organochlorine measurements, covariates, and pregnancy outcomes. Exposures to organochlorines were divided into quintiles, and levels were much higher in these patients recruited from 1959 to 1965 compared to levels in the general population at present. Among included women, 364 developed gestational hypertension (hypertension without proteinuria) and 131 developed preeclampsia (hypertension with proteinuria). We found essentially no association between serum DDE and total PCBs and risk of either gestational hypertension or preeclampsia. Results for other organochlorines showed varying patterns of results: DDT was inversely associated with risk of gestational hypertension (p for trend <0.001), B-Hexachlorocyclohexane and heptachlor epoxide were inversely related to gestational hypertension (p trend <0.01 and 0.10, respectively), dieldrin had a modestly positive association with gestational hypertension (p for trend$=0.12$), and hexachlorobenzene, trans-nonachlor, and oxychlordane yielded results close to the null. Hexachlorobenzene showed an inverse association with preeclampsia (p for trend <0.001). The study suggests that persistent organochlorines present at historically high level are not likely to increase the risk of hypertensive disorders of pregnancy, suggesting that other toxicants that have similar biologic effects are also unlikely to do so.

1. Introduction

Hypertensive disorders are common pregnancy complications that adversely affect the health of the mothers and fetus (Duckitt and Harrington, 2005; Trogstad et al., 2011). The condition is referred to as "gestational hypertension" when the hypertension is not accompanied by proteinuria and as "preeclampsia" when proteinuria is present. Preeclampsia is associated with fetal growth restriction and spontaneous preterm birth as well as medically indicated preterm birth (Hutcheon et al., 2011) since only delivery resolves the condition. Established risk factors for both gestational hypertension and preeclampsia are nulliparity and obesity, and tobacco use has been found to be associated with reduced risk (Trogstad et al., 2011).

The potential for environmental contributors to hypertensive disorders of pregnancy has received little attention. A few studies, however, suggest that exposures such as air pollution (Lee et al., 2013; Wu et al., 2009), lead (Kennedy et al., 2012), or perfluoroalkyl substances (Savitz et al., 2012a, 2012b) may increase risk. While some evidence links the persistent organic pollutants PCBs and DDE with risk of hypertension and metabolic syndrome in nonpregnant adults (Lind et al., 2013; Uemura et al., 2009), their relation to hypertensive disorders of pregnancy has not been examined.

2. Materials and methods

2.1. Study population

The participants were women enrolled in the Collaborative Perinatal Project (CPP), a prospective study of neurologic disorders and other conditions in children (Broman, 1984; Niswander and Gordon, 1972). Pregnant women were recruited from 1959 to 1965 at 12 U.S. study centers. Women were ineligible if they were incarcerated, if they were planning to leave the area or to give the child up for adoption, or if they gave birth on the day they were recruited into the study. The characteristics of women in the sample were, at registration, essentially the same

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as those in the sampling frame (Niswander and Gordon, 1972). Once enrolled, the mothers' non-fasting blood was collected approximately every 8 weeks for the remainder of the pregnancy, at delivery, and 6 weeks postpartum. Sera were stored in glass at −20 °C with no recorded thaws. Approximately 42,000 women were enrolled and 53,000 children born in the study.

We measured serum organochlorine levels in a subset of these mothers. Eligibility criteria were delivery of a live-born singleton and availability of a 3 mL aliquot of third-trimester maternal serum. Of the 43,628 mother-child pairs who met the eligibility criteria, 1200 were selected at random and 1623 were selected according to sex-specific birth defects or performance on various neurodevelopmental tests (Longnecker et al., 2001). This research was approved by the National Institute of Environmental Health Sciences Institutional Review Board.

2.2. Measurement of organochlorines

Maternal serum samples were analyzed for β-hexachlorocyclohexane (HCH), p,p'-dichlorodiphenyldichoroethene (DDE), p,p'-dichlorodiphenyltrichloroethane (DDT), dieldrin, heptachlor epoxide, hexachlorobenzene, trans-nonachlor, oxychlordane, and 11 polychlorinated biphenyl (PCB) congeners (28, 52, 74, 105, 118, 138, 153, 170, 180, 194, and 203) at the Centers for Disease Control and Prevention (CDC) from 1997 to 1999. Quantification of these organochlorines was done using electron capture detection after solid-phase extraction, cleanup, and dual-column gas chromatography (Brock et al., 1996). Measured levels reported by the laboratory that were below the limit of detection (LOD) were used in the analyses (Longnecker et al., 2005). For the present analysis, the concentrations of the 11 PCB congeners were summed to calculate total PCBs. Serum triglycerides and total cholesterol (mg/dL) were measured with standard enzymatic methods (Longnecker et al., 2005).

2.3. Definition of gestational hypertension and preeclampsia

We applied the algorithm of Roberts et al. (2010) to the pregnancies in our study. To be eligible for inclusion in the data analysis, the participant must have had no history of chronic hypertension, chronic renal disease, or diabetes prior to pregnancy, and not had a blood pressure measurement before 20 weeks' gestation that was ≥90 mm Hg diastolic or ≥140 mm Hg systolic, or proteinuria before 20 weeks' gestation. Gestational hypertension was defined as at least two blood pressure measurements that were ≥90 mm Hg diastolic or ≥140 mm Hg systolic within 14 days of one another, taken between 20 weeks of gestation and 2 weeks postpartum. If accompanied by proteinuria (30+ mg/L of albumin on dipstick) within 14 days of an elevated blood pressure measurement, preeclampsia was considered to be present, and if not accompanied by proteinuria, gestational hypertension was assigned.

2.4. Data analysis

Starting with 2823 pregnancies, we excluded subjects for the following reasons (*n*): history of chronic hypertension (111), history of diabetes mellitus (15), elevated blood pressure observed before 20 weeks of gestation (147), proteinuria before 20 weeks of gestation (44), missing data on DDE or PCBs (192) or on another covariate, mostly prepregnancy BMI (380), leaving 1933 in the final analysis. Gestational hypertension and preeclampsia were modeled separately, as mutually exclusive outcomes in two separate regression models. We divided women into quintiles of exposure for each organochlorine based on the distribution in the entire sample and compared each of the upper four quintiles to the lowest as the referent. The first two quintiles of trans-nonachlor and oxychlordane were combined as the referent because of the relatively large percentage of values below the limit of detection (29%, 31%, respectively).

The covariates selected for adjustment were identified considering known relationships with the exposures and outcomes (Hutcheon et al., 2011) using a directed acyclic graph and included: center (11 indicator variables), prepregnancy body mass index (continuous), socioeconomic index (continuous measure calculated as the mean of the percentile scores for education, occupation, and family income), race (white, black, other), maternal age (≤19, 20–29, and ≥30 years), previous pregnancy (with categories of none, less than two years since most recent delivery, two or more years since most recent delivery), smoking (never smoked, past smoker, and current smoker of <10 cigarettes/day, 10–19/day, or ≥20/day) and serum triglycerides and cholesterol (both continuous).

Odds ratios (ORs) and 95% confidence intervals were estimated using logistic regression models that employed weights equal to the inverse of the sampling probability (Zhou et al., 2007). In addition to representing exposure categorically in the models, we also conducted trend tests (Greenland, 1995). Sensitivity analyses were performed to examine results when the analysis was restricted to nulliparous women (since their risk for the outcomes is markedly greater, (Hutcheon et al., 2011)) and when restricted to those selected to be in the random sample of the CPP, removing biases that may have resulted from outcome-dependent selection.

Table 1
Characteristics of study participants by gestational hypertension and preeclampsia: Collaborative Perinatal Project, 1959–1966.

Characteristic	Pregnancies *n*=1933	Gestational hypertension *n*=364			Preeclampsia *n*=131		
	No.	%	OR[a]	95% C.I.	%	OR[a]	95% C.I.
Age (year)							
≤19	515	24.3	1.0	.	13.4	1.0	.
20–29	1082	22.7	1.1	0.7–1.6	6.7	0.8	0.4–1.5
≥30	336	36.4	1.8	1.1–3.1	11.0	1.0	0.4–2.4
Race							
White	849	23.5	1.0	.	7.7	1.0	.
Black	974	26.2	1.1	0.7–2.0	10.1	1.6	0.7–3.7
Other	110	32.9	1.3	0.6–2.8	11.8	1.5	0.5–4.7
Previous pregnancies							
None	664	28.6	1.0	.	15.2	1.0	.
One or more	1269	23.8	0.6	0.4–0.9	6.3	0.3	0.2–0.6
Prepregnancy body mass index (kg/m^2)							
<25	1543	22.8	1.0	.	8.1	1.0	.
≥25	390	36.7	1.4	1.0–2.0	13.9	2.3	1.3–4.1
Socioeconomic index[b]							
≤5	1197	26.1	1.0	.	10.3	1.0	.
>5	736	24.1	1.0	0.7–1.5	7.3	0.7	0.4–1.5
Smoking status							
Nonsmoker	770	26.7	1.0	.	9.4	1.0	.
Past smoker	294	22.7	0.9	0.6–1.5	8.0	0.9	0.4–2.0
Current smoker, <10/day	370	23.5	0.9	0.6–1.3	10.1	1.1	0.6–2.2
Current smoker, 10–19/day	244	30.5	1.4	0.9–2.2	7.3	1.0	0.4–2.8
Current smoker, ≥20/day	255	22.3	0.8	0.5–1.3	9.8	1.2	0.6–2.5
Interpregnancy interval (year)[c]							
<2	913	23.6	1.0	.	5.2	1.0	.
≥2	356	24.3	0.9	0.5–1.4	9.0	1.0	0.4–2.1

[a] Adjusted for all covariates shown in table, study center and survey weight.
[b] Approximately equal to percentile rank among contemporaneous U.S. households, divided by 10.
[c] Most recent pregnancy, parous only.