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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 of this question. In this cohort study, sampled from the Collaborative Perinatal Project, 1,933 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 1959–1965 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,

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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.

Keywords

organochlorines; PCBs; DDT; gestational hypertension; preeclampsia

1.1 Introduction

Hypertensive disorders are common pregnancy complications that adversely affect the health of the mothers and fetus (Duckitt, 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.*, 2012; Savitz *et al.*, 2012) 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.

2.1 Materials and Methods

2.1.1 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, 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 as those in the sampling frame (Niswander, Gordon, 1972). Once enrolled, the mothers’ nonfasting 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, 1,200 were selected at random and 1,623 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.

2.1.2 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).

2.1.3 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.

2.1.4 Data Analysis

Starting with 2,823 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 1,933 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 6 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/d, 10–19/d, or ≥20/d) 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.

3.1 Results

Among the 1,933 pregnancies included in the analysis, 364 (18.8%) were identified as having developed gestational hypertension and 131 (6.8%) were identified as having developed preeclampsia. Both gestational hypertension and preeclampsia were more common among women with no prior pregnancies and those with BMI ≥25. Gestational hypertension was increased among older mothers, and preeclampsia risk increased with higher levels of total cholesterol and triglycerides (Table 1). The expected inverse association with smoking was not seen. Serum DDE and PCB levels (Appendix Table A.1) were markedly higher than levels seen in more recent years.

We found essentially no association between serum DDE and total PCBs and risk of either gestational hypertension or preeclampsia (Table 2). DDT was associated with lower odds of gestational hypertension, much less so for preeclampsia. When the analysis was restricted to nulliparous women (Appendix Table A.2), the precision was reduced and there was some evidence of an inverse association between DDE and gestational hypertension. Restriction to the random sample from the CPP (Appendix Table 3) yielded some support for a positive association between total PCBs and gestational hypertension but otherwise the results maintained the same patterns as for the total population studied.

The findings for other organochlorines (Table 2) showed varying patterns of results. Bhexachlorocyclohexane and heptachlor epoxide were inversely related to gestational hypertension, dieldrin had a modestly positive association with gestational hypertension, and hexachlorobenzene, trans-nonachlor, and oxychlordane yielded results close to the null.

Hexachlorobenzene showed an inverse association with preeclampsia, but none of the other organochlorines were associated with increased or decreased risk. Restriction to nulliparous women or to those selected in the random sample had little impact on the overall pattern of results.

4.1 Discussion

Based on a population exposed to persistent organochlorines at markedly higher levels than are found at present, we found essentially no evidence of an increased risk among those with higher exposure. In fact, there was sporadic evidence of an inverse association between some of the organochlorines and gestational hypertension and preeclampsia, which had in some cases rather substantial, monotonic gradients. Although there may be a direct effect of loss of albumin reducing organochlorines bound to albumin, this would not likely be sufficient to explain the inverse association seen between hexachlorobenzene and preeclampsia, making the basis for the observed inverse associations unclear. Random error, unrecognized biases, and reverse causation seem more plausible than a true protective effect of these exposures. While there were isolated findings of positive gradients for specific compounds, and there may be unidentified biases towards the null such as a protective effect of the same dietary constituents that elevate organochlorine levels, the overall pattern is most parsimoniously interpreted as a lack of support for an adverse effect of these chemicals on the development of gestational hypertension and preeclampsia. It is plausible that even if these compounds are in fact related to hypertension in the non-pregnant population (Lind *et al.*, 2013; Uemura *et al.*, 2009) that they would not be related to the analogous disorders during pregnancy.

The assignment of the outcomes of interest is likely to be accurate, following a rigorous protocol (Roberts *et al.*, 2010) and generating most of the expected associations between covariates and the health outcomes. However, in this cohort smoking was not related to a reduced risk of gestational hypertension or preeclampsia as has been found in other studies (Hutcheon *et al.*, 2011). The restriction to live birth outcomes may have excluded a significant number of women with severe preeclampsia, with unknown impact on the measures of association. The information on preexisting hypertension and diabetes from this time period may well be incomplete, but insofar as organochlorines are related to increased risk of hypertension, any biases would tend to shift effect estimates upward, The absolute frequency of gestational hypertension and preeclampsia were higher than is commonly observed, but not inconsistent with some other monitored pregnancy cohorts (Macdonald-Wallis *et al.*, 2013) and with the high proportion of African-American women included in our sample (Savitz *et al.*, 2013). The laboratory assays of organochlorines used current technology and are likely accurate measures of serum levels, despite the long period of sample storage.

A substantial proportion of the original population was excluded due to missing data, with a greater proportion of older mothers than younger mothers (21% missing under age 20, 32% age 20–29, 42% age 30+), as expected due to the increasing presence of chronic diseases. Women with BMI ≥25 were somewhat more likely to be missing than women with lower BMI (35% vs. 24%), and women with a prior pregnancy were more likely to be missing than

nulliparous women (34% vs. 25%). The proportion missing by race/ethnicity, socioeconomic status, and smoking did not differ. The more critical question which cannot be answered is whether the association between organochlorines and hypertensive disorders differs between missing and non-missing women.

The markedly elevated organochlorine exposures in the 1960s, when these pregnancies occurred, relative to present-day levels in the general population, provide some assurance that we would have detected reasonably strong associations had any been present. While there are significant limitations, given exposure levels that are now orders of magnitude lower than at the time of the original study, our results provide little support for mounting new studies of these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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This research was reviewed and approved by the National Institute of Environmental Health Sciences IRB and was found to be exempt from Institutional Review Board review at Brown University.

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Highlights

- Organochlorines not associated with increase in hypertension in in pregnancy
- DDT, B-Hexachlorocyclohexane, and heptachlor showed sporadic inverse associations
- DDT, B-Hexachlorocyclohexane, and heptachlor showed sporadic inverse associations

Table 1

Characteristics of study participants by gestational hypertension and preeclampsia: ollaborative Perinatal Project, 1959–66

Characteristic		Pregnancies n = 1,933	Gestational hypertension n = 6474			Preeclampsia n = 315		
		No.	%	OR[c]	95% C.I.	%	OR[c]	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/m2)	< 25	1543	22.8	1.0 6	.	8.1	1.0	.
	>=25	390	36.7	1.4	1.0 – 2.0	13.9	2.3	1.3 – 4.1
Socioeconomic index[a]	<=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 –00201.5
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)[b]	< 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] Approximately equal to percentile rank among contemporaneous U.S. households, divided by 10.

[b] Most recent pregnancy, parous only (n = 1322, 87).

[c] Adjusted for all covariates shown in table, study center and survey weight.

Table 2

Maternal serum organochlorine concentrations in relation to odds of gestational hypertension and preeclampsia: Collaborative Perinatal Project, 1959–1966

		Gestational hypertension				Preeclampsia			
Organochlorine	**Quintile**	**N**[a]	**Crude OR**	**Adj OR**[b]	**95% CI**	**N**[a]	**Crude OR**	**Adj OR**[b]	**95% CI**
p, p' – DDE	1	76	1.0	1.0		25	1.0	1.0	
	2	84	1.1	1.0	0.7 – 1.6	23	1.2	1.2	0.5 –2.6
	3	63	0.8	0.7	0.4 – 1.1	27	0.9	0.8	0.3 – 1.7
	4	71	0.8	0.8	0.5 – 1.3	29	0.9	0.7	0.3 – 1.7
	5	70	1.0	0.9	0.6 – 1.5	27	1.2	0.8	0.4 – 1.8
				P for trend = 0.78				P for trend = 0.50	
p, p' – DDT	1	70	1.0	1.0		22	1.0	1.0	
	2	86	1.2	1.0	0.6 – 1.6	25	1.4	1.1	0.5 – 2.5
	3	64	0.8	0.5	0.3 – 0.9	29	1.3	0.6	0.3 – 1.5
	4	85	1.3	0.8	0.5 – 1.3	20	1.0	0.4	0.2 – 1.1
	5	59	0.7	0.4	0.2 – 0.7	35	1.6	0.6	0.2 – 1.5
				P for trend = 0.002				P for trend = 0.23	
Total PCBs with possibly imputed congeners	1	60	1.0	1.0		22	1.0	1.0	
	2	72	1.1	1.1	0.6 – 1.8	29	1.0	0.7	0.4 – 1.5
	3	69	1.3	1.0	0.6 – 1.7	26	1.1	0.8	0.4 – 1.7
	4	69	1.2	0.9	0.5 – 1.5	29	1.0	0.6	0.2 – 1.5
	5	94	1.7	1.3	0.8 – 2.2	25	0.8	0.5	0.2 – 1.3
				P for trend = 0.39				P for trend = 0.19	
B-Hexacholorocyclohexane	1	77	1.0	1.0		26	1.0	1.0	
	2	93	1.0	0.8	0.5 – 1.3	22	0.8	0.7	0.3 – 1.7
	3	69	0.7	0.6	0.4 – 0.9	19	0.7	0.8	0.4 – 1.9
	4	66	0.7	0.5	0.3 – 0.8	23	0.6	0.5	0.2 – 1.3
	5	57	0.6	0.5	0.3 – 0.8	38	1.4	1.2	0.5 – 3.2
				P for trend = 0.01				P for trend = 0.41	
Dieldrin	1	45	1.0	1.0		21	1.0	1.0	
	2	67	1.4	1.4	0.8 – 2.3	24	1.1	0.9	0.4 – 2.1

Organochlorine	Quintile	Gestational hypertension				Preeclampsia			
		N[a]	Crude OR	Adj OR[b]	95% CI	N[a]	Crude OR	Adj OR[b]	95% CI
	3	85	1.9	1.9	1.1 – 3.2	18	0.8	0.7	0.3 – 1.7
	4	82	1.7	1.8	1.0 – 3.0	30	1.0	0.7	0.3 – 1.7
	5	74	1.8	1.7	1.0 – 3.0	35	1.6	1.0	0.4 – 2.2
				P for trend = 0.12				P for trend = 0.95	
Heptachlor Epoxide	1	64	1.0	1.0		31	1.0	1.0	
	2	58	0.6	0.5	0.3 – 0.9	23	1.0	0.7	0.3 – 1.5
	3	75	0.9	0.7	0.4 – 1.1	20	0.8	0.6	0.2 – 1.4
	4	83	1.1	0.7	0.4 – 1.3	24	1.1	0.7	0.3 – 1.8
	5	72	1.0	0.5	0.3 – 1.0	28	0.9	0.9	0.3 – 3.0
				P for trend = 0.11				P for trend = 0.98	
Hexachlorobenzene	1+2	140	1.0	1.0		58	1.0	1.0	
	3	70	1.0	1.0	0.7 – 1.6	28	0.8	0.9	0.5 – 1.8
	4	85	0.9	0.8	0.5 – 1.3	17	0.4	0.3	0.1 – 0.6
	5	62	0.9	1.0	0.6 – 1.6	25	0.5	0.4	0.2 – 0.9
				P for trend = 0.72				P for trend = 0.01	
trans-Nonachlor	1+2	144	1.0	1.0		40	1.0	1.0	
	3	69	1.1	0.9	0.6 –1.4	33	1.3	1.1	0.5 –2.3
	4	71	0.9	0.8	0.5 – 1.3	28	0.9	0.6	0.3 – 1.4
	5	78	1.0	0.9	0.5 – 1.4	30	1.5	0.8	0.3 – 1.8
				P for trend = 0.51				P for trend = 0.47	
Oxychlordane	1+2	124	1.0	1.0		45	1.0	1.0	
	2	71	1.0	0.8	0.5 – 1.2	23	0.9	0.7	0.3 – 1.6
	3	70	1.2	1.0	0.6 – 1.5	27	1.0	0.8	0.4 – 1.8
	4	78	1.2	0.9	0.6 – 1.6	24	0.9	1.0	0.4 – 2.5
				P for trend = 0.93				P for trend = 0.96	

[a] Number after restrictions for adjusted analyses

[b] Adjusted for age groups (3 indicators), center (11 indicators), triglycerides (continuous), cholesterol (continuous), prepregnancy BMI (continuous), previous pregnancy with IPI < 2years (nullips in reference group), previous pregnancy with IPI >= 2 years, race (two indicator variables), SES (continuous), maternal age (2 indicators) and smoking status (4 indicators).