Polychlorinated Biphenyl Serum Levels in Pregnant Subjects With Diabetes

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OBJECTIVE — Polychlorinated biphenyls (PCBs) are persistent pollutants that are ubiquitous in the food chain; detectable amounts are in the blood of nearly everyone. Their effect on humans at background levels of exposure is an area of active investigation. Increased blood levels of dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin), a PCB-like compound, have recently been reported among subjects with diabetes, suggesting that PCB levels could be similarly elevated. To test this hypothesis, we examined a group of pregnant women whose serum PCB levels had been measured and whose diabetes status had been previously recorded.

RESEARCH DESIGN AND METHODS — Using stored serum from a large birth cohort study, we conducted a cross-sectional study of 2,245 pregnant women, of whom 44 had diabetes (primarily type 1) and 2,201 were control subjects.

RESULTS — The adjusted mean serum level of PCBs among the subjects with diabetes was 30% higher than in the control subjects ($P = 0.0002$), and the relationship of PCB level to adjusted odds of diabetes was linear.

CONCLUSIONS — The possibility exists that PCBs and diabetes are causality related; alternatively, the pharmacokinetics of PCBs could be altered among patients with diabetes. At any event, if the association is replicated in other studies, increased serum levels of PCBs in subjects with diabetes or their offspring may put them at increased risk of PCB-induced changes in thyroid metabolism or neurodevelopment.

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Polychlorinated biphenyls (PCBs) and tetrachlorodibenzo-*p*-dioxin (TCDD) are persistent pollutants that are ubiquitous in the food chain, and detectable amounts are in the blood of nearly everyone (1). PCBs and TCDD have similarities with respect to pharmacokinetics and toxicity. We recently reported that among men with no unusual exposure to TCDD, higher serum TCDD levels were associated with increased prevalence of type 2 diabetes (2). That association prompted us to examine the relationship between PCBs and diabetes in another data set.

RESEARCH DESIGN AND METHODS

— The Collaborative Perinatal Project (CPP) was a joint effort of scientists at National Institutes of Health and 12 U.S. academic centers to investigate the cause of neurological disorders and other diseases in children (3). Over 56,000 pregnant women were enrolled from 1959 to 1966, and their children were systematically followed to 7 years of age. Because some of the CPP investigators were especially interested in the effect of diabetes in pregnancy on offspring, recruitment at the Boston center included subjects from the Joslin Clinic for diabetes. Sera were collected from the mothers and stored in glass containers at −20°C, with no recorded thaws. To study health effects in children of early life exposure to organochlorines, third-trimester serum from 2,739 women in the CPP was recently analyzed for PCBs, triglycerides, and cholesterol at the Centers for Disease Control.

Serum levels of PCBs were measured in 1997–1999 after solid-phase extraction, clean-up, and dual-column gas chromatography using electron capture detection (4). A total of 87% of the batches contained an aliquot from a single large pool used to calculate the between-assay coefficient of variation (CV). The between-assay CV was 19% at 3.49 μg PCB/l ($n = 299$). The specimens from subjects with diabetes were distributed at random throughout the analytical batches. The laboratory personnel were blind to the type of sample. Serum levels of cholesterol and triglycerides were measured using standard enzymatic methods.

We used three sampling methods to select children for inclusion in our study. First, we took a simple random sample ($n = 1,168$). Second, we selected all males with cryptorchidism, hypospadias, or polythelia ($n = 222$, 208, and 179, respectively). A third group of 962 children was selected according to their performance on tests of neonatal tone, neonatal reflexes, Bayley Scale of Infant Development at 8 months, intelligence quotient on the Weschler Intelligence Scale for Children at 7 years of age, and audiometry results at 7 years of age. Among the 2,739 women, the distributions of age, race, smoking status, socioeconomic index, and study center were essentially the same as for all CPP mothers.

Among the 2,739 women whose serum PCB levels were measured, 44 had diabetes. The CPP records did not indicate the type of diabetes. Of the 44 cases,

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Abbreviations: CPP, Collaborative Perinatal Project; CV, coefficient of variation; PCB, polychlorinated biphenyl; TCDD, tetrachlorodibenzo-*p*-dioxin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of subjects*

	Diabetic subjects	Control subjects
n	44	2,201
Age (years)	28 ± 7	24 ± 6*
Race (% white)	84	45*
Socioeconomic index	64 ± 25	48 ± 22*
BMI prepregnancy (kg/m^2)	23 ± 4	23 ± 4
Serum triglycerides (mg/dl)	304 ± 94	208 ± 79*
Serum cholesterol (mg/dl)	235 ± 60	239 ± 67

Data are means ± SD, unless otherwise stated. *The difference between the case and control values was statistically significant ($P < 0.05$) by *t*-test, and a χ^2 test was done for race.

however, 37 had diabetes before pregnancy, i.e., they did not have gestational diabetes (5). In combination with the young age of the subjects, this suggests that most of the 44 case subjects had type 1 diabetes. Of these subjects, 30 were from the study center in Boston, which included subjects seen at the Joslin Clinic. Among all subjects with a PCB measurement who were from study centers other than Boston, 0.9% had diabetes. If we apply this percentage to the number of control subjects from Boston, about five cases of diabetes would have been expected; thus, we estimate that 25 case subjects were from the Joslin Clinic. The 0.9% prevalence of diabetes in the non-Boston centers was consistent with the underdiagnosis of gestational diabetes in the CPP.

We excluded 494 subjects from the analysis for the following reasons: diabetes status could not be determined ($n = 14$), missing data on socioeconomic index ($n = 32$), and missing values for serum lipids ($n = 2$). Cases of diabetes occurred at 9 of the 12 study centers. Because we matched by study center in the analysis (see below), control subjects ($n = 446$) from the three centers in which there were no cases of diabetes were also excluded from the analysis. Among the subjects included in the analysis (Table 1), the patients with diabetes were slightly older, a greater proportion were white, and the socioeconomic index was higher compared with the subjects without diabetes.

We examined the case-control difference in PCB levels in a linear model of $\log_e$(PCB) adjusted for age, race, socioeconomic index, center, serum triglycerides, and cholesterol. We also used conditional logistic regression (conditional on center) to calculate the odds ratio for diabetes in relation to serum level of PCBs, adjusting for the same factors as previously stated. An alternative analytical strategy with control subjects individually matched to cases (conditional logistic regression) by age (±1 year), race, center, and quartile of socioeconomic index, with adjustment for triglycerides and cholesterol as continuous variables, gave results that were essentially the same as those shown.

RESULTS — The median PCB level among the subjects with diabetes was 3.77 μg/l and among the control subjects was 2.79 μg/l (Fig. 1). The median PCB level among control subjects was slightly higher than the value of 1.7 μg/l reported in a more recent study of pregnant women from the U.S. (6). The adjusted mean PCB level in case subjects, expressed in its original scale, was 3.71 μg/l, compared with 2.86 μg/l among control subjects, a 30% difference ($P = 0.0002$). The similarity of the crude and adjusted case-control differences reflected that there was little confounding in these data.

With increasing PCB level, the odds ratio for diabetes increased monotonically (Table 2). Further adjustment of the odds ratios had no appreciable effect on the association; the additional variables considered were: prepregnancy BMI, smoking, squared values of triglycerides or cholesterol, and variables indicating whether the mother had been selected because the child had one of the outcomes under study. The association was essentially unchanged when the analysis was restricted to subjects with diabetes before pregnancy or when PCB levels were expressed on a per serum-lipid basis (in a model without triglycerides or cholesterol as covariates). In addition, when we systematically excluded each diabetic subject from the analysis and refitted the model, the results were essentially unaffected. The median levels of triglycerides (194 mg/dl) and cholesterol (233 mg/dl) among control subjects were essentially the same as in fresh sera.

CONCLUSIONS — These data show a clear association between PCB levels and diabetes, but they are uninformative regarding which came first. Perhaps diabetes causes higher organochlorine levels.

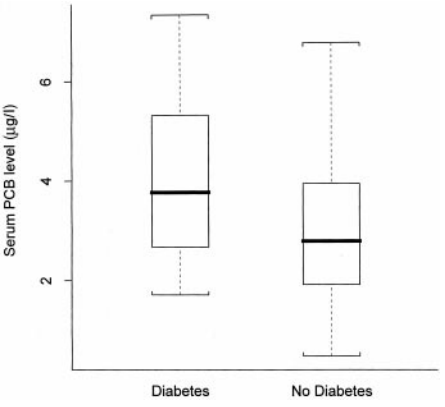

Figure 1—*Percentiles of the distribution of serum PCB concentration (5th, 25th, 50th, 75th, and 95th) by whether the subject had diabetes*

Both type 1 and type 2 diabetes alter the pharmacokinetics of selected drugs (7), but so few agents have been studied that one cannot predict the fate of lipophilic compounds that are resistant to metabolism, such as PCBs. Patients with diabetes tend to have an increased serum triglyceride concentration, and serum organochlorine levels increase with lipid levels, thus raising the possibility that the association could be an artifact. However, our results were adjusted for serum triglycerides to account for this possibility.

Studies of PCB-exposed workers reveal no suggestion of an increased level of glucose (8,9), morbidity, or mortality from diabetes (10,11). However, the diabetes in such studies would be primarily type 2. Although the production of PCBs in the U.S. was banned in 1977, much of the material produced is still in use in

Table 2—*Adjusted odds ratio for diabetes according to serum level of PCBs among pregnant women in the Collaborative Perinatal Project*

Total PCBs (μg/l)	Case subjects	Control subjects*	OR†	95% CI
<2.50	9	926	1.0	—
2.50<3.75	13	666	2.9	1.1–7.3
3.75<5.00	9	309	4.4	1.6–12.5
≥5.00	13	300	5.1	1.9–13.8

Data are *n*, unless otherwise stated. *Only the control subjects from centers that had at least one case of diabetes are shown (total number of control subjects in the table is 2,201); †adjusted for age, socioeconomic index, serum triglycerides, and cholesterol as continuous variables and for race (white versus nonwhites). $P = 0.004$ for trend, with PCB as a continuous variable. OR, odds ratio.

transformers, capacitors, and other applications.

One potential mechanism by which PCBs might cause diabetes is the depletion of β-cell insulin, an effect seen in vitro in RINm5F cells (12). In addition, some PCBs bind with the Ah-receptor, and the binding of TCDD with this receptor mediates TCDD toxicity. TCDD reduces cellular glucose uptake, possibly by altering glucose transporter activity (13). Because the levels of PCB and TCDD used in these experiments (12,13) were relatively high, the relevance to humans at background levels of exposure is unclear. However, recent studies in humans suggest that within the range of background exposure, higher TCDD levels were associated with increased insulin resistance (2,14). At background levels of exposure, the extent of PCB binding with the Ah-receptor is enough (15) that PCBs, like TCDD, could be associated with increased insulin resistance.

Even if patients with diabetes accrue higher body burdens of PCBs than do subjects without diabetes, the levels in patients with diabetes and their offspring are relatively low. Nonetheless, low levels may have adverse effects on thyroid metabolism (16,17) and neurodevelopment (18–20).

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