The Association of Polychlorinated Biphenyls and Pesticides with Infertility

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Introduction

Polychlorinated biphenyls (PCBs) are widely occurring environmental contaminants to which the general population is routinely exposed. PCBs are lipophilic, bioconcentrate in the food chain, and are present in detectable amounts in the fat of all human populations on which monitoring data are available (1). Commercial PCB formulations have been used worldwide as nonflammable dielectrics in transformers and electronic parts, and as vehicles for pesticide application. Much of the industrial world banned the use of PCBs over the past two decades, but, because of their refractory nature, significant exposures still occur and are expected to continue for decades.

Estrogenic activity has been described for a variety of halogenated aromatic hydrocarbons including certain PCB congeners. Structural homology and competition for estrogen receptor binding may be one mechanism for this activity (2). In addition, PCB induction of mixed-function oxidase enzymes could affect metabolism and availability of estrogens (3). Wildlife studies have demonstrated reproductive failures associated with PCB exposures that are likely to be mediated through endocrine disrupting mechanisms (4, 5). In experimental models, decreased fertility has been associated with PCB exposure in female monkeys and mink (6, 7). Preliminary data in human populations suggest an association between follicular fluid PCB concentrations and poor *in vitro* fertilization outcomes (8). The aim of the current case-control study is to assess the effect of human exposures to PCBs on the development of infertility.

Material and Methods

Study participants are being recruited from residents of an industrial community 90 kilometers from Moscow, Russia. This community has a stable population of approximately 142,000 and one of its main industries is a capacitor manufacturing plant which is estimated to have used 1400 tons of PCBs annually between the 1960's and 1988 (9). Effluent from this facility and run-off from a nearby PCB storage site were sources of significant PCB contamination of this community, including areas where local food crops and livestock were produced (9). Recruitment began in April, 1997 and is ongoing. Couples with recently diagnosed primary infertility are identified from patients seen at the local infertility clinic. Couples with a diagnosis of acquired infertility (secondary to infection or surgery, for example) are excluded. Control couples are selected from pediatric birth records such that the year of birth of their first child coincides with the year of diagnosis of infertility for the case couple. Control couples with a history of infertility or delayed conception are excluded. Volunteer couples who agree to participate in the study are evaluated at one of the community pediatric or gynecology clinics by trained study personnel who administer a questionnaire eliciting detailed medical, reproductive, and exposure histories (including occupational and diet histories) to ascertain risk factors for PCB exposure and infertility.

Approximately 30 ml of whole blood is drawn during the study evaluation. The serum is then separated by centrifugation and stored at -20^{O} C until extraction. Samples are analyzed for 59 individual PCB congeners and dichlorodiphenyl dichloroethene (p,p'-DDE). The choice of congeners was based on their potential toxicity, environmental persistence, and prevalence in commercial mixtures and human serum. Samples are extracted using a U.S. Centers for Disease Control method modified to conform to ultra trace level analysis (10). The extracts are analyzed by gas chromatography with electron capture detection (GC/ECD) using a Hewlett-Packard 5870A GC with a capillary column and temperature programming. Quantitation is based on the response factors of individual PCB congeners relative to the internal standard which is added to all samples prior to instrumental analysis. Serum percent lipid content is determined gravimetrically by weighing an aliquot of sample extract evaporated to dryness. The concentration of each PCB congener is corrected by the amount present in the procedural blank run with the same analytical batch. PCB concentrations are reported as individual congeners and as the sum of all congeners in units of ng/g serum and ng/g lipid.

Results and Discussion

These preliminary analyses include the 36 female cases and 38 female controls on whom serum PCB levels are available. Cases were older (27 versus 23 years, $p=0.0001$) and had higher serum lipid content (0.42% versus 0.36%, $p=0.0002$) than controls. Cases were also more likely to be university educated (89% versus 50%, $p=0.002$) and to report exposure to household paints (75% versus 37%, $p=0.001$) compared with controls. Otherwise cases and controls did not differ significantly with regard to body mass index, residence time in the study community, ingestion of locally grown foods, alcohol consumption, tobacco use, pesticide use, reported history of PCB

exposure (including via occupation or maternal exposures), or frequency of intercourse. Only one participant (a control) had a history of work at the local capacitor manufacturing facility.

The sum of PCB congeners were used in these analyses. Cases had significantly higher mean serum PCB concentrations compared with controls (2.0 versus 1.5 ng/g, $p=0.03$). However, after adjustment for age and frequency of intercourse, cases' and controls' mean (±standard error) serum PCB values (2.0 ± 0.2 and 1.5 ± 0.2 ng/g, respectively) were no longer significantly different ($p=0.09$). When adjusted for serum lipid, age, and frequency of intercourse, the mean PCB serum concentration for cases was 465 ± 39 ng/g lipid compared to 429 ± 38 ng/g lipid for controls ($p=0.54$). There were no significant differences between cases' and controls' serum DDE concentrations. In logistic regression models adjusted for age and frequency of intercourse, there was a 1.7 increased odds (95% confidence interval 0.9 to 3.3) of being a case for each ng/g increase in serum PCB and a 1.1 (95% confidence interval 0.9 to 1.4) increased odds of being a case for each ng/g lipid increase in serum PCB.

These results suggest a moderate increased risk of female infertility in association with environmental PCB exposures. However, these preliminary analyses were based on small numbers and did not achieve statistical significance after adjustment for age and serum lipid content. When data collection for this study has been completed, we will re-assess these associations among the larger, final cohort.

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