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Association of prenatal and early life exposure to tetrachloroethylene (PCE) with polycystic ovary syndrome and other reproductive disorders in the cape cod health study: A retrospective cohort study

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ABSTRACT

Background: Tetrachloroethylene (PCE) is an organic lipophilic solvent with possible neuroendocrine toxicity. The objective of this study was to determine the association of prenatal and early childhood exposure to PCE-contaminated drinking water and development of adult-onset Polycystic Ovary Syndrome (PCOS), endometriosis, difficulty conceiving and miscarriage.
Methods: Five-hundred exposed and 331 unexposed female participants born between 1969 and 1983 completed questionnaires on demographic and lifestyle characteristics, and reproductive disorders. Residential locations from the prenatal period through five years of age were used to estimate early life PCE exposure with water modeling software.
Results: For any early life exposure to PCE, the adjusted risk ratio for PCOS was 0.9 (95% CI: 0.5-1.6). No statistically significant associations were observed for increasing levels of exposure with PCOS or the other reproductive disorders.
Conclusion: No meaningful associations were found among adult women with early life exposure to PCE-contaminated drinking water and adult-onset reproductive disorders.

1. Introduction

Tetrachloroethylene (PCE) is an organic lipophilic solvent commonly used in dry cleaning of fabric, degreasing of metals, and in the synthesis of other chemicals. Commonly found in chemical waste, it can easily evaporate and aerosolize, and may leach into contact solutions, such as drinking water [1]. Before harmful health effects were known, PCE was used to apply a vinyl lining to asbestos-cement (AC) water distribution pipes in the Cape Cod area of Massachusetts. The vinyl lining was introduced as a barrier to unacceptable taste and odor problems and to minimize corrosion associated with conventional AC water mains [2]. It was assumed that the PCE solvent would completely evaporate prior to the installation of the pipes carrying drinking water for human use. However, in 1980 Massachusetts officials found that PCE was leaching into public drinking water supplies from the vinyl liner (VL) that had been applied to the AC pipes [3]. There were two distinct features of this exposure setting: (1) an irregular pattern of exposure corresponding to the pattern of VL/AC pipe installation, and (2) a wide range of PCE levels in the water. In one town, exposure levels ranged from undetectable to 80 μg/L in high flow pipes compared to 1600 to 7750 μg/L in low flow pipes, such as those found on dead end streets [4].

Polycystic Ovary Syndrome (PCOS) is a multifactorial disorder affecting the hypothalamic- pituitary-ovarian axis that presents with a combination of the following: oligomenorrhea, clinical or biochemical evidence of hyperandrogenism, and ultrasonographic evidence of polycystic ovary morphology. There is a paucity of literature on PCE and reproductive physiology. Tri- and tetrachloroethylene are noted to cross the placenta after inhalational exposure in a murine model [5]. Other organic solvents, such as chlorinated hydrocarbons are secreted into breastmilk among women with and without occupational exposure [6,7], and benzene is detectable in the follicular fluid surrounding the oocyte among *in vitro* fertilization (IVF) patients at the time of egg retrieval

Abbreviations: CI, confidence interval; DEP, Department of Environmental Protection; GEE, generalized estimating equation; PCE, tetrachloroethylene; RR, risk ratio; VL/AC, vinyl-lined asbestos-cement.

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[8]. Prenatal exposure to organic solvents during brain formation can trigger substantial cell death, potentially leading to structural damage of the neuroendocrine axis [9]. There is literature demonstrating modest associations between organic solvent exposures and adverse reproductive effects. One cross-sectional study in China among occupational petrochemical workers exposed to organic solvents (benzene, styrene, toluene, or xylene) demonstrated menstrual cycle prolongation with adjusted odds ratios for each additional year of work with exposure and for 3 or more years of exposure compared to no exposure were 1.07 (95% CI: 1.00-1.14) and 1.53 (95% CI: 1.00–2.34) respectively [10]. Another study of females with occupational exposure to organic solvents in the pharmaceutical industry demonstrated an increased odds of menstrual disturbances in highly exposed women (OR: 9.7, p = 0.001) [11]. A cross-sectional study of female liquid crystal display-manufacturing workers (with exposure to acetone and ethanol) noted a higher prevalence of short menstrual cycle with an adjusted odd ratio of 7.68 (95% CI: 1.51–39.15) [12]. Three studies reported on reduced fertility and subfertility after exposure to organic solvents [13–16]. In a retrospective time-to-pregnancy study, those with daily or high exposure to organic solvents had reduced fecundability with an adjusted incidence density ratio of clinical pregnancies of 0.41 (95% CI: 0.27–0.62) [13]. Among female workers at a semi-conductor manufacturing plant, high ethylene glycol exposure conferred an increased risk of miscarriage (RR: 2.8, 95% CI: 1.4–5.6) and subfertility (RR: 4.6, 95% CI: 1.6–13.3) [15]. In a prospective cohort study in women with occupational exposure to organic solvent, the occurrence of a major fetal malformation was increased among women with a risk ratio of 13 (95% CI: 1.8–99.5) [17]. Additionally, associations have been previously reported from this cohort between prenatal PCE exposure and neurological outcomes such as color vision deficits, diminished performance on neuropsychological tests of visuospatial functioning, learning and memory, motor, attention and mood [18–20], stillbirths (RR: 2.38, 95% CI: 1.01–5.59), placental abruption (RR:1.35, 95% CI: 0,68–2.67) [21], central nervous system birth defects (OR: 3.1, 95% CI: 0.9–11.0) and oral clefts (OR: 3.2, 95% CI: 0.7–15) [22]. However, few studies have assessed the association of prenatal PCE exposure and PCOS, as well as other adult onset reproductive disorders in women.

The objective of this retrospective cohort study was to determine the association of prenatal and early childhood exposure to PCE-contaminated drinking water and later onset of PCOS and other reproductive disorders including endometriosis, difficulty conceiving, and miscarriage.

2. Methods

2.1. Selection of study population

The Cape Cod Health Study is a closed two-stage transgenerational retrospective cohort study. The mother's cohort was comprised of married women who resided in the Cape Cod area of Massachusetts from 1969 through 1983 in one of eight towns with VL/AC water distribution pipes and who had at least one birth (termed index birth) during this time period. Enrollment methods have been previously described [18] and are summarized here. Eligible mothers were identified by reviewing birth certificates and cross-matching the address on the birth certificate with information collected from water companies on the location and installation year of VL/AC pipes. Mothers were enrolled in 2002–2003 and completed a self-administered questionnaire. Exposure status of the mother's index birth was initially assigned by visually inspecting maps depicting the pipe distribution network in the vicinity of the birth address. Index births were tentatively designated as "exposed" when their residence was either directly adjacent to a VL/AC pipe or indirectly adjacent to a pipe connected to a VL/AC pipe with the only possible water flow through a VL/AC pipe (N = 1910). Births who were initially designated as "unexposed" were randomly selected from the remaining resident births during this time period and frequency matched to exposed subjects on month and year of birth (N = 1928). In addition, 1202 older siblings of exposed and unexposed index subjects were identified if they were born in Massachusetts during 1969–1983. These older siblings were initially considered unexposed because they were born before the family moved to an affected Cape Cod residence. The initial exposure status of all subjects was considered tentative until more extensive exposure assessments were completed, as described below.

The survey administered to the mothers collected information on reproductive and developmental disorders, confounding variables, and the family's residential history. Data collected included the mother's demographic characteristics, menstrual abnormalities, delayed time to conception, pregnancy outcomes, breastfeeding practices, medical conditions, environmental and occupational exposures, use of tap and bottled water, dry cleaning for clothing, residence near dry cleaning facilities, and a residential history since 1969.

The study was approved by the Institutional Review Boards of the Massachusetts Department of Public Health and Boston University Medical Center and by the 24A/B/11B Review Committee at the Massachusetts Department of Public Health.

2.2. Follow-up and enrollment

Follow-up and enrollment of index children and their siblings occurred during 2006–2008. A self-administered questionnaire was sent to all successfully traced subjects (40.5% of those selected) to gather information on their health status including height and weight (to estimate body mass index), reproductive disorders such as polycystic ovary syndrome, endometriosis, difficulty conceiving, miscarriage, and chronic conditions. In addition, these surveys gathered information on current demographic characteristics; lifestyle characteristics (smoking, alcohol, caffeine consumption, and recreational drugs); history of chronic illnesses, medications, family medical history; occupational and non-occupational sources of solvent exposure and residential locations from birth through 1990, including the exact street address and calendar years of residence for all Cape Cod residences. All disease-related questions asked if a doctor or health care provider had ever stated that the participant had a particular condition and what year the condition was diagnosed.

2.3. Reproductive disorder assessment

The survey administered to female children included the following questions reported here by diagnosis.

2.3.1. Polycystic ovary syndrome

"Has a doctor or health care provider ever said that you had polycystic ovarian disease?" If the daughter said, "yes," she was asked, "In what year were you diagnosed with polycystic ovarian disease?"

2.3.2. Endometriosis

"Has a doctor or health care provider ever said that you had endometriosis?" If the daughter said, "yes," she was asked, "In what year were you diagnosed with endometriosis?"