Exposure to polycyclic aromatic hydrocarbons and missed abortion in early pregnancy in a Chinese population

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ABSTRACT

Background: Polycyclic aromatic hydrocarbons (PAHs) are formed during incomplete burning of fossil fuels, wood, and tobacco products. High PAH exposure has been associated with low birth weight, intrauterine growth restriction, and preterm birth, but little is known about its impact on adverse outcomes in early pregnancy such as in-utero fetal death.
Objectives: To examine associations between exposure to PAHs and missed abortion in which the embryo has died but a miscarriage has not yet occurred during early pregnancy in a Chinese population in Tianjin.
Methods: A case–control study was conducted from April to November, 2007 in Tianjin, China. Cases experienced a missed abortion while controls underwent elective abortions before 14 weeks of pregnancy. Eighty-one cases were recruited from four hospitals, with the same number of controls matched on hospital, maternal age (± 8 years), gravidity (1 or >1), and gestational age (± 30 days). Two maternal measures of PAH exposures were obtained based on benzo[a]pyrene (BaP) DNA adducts in 1) aborted tissues and 2) maternal blood (for a subset of subjects). In addition, proxy measures for PAH exposures from different sources were derived from maternal interviews.
Results: In conditional logistic regression analyses, we estimated more than 4-fold increase in risk of having experienced a missed abortion in women with above the median levels of blood BaP-DNA adducts (adjusted OR = 4.27; 95% CI, 1.41–12.99); but no increase with adduct levels in aborted tissues (adjusted OR = 0.76; 95% CI, 0.37–1.54). BaP-DNA adduct levels in maternal blood and aborted tissues were poorly correlated ($r = -0.12$; $n = 102$). Missed abortion risk also was higher among women reporting traffic congestion near the residence, commuting by walking, and performing regular cooking activities during pregnancy.
Conclusion: High levels of maternal PAH exposures may contribute to an increased risk of experiencing a missed abortion during early pregnancy.

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1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a group of ubiquitous persistent organic pollutants released into the atmosphere during incomplete combustion and/or pyrolysis of fossil fuel, industrial or domestic coal, wood, cigarettes, and food items (Bostrom et al., 2002). Human exposure to PAHs occurs largely through inhalation and diet. In animal studies transplacental exposure to benzo[a]pyrene (BaP), one of the PAH species, has been associated with an increase in xenobiotic metabolism in the placental tissues (Sanyal, et al. 1994) and has been linked to fetal loss and a decrease in plasma hormone levels of progesterone, estrogen, and prolactin (Archibong et al., 2002). Exposure of rat fetuses to BaP during organogenesis reduced birth weight, crown-rump length, and placental proficiency as measured by protein weight and diameter (Sanyal and Li, 2007a).

In humans, studies conducted in the U.S. (Choi et al., 2006; Choi et al., 2008; Perera et al., 2003; Perera et al., 2004), Poland (Choi et al., 2006), and the Czech Republic (Dejmek et al., 2000) suggested that PAHs adversely impact birth outcomes and cognitive development in early childhood; including decreased head circumferences, birth length, and birth weight (Choi et al., 2006; Perera et al., 2003; Perera et al., 2005c; Perera et al., 1998; Tang et al., 2006), intrauterine growth retardation (Choi et al., 2008; Dejmek et al., 2000), preterm birth (Choi et al., 2008; Singh et al., 2008), and neurocognitive development in children (Perera et al., 2005b; Tang et al., 2006).

Most prior studies examined outcomes in live births only and were based on measures of PAH exposure taken in the later part of the pregnancy (e.g. the 3rd trimester). However, fetuses may be particularly sensitive to the impact of toxic PAHs during early pregnancy (e.g. the 1st trimester) because of the rapid development of fetal organs and the higher exposure per body weight of the fetus

during this period compared to later pregnancy periods (Pinkerton and Joad, 2006; Schwartz, 2004). No study to date has investigated the potential impact of PAH exposure on outcomes such as abnormal fetal development and in-utero fetal death during early pregnancy. Missed abortion refers to an intrauterine pregnancy in which the fetus does not develop normally over a prolonged period of time, typically 6 weeks, or the fetus is already known to have died but the products of conception remain in-utero. Missed abortion is a complication of early pregnancy that occurs in up to 15% of all clinically recognized pregnancies (Daya, 2000), and can have severe social, emotional, and psychological impacts due to the failure of the pregnancy. Approximately 90% of all missed abortions occur before 14 weeks of gestation or in the 1st trimester.

We conducted a case–control study examining the influence of maternal exposure to PAHs on missed vs. induced abortions in Tianjin, an industrial city in northern China. Maternal PAH exposures were measured via biomarker in 1) maternal blood and 2) aborted tissues; we also conducted an interview survey to identify potential sources of environmental PAH exposures in these women.

2. Methods

2.1. Study area

The study was conducted in Tianjin, the second largest city in northern coastal China with a total area of 11,760 km², and a population of 11.2 million in 2007. Tianjin is located at the lower reaches of the Haihe River and adjacent to the Bohai Sea, and is an important industrial center and a well-developed hub with a sea–land–air transportation network. As one of the fastest growing areas in coastal China, Tianjin measures atmospheric concentrations for PAHs much higher than many other cities worldwide (Wu et al., 2005). The major contributors to PAH pollution are coal combustion, vehicle emission, coking industry, and biomass burning (Zuo et al., 2007).

2.2. Subject selection

Using a case–control study design, between early April and end of November 2007 we enrolled cases with missed abortions and controls seeking induced abortion services in four hospitals, including the Main Hospital of Tianjin Medical University, the 2nd Hospital of Tianjin Medical University, the Hospital of Chinese People's Armed Police Forces, and Dongli Hospital. The study was approved by the Institutional Review Board of each of the four hospitals. Cases were pregnant women carrying an in-utero fetus that was confirmed as dead by ultrasound measurements before 14 weeks of gestation. Controls were women with normal pregnancies who requested an induction of an abortion due to an unplanned and unwanted pregnancy. Each case was assigned one control matched on hospital, maternal age (within ± 8 years), and gravidity (the total number of times a woman has been pregnant; one or more than one). Because no reliable data for cases were available to determine the exact date when the fetus died in-utero, we loosely matched the case control pairs on gestational age at time of abortion requiring the control's gestational age to be within 30 days of the case's. In the final matched dataset, cases had slightly longer gestational age (4 days) than controls because some case mothers wishing to maintain the pregnancy preferred to wait longer to confirm the death of the fetus. Yet, case and control fetuses may have been more similar in their actual gestational age at demise, i.e. the fetus of the missed abortion cases remained in-utero longer.

All study participants were screened to exclude smokers, women with chronic diseases (e.g. hypertension, heart disease, and diabetes) and pregnancy complications (e.g. vaginal infection), women with potentially high occupational exposures to PAH according to the literature (e.g. bus or taxi drivers, traffic police officers, coal plant workers, coke oven workers, cooks), and those who had resided in Tianjin for less than one year. All cases and controls were approached by trained research staff in the surgery room immediately following the abortion procedure. A total of 84 eligible cases were contacted and 81 of them agreed to participate in the study. Eight-one matched controls were recruited out of 89 eligible subjects approached.

2.3. Environmental and health survey

Approximately 1 h after the abortion procedure, we consented eligible subjects for the collection of biospecimen (aborted tissues and/ or blood draws) and the administration of a 15–20 min standardized interview administered by trained personnel. Each matched pair was interviewed by the same interviewer. We asked for three types of information: (i) demographics and socioeconomic information (e.g. age, home address, duration of residence in Tianjin, education, occupation, and income); (ii) reproductive history (e.g. previous abortion history, and number of previous birth to a fetus with a gestational age of 24 weeks or more − parity); and (iii) factors that may influence exposure to PAHs during pregnancy (e.g. time spend outdoors and in-transit, nearby industrial facilities, traffic activities near residence, cooking activities and fuels used, dietary PAH exposure via grilled, smoked, or barbecued foods, exposure to environmental tobacco smoke (ETS) etc.). We also ascertained information about other maternal risk factors suspected to affect pregnancy outcomes (e.g. virus infection, medication, X-ray exposure, and emotional disturbances); yet, very few cases ($n = 0$–6) and controls ($n = 1$–3) responded positive to these questions and excluding these participants did not change the main results of missed abortion (data not shown); thus we did not further consider these factors in our analyses.

2.4. Biomarker measurements

All four hospitals allowed us to collect the aborted tissues, but only two of the hospitals gave us permission for a maternal blood draw. Thus, maternal blood samples were collected for only a subset of the matched case–control pairs. The two hospitals that allowed blood draws were within 6 km of the other two hospitals not permitting these procedures. All four hospitals employed the same diagnostic criteria, served a similar population, and were located within 5–13 km of each other.

Right after the interview, we collected 2 ml of maternal blood for the consented women by syringing blood into a heparinized EDTA-K2 glass tube (Nantong Fulilai Medical Instrument Co., Ltd., Jiangshu Province, China) to avoid clotting. The aborted tissue was analyzed in total because it is difficult to separate the villous from the embryo early in pregnancy, i.e. all samples contained both embryo and villous materials together. The aborted tissue was prewashed using 0.9% NaCl saline solution, and stored in 2 ml sample bottle (Vigorous Biotechnology, Inc., Beijing, China). All samples were put on ice and transported to the Medicinal Chemistry Laboratory of the Basic Medical Science Center at Tianjin Medical University immediately after collection for storage and processing. The whole blood samples were refrigerated at −20 °C, and the aborted tissues at −70 °C until analysis. Whole blood samples were extracted every week for genomic DNA using Human Whole Blood Genomic DNA Purification Kit (MagneSil, Promega Madison, WI, USA) and aborted tissues using Tissue/Cell Genomic DNA Purification Kit (GaiNing Biotechnology Co., Ltd., Beijing, China). BaP-DNA adducts in extracted DNA were analyzed using the high-performance liquid chromatography-fluorescence method (Alexandrov et al., 1992), which detects benzo[a] pyrene diol-epoxide (BPDE) tetrols. The assay is a sensitive and specific method for measuring BaP-DNA adducts in individuals (Bartsch and Hietanen, 1996). UV-260 spectrophotometer was used to analyze total DNA. Finally, standardized BaP-DNA adduct levels were calculated by dividing the BPDE concentrations by the total DNA concentrations.