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Associations between prenatal arsenic exposure with adverse pregnancy outcome and child mortality

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ABSTRACT

Background: Chronic arsenic exposure is a public health concern in many parts of the world, with elevated concentrations in groundwater posing a threat to millions of people. Arsenic is associated with various cancers and an array of chronic diseases; however, the relationship with adverse pregnancy outcomes and child mortality is less established.

Objectives: We evaluated associations between individual-level prenatal arsenic exposure with adverse pregnancy outcomes and child mortality in a pregnancy study among 498 women nested in a larger population-based cohort in rural Bangladesh.

Methods: Creatinine-adjusted urinary total arsenic concentration, a comprehensive measure of exposure from water, food, and air sources, reflective of the prenatal period was available for participants. Self-reported pregnancy outcomes (livebirth, stillbirth, spontaneous/elective abortion) were ascertained. Generalized estimating equations, accounting for multiple pregnancies of participants, were used to estimate odds ratios and 95% confidence intervals in relation to adverse pregnancy outcomes. Vital status of livebirths was subsequently ascertained through November 2015. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals in relation to child mortality.

Results: We observed a significant association between prenatal arsenic exposure and the risk of stillbirth (greater than median; adjusted OR = 2.50; 95% CI = 1.04, 6.01). We also observed elevated risk of child mortality (greater than median; adjusted HR = 1.92; 95% CI = 0.78, 4.68) in relation to prenatal arsenic exposure.

Conclusions: Prospective studies should continue to evaluate prenatal and early life health effects of arsenic exposure and arsenic remediation strategies for women of child-bearing age.

1. Introduction

Arsenic is ubiquitous in the environment, with human exposure occurring through dietary intake, inhalation of contaminated air, and ingestion of contaminated soil/dust (Joseph et al., 2015). However, the consumption of arsenic-contaminated drinking water is the major exposure route that affects more than 200 million people worldwide, including approximately 77 million in Bangladesh and 17 million in the United States (US) (BBS/UNICEF, 2014; IARC, 2004). With respect to its frequency, toxicity, and potential for human exposure, arsenic holds the highest ranking since 1997 on the US Agency for Toxic Substances and Disease Registry (ATSDR) substance priority list.

Chronic exposure to arsenic has been associated with a number of health outcomes, including increased risk of cancers (skin, lung, liver, bladder, and kidney), cardiovascular disease (coronary heart disease, acute myocardial infarction, and hypertension), respiratory disease,

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and diabetes mellitus (Abdul et al., 2015; Maull et al., 2012; Moon et al., 2012; Sanchez et al., 2016). While there is extensive literature on the health impacts of arsenic exposure in adult populations and a growing literature on impaired neurodevelopment function in children (Tsuji et al., 2015), there is relatively little epidemiologic research evaluating the effects of in utero arsenic exposure on pregnancy outcomes and early life. Arsenic readily crosses the placental barrier and thus may influence fetal development. Strong correlations have been observed between concentrations of arsenic in placenta and cord blood arsenic levels in an Argentine population (Concha et al., 1998), maternal blood and cord blood arsenic levels in a Bangladeshi population (Hall et al., 2007), and placental, maternal, and infant arsenic levels in a US population (Punshon et al., 2015).

A recent meta-analysis evaluating associations of arsenic exposure with adverse pregnancy outcomes and infant mortality reported significantly elevated risks of spontaneous abortion, stillbirth, neonatal mortality, and infant death based on published research from Asia and the US (Quansah et al., 2015). However, the majority of the existing studies utilized ecologic exposure assessments of arsenic concentrations in drinking water. The best evidence to date comes from a prospective cohort study of women in rural Bangladesh with individual-level measures of urinary total arsenic concentrations during pregnancy. The study observed a significant dose-response relationship with infant mortality as well as elevated risks of spontaneous abortion and stillbirth, although these were associated with wide confidence intervals and no clear dose-response association (Rahman et al., 2010).

Thus, prospective, individual-level evidence supporting adverse effects of arsenic exposure with pregnancy outcomes and infant mortality is still limited. In this study, we sought to evaluate the association of individual-level prenatal arsenic exposure based on maternal creatinine-adjusted urinary total arsenic concentration with risk of adverse pregnancy outcome (stillbirth, spontaneous abortion, and therapeutic/elective abortion) as well as child mortality in a pregnancy study among 498 women nested in a larger population-based cohort in rural Bangladesh.

2. Methods

2.1. Study population

The Bangladesh vitamin E and Selenium Trial (BEST) is a 2×2 factorial randomized control trial of 7000 participants (2840 males and 4160 females) aged 25–65 years with manifest arsenical skin lesions living in rural Bangladesh. The aim of the trial was to evaluate selenium and/or vitamin E in relation to risk of non-melanoma skin cancer. Detailed information including study design, ascertainment of arsenic exposure, data collection and demographic characteristics of participants have been described elsewhere (Argos et al., 2013). Women self-reporting a pregnancy at the semiweekly home visit by a village health worker during the course of the study were temporarily suspended from the trial and discontinued randomized study vitamins for the duration of the pregnancy, plus an additional 6 months following a livebirth. Of the 4160 women in the BEST cohort, 510 women reported a pregnancy during the trial and completed a pregnancy follow-up questionnaire (622 pregnancies total) between February 2007 and October 2015. For the purposes of these analyses, we included only singleton births (10 twin birth pregnancies excluded). Of the remaining 612 pregnancies, data were missing for arsenic exposure on 14 pregnancies, yielding 598 pregnancies (in 498 women) contributing data to these analyses. Informed consent was obtained from all women, and study procedures were approved by the institutional review boards at each research institution.

2.2. Assessment of pregnancy outcome and child mortality

Village health workers visited study participants reporting a pregnancy on a monthly basis and collected information on the status of the pregnancy. As soon as a pregnancy outcome was reported to the village health worker, a study physician interviewer administered a pregnancy follow-up questionnaire in-person to the participant. As part of the pregnancy questionnaire, self-reported data were collected on the outcome of the pregnancy, including livebirth, stillbirth (defined as fetal loss after 20th week of gestation), spontaneous abortion (defined as fetal loss up to 20th week gestation), and therapeutic/elective abortion. Among all livebirths (n = 489), vital status was subsequently ascertained by a village health worker through November 2015, with an average follow-up of 4.7 years, for a total of 2270.2 person-years of follow-up.

2.3. Assessment of arsenic exposure

A spot urine sample was collected at baseline and biennially thereafter from all trial participants by a trained study physician interviewer. Urine was collected in a 50 ml acid washed tube and was stored in −20 °C in the field laboratory until shipment on dry ice to the Trace Metals Core Facilities Laboratory at Columbia University. Upon arrival to Columbia University, all samples were stored in −20 °C until analysis. Urinary total arsenic concentration was measured by graphite furnace atomic absorption spectrometry, with a detection limit of 2 μg/L (Nixon et al., 1991). Urinary creatinine concentration was measured by a colorimetric method based on the Jaffe reaction in the same laboratory (Heinegard and Tiderstrom, 1973). For livebirths, prenatal arsenic exposure was assigned based on the urine sample closest to the date of delivery. The spot urine sample was collected on average 428 days (median = 408 days) prior the date of birth. For adverse pregnancy outcomes (stillbirth, spontaneous abortion, and therapeutic/elective abortion), prenatal arsenic exposure was assigned according to the measurement just preceding the date of the adverse pregnancy event. For adverse pregnancy outcomes, the assigned arsenic exposure was ascertained from a spot urine sample collected on average 395 days (median = 400 days) prior to the reported event. For the purposes of these analyses, creatinine-adjusted urinary total arsenic concentration (μg/g creatinine) was derived by dividing the arsenic concentration by creatinine concentration of the sample. Creatinine adjustment was used to account for hydration status and thus variable dilution of the spot urine samples. Analyses were conducted with arsenic modelled as a binary variable (dichotomized at the median value) as well as a continuous variable.

2.4. Assessment of covariates

Maternal characteristics including years of education and arsenical skin lesion severity were ascertained from the baseline questionnaire of BEST (administered between 2006 and 2009). Skin lesion severity was determined by a comprehensive skin examination conducted by a trained study physician interviewer, and categorized as mild for presence of melanosis or leucomelanosis and severe for the presence of keratosis (Argos et al., 2013). Maternal self-reported reproductive- and pregnancy-related characteristics for each reported pregnancy were derived from the pregnancy questionnaire, including prenatal care (yes, no), number of prenatal visits, maternal smoking (yes, no), regular exposure to second-hand smoke in the home (yes, no), physician-diagnosed gestational hypertension (yes, no), physician-diagnosed pre-eclampsia (yes, no), physician-diagnosed gestational diabetes (yes, no), gravidity, parity, and prior stillbirth (yes, no).

2.5. Statistical analysis

Descriptive analyses were conducted using Wilcoxon rank sum test for continuous variables, Mantel-Haenszel chi-squared test for ordinal variables, and Pearson chi-squared test for nominal and dichotomous variables. Since multiple pregnancies were observed for some women,