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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

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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, 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 7,000 participants (2,840 males and 4,160 females) aged 25 to 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 4,160 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 20^{th} week of gestation), spontaneous abortion (defined as fetal loss up to 20^{th} 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 2,270.2 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 to 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 preeclampsia (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, generalized estimating equation (GEE) models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between arsenic exposure and adverse pregnancy outcomes. In initial analyses, a dichotomous outcome was specified for adverse pregnancy outcome (stillbirth, spontaneous abortion, or therapeutic/elective abortion versus livebirth). Three models were fit: 1) unadjusted; 2) adjusted for maternal age (years); and, 3) fully adjusted including maternal age (years), maternal years of education (years), BEST treatment assignment (placebo, selenium, vitamin E, selenium and vitamin E), and skin lesion severity (mild, severe). Subgroup analyses were also implemented to evaluate stillbirth, spontaneous abortion, and therapeutic/elective abortion separately. Stillbirth

outcomes were additionally adjusted for parity and previous stillbirth based on *a priori* knowledge (Abu-Heija and Chalabi 1997; Di Mario et al. 2007; McClure et al. 2006), and the observed association of stillbirth with both parity and previous stillbirth in this study sample. Other potential confounders were additionally selected based on *a priori* knowledge (Kumar 2011; McClure et al. 2006; Shah et al. 2011).

Marginal Cox proportional hazards models with the robust sandwich estimate for estimating the covariance matrix were used to estimate hazard ratios (HRs) and 95% CIs for the association between prenatal arsenic exposure and child mortality (Lee 1992). Vital status was ascertained through November 2015. Follow-up time was calculated as the number of days between date of birth and date of death or, if alive, date of the last report of being alive; such participants were censored. Three models were fit: 1) unadjusted; 2) adjusted for maternal age (years); and, 3) fully adjusted including maternal age (years), maternal years of education (years), BEST treatment assignment (placebo, selenium, vitamin E, selenium and vitamin E), maternal skin lesion severity (mild, severe), exposure to passive tobacco smoke (yes, no) and child sex (male, female). Subgroup analyses evaluating the association between prenatal arsenic exposure and infant mortality before one year of age (restricted to 12 deaths) were also conducted; children who died after one year of age were censored in this analysis.

Sensitivity analyses were conducted in relation to adverse pregnancy outcomes and child mortality restricted to pregnancies from women with prenatal arsenic exposure classified based on available data within one year of the pregnancy.

3. Results

Maternal characteristics for all observed pregnancies are shown in Table 1. The mean maternal age of the study sample was 32.2 years. The median creatinine-adjusted urinary arsenic concentration was 555 μg/g creatinine, ranging from 17 to 3,712 μg/g creatinine. Adverse pregnancy outcomes were reported in 109 (18.3%) of the reported pregnancies in the study, including 23 (3.9%) stillbirths, 60 (10.0%) spontaneous abortions, and 26 (4.4%) therapeutic/elective abortions. While almost all females in the study were non-smokers (n=594, 99.2%), 200 (39.1%) women reported regular exposure to environmental tobacco smoke inside their homes during pregnancy. Increased maternal age (OR=1.12; 95% CI=1.07, 1.17) and prior stillbirth pregnancy (OR=3.64; 95% CI=1.66, 7.98) were associated with having an adverse pregnancy outcome; whereas, parity (OR=0.68; 95% CI=0.50, 0.94) was inversely associated with having an adverse pregnancy outcome.

Associations between prenatal arsenic exposure and adverse pregnancy outcomes are summarized in Table 2. Higher prenatal urinary total arsenic concentration (>555 μg/g creatinine) was associated with increased risk (adjusted OR=1.59; 95% CI=1.02, 2.46) of adverse pregnancy outcome, defined as stillbirth, spontaneous abortion, or therapeutic/elective abortion. When considering creatinine-adjusted arsenic concentration as a continuous exposure measure, a 50 μg/g increase in arsenic exposure was associated with a 2% (95% CI=1.01, 1.04) increased risk of adverse pregnancy outcome. Additionally, we conducted subgroup analyses to evaluate the associations between prenatal arsenic exposure

and each individual adverse pregnancy outcome. A significantly increased risk of stillbirth was associated with high prenatal arsenic exposure (adjusted OR=2.50; 95% CI=1.04, 6.01). A 50 μg/g increase in creatinine-adjusted arsenic concentration was associated with a 2% (95% CI=1.00, 1.05) increased risk of stillbirth when modelling arsenic as a continuous exposure measure.

In Table 3, associations between prenatal arsenic exposure and child mortality are summarized. Among the 489 livebirths, we ascertained vital status through November 2015 on 483 (98.8%) children, with 21 deaths observed. Although the confidence intervals included the null, an elevated risk of child mortality was observed in relation to higher prenatal arsenic exposure (adjusted HR=1.92; 95% CI=0.78, 4.68). When considering creatinine-adjusted arsenic concentration as a continuous exposure measure, a 50 μg/g increase in creatinine-adjusted arsenic concentration was associated with a 4% (95% CI=1.01, 1.07) increased risk of child mortality. In subset analyses evaluating the association with infant mortality (death before 1 year of age), 12 infant deaths were observed. An elevated risk of infant mortality was also observed in relation to higher prenatal arsenic exposure (adjusted HR=2.30; 95% CI=0.63, 8.41). A 50 μg/g increase in creatinine-adjusted arsenic concentration was associated with a 7% (95% CI=0.99, 1.15) increased risk of infant mortality when modelling arsenic as a continuous exposure measure.

Sensitivity analyses were conducted to evaluate associations between prenatal arsenic exposure and adverse pregnancy outcomes as well as child mortality among pregnancies with prenatal arsenic exposure derived from within one year of the reported pregnancy (restricted to 260 (43.5%) pregnancies and 203 (41.5%) livebirths from the primary analyses). Findings from these sensitivity analyses were not appreciably different from the overall analyses presented (data not shown). We also conducted the overall analyses unadjusted for urinary creatinine as well as separately adjusting for urinary creatinine as an independent covariate in the model (Supplemental Table 1), with no appreciable difference in the results from those presented.

4. Discussion

In the present study, we observed an association between high prenatal arsenic exposure (>555 μg/g creatinine) in relation to adverse pregnancy outcomes, particularly stillbirths. There was also modest evidence of elevated risk of child mortality in relation to high prenatal arsenic exposure.

An increased risk of adverse pregnancy outcomes in relation to prenatal arsenic exposure has been observed previously and evaluated in a recent meta-analysis (Quansah et al. 2015). The strongest association in the present analyses was observed for stillbirths in relation to prenatal arsenic exposure. In previous studies, no significant association with stillbirths was observed in relation to well water arsenic concentration (Myers et al. 2010; Rudnai et al. 2006) and prenatal urinary total arsenic concentration (Rahman et al. 2010). However, increased associations were observed with well water arsenic concentration in other studies (Ahmad et al. 2001; Cherry et al. 2008; Hopenhayn-Rich et al. 2000; Milton et al. 2005; von Ehrenstein et al. 2006) as well as with airborne arsenic emissions (Ihrig et al. 1998). For

spontaneous abortion, a significant increased risk was observed in relation to higher arsenic levels in drinking water in a large ecological study (Rudnai et al. 2006). However, in a population-based prospective cohort study, no significant association between prenatal urinary total arsenic concentration and spontaneous abortion was observed, although there was an increased association with infant mortality (Rahman et al. 2010). A recent case-control study conducted in Romania also similarly showed no association between drinking water arsenic and spontaneous abortion (Bloom et al. 2014).

Increased risks have been previously observed with child mortality (Hall et al. 2007; Hopenhayn-Rich et al. 2000; Myers et al. 2010; Rahman et al. 2010) in relation to arsenic levels in well water, although some of these associations were associated with wide confidence intervals. While we did not have data available on cause of death in this study sample, it is possible that *in utero* arsenic exposure is associated with an increased risk of acute lower respiratory infections, the leading cause of childhood morbidity and mortality globally (Liu et al. 2015). Prior studies have shown that prenatal arsenic exposure is associated with both the frequency and severity of respiratory tract infections among infants (Farzan et al. 2016; Rahman et al. 2011).

In many of the previous studies, prenatal arsenic exposure was defined based on an ecologic exposure measure from only a single source (Ahmad et al. 2001; Aschengrau et al. 1989; Cherry et al. 2008; Rahman et al. 2007); whereas, in the present study, creatinine-adjusted urinary total arsenic concentrations were used. This biomarker of arsenic exposure reflects arsenic exposure from multiple sources, including drinking water, food consumption, soil, and dust (Hughes 2006).There are certain limitations in the present study that we consider. First, the proportion of spontaneous abortion events reported in the population is lower than expected. Since pregnancy was self-reported by female study participants, it is likely that participants were unaware of some early pregnancy losses. The underreporting and misclassification of spontaneous abortion outcomes in this study could have led to an underestimation of the association between prenatal arsenic exposure and early pregnancy loss. Second, previous studies have shown that arsenic metabolism efficiency among pregnant women varies across trimesters, with evidence to suggest that metabolism efficiency increases in the first trimester (Gardner et al. 2011; Hopenhayn et al. 2003). However, it was not possible to evaluate the effect of trimester-specific arsenic exposure in this study. Women enrolled in the BEST cohort had a spot urine sample collected every two years for the measurement of urinary total arsenic concentration, from which prenatal arsenic exposure was assigned for the present study. Therefore, the potential misclassification of arsenic exposure might obscure trimester-specific associations. However, since the correlation of urinary total arsenic concentration between biennial samples among women in this study is high (r=0.62-0.68), we infer that the classification of prenatal arsenic exposure in this study is reasonable despite not being systematically measured during pregnancy. Given this, arsenic exposure across trimesters is also likely to be highly correlated; therefore, we would not be able to evaluate trimester-specific effects in this study population. Third, spot urine samples are more influenced by factors such as hydration status and physical activity than 24-hour urine. In spite of the potential higher intra-individual variation, it has been reported that spot urine samples may be adequate biomarkers to derive reasonably accurate measurements of environmental exposure (Rivera-

Nunez et al. 2010; Woods et al. 1998). Urinary creatinine concentrations were also used to adjust urinary arsenic for variation in hydration status. Although creatinine adjustment could introduce bias to the association estimates since urinary creatinine is affected by age, sex, and body size (Nermell et al. 2008), no appreciable differences in results were observed based on the unadjusted urinary total arsenic concentration (μg/L) analyses. Moreover, urinary arsenic concentration is primarily reflective of recent arsenic exposure and not cumulative tissue burden. However, urinary total arsenic concentration may be a relatively good marker of exposure in this study population since exposure is chronic and primarily through drinking water. It will be important for future research to investigate the relationship between other biomarkers of arsenic exposure (e.g., toenail or blood arsenic concentrations) and adverse pregnancy outcome. Fourth, it is possible that other variables, such as other environmental exposures or genetic factors that were unmeasured in this study population, may be unaccounted for in our statistical analyses. Additionally, data after baseline was not available on time-varying covariates (e.g., exposure to passive tobacco smoke) for the childhood mortality analyses, which may also have resulted in residual confounding in those analyses. Fifth, logistic regression analyses were conducted in the present study to estimate odds ratios, which may be an overestimate of the relative risks since the prevalence of adverse birth outcomes is common in this population (18.3%). In a comparison of the crude odds ratio estimates to crude relative risk estimates from a log-binomial model, no appreciable overestimation was observed; therefore, we deem the odds ratios to be a good approximation of the underlying relative risks in this analysis. Finally, the study sample included only women with manifest arsenic skin lesions. These women may be more susceptible to arsenic due to genetics or other risk factors, which may have implications for the generalizability of these results to less susceptible populations.

Despite the limitations noted, there is biological support for our findings stemming from several animal studies. Specifically, mice treated by sodium arsenite showed that meiotic aberration caused by arsenite may contribute to decreased preimplantation development and further disrupt embryo development (Navarro et al. 2004). Furthermore, a study in pregnant mice indicated that arsenic exposure is associated with mammalian spontaneous abortion by aberrant placental vasculogenesis and placental insufficiency (He et al. 2007). Particular strengths of the study include individual-level measurement of urinary total arsenic concentration and the prospective study design.

5. Conclusions

The epidemiologic literature evaluating prenatal arsenic exposure and pregnancy outcomes is still equivocal. The present study provides evidence supporting an adverse association between prenatal arsenic exposure and stillbirth in a population with moderate to high arsenic exposure, as well as a possible adverse association with child mortality. These findings encourage further research to evaluate the health impacts of prenatal and early life arsenic exposure in children as well as arsenic remediation strategies for women of child-bearing age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Abdul KSM, Jayasinghe SS, Chandana EPS, Jayasumana C, De Silva PMCS. Arsenic and human health effects: A review. Environ Toxicol Phar. 2015; 40:828–846.

Abu-Heija AT, Chalabi HE. Great grand multiparity: Is it a risk? International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 1997; 59:213–216.

Ahmad SA, Sayed MH, Barua S, Khan MH, Faruquee MH, Jalil A, et al. Arsenic in drinking water and pregnancy outcomes. Environmental Health Perspectives. 2001; 109:629–631. [PubMed: 11445518]

Argos M, Rahman M, Parvez F, Dignam J, Islam T, Quasem I, et al. Baseline comorbidities in a skin cancer prevention trial in bangladesh. European Journal of Clinical Investigation. 2013; 43:579–588. [PubMed: 23590571]

Aschengrau A, Zierler S, Cohen A. Quality of community drinking water and the occurrence of spontaneous abortion. Archives of Environmental Health. 1989; 44:283–290. [PubMed: 2554824]

UNICEF Ba. , editor. BBS/UNICEF. Progotir pathey: Bangladesh multiple indicator cluster survey 2012 - 2013. Dhaka, Bangladesh: 2014.

Bloom MS, Neamtiu IA, Surdu S, Pop C, Lupsa IR, Anastasiu D, et al. Consumption of low-moderate level arsenic contaminated water does not increase spontaneous pregnancy loss: A case control study. Environmental Health. 2014; 13:81. [PubMed: 25311704]

Cherry N, Shaikh K, McDonald C, Chowdhury Z. Stillbirth in rural bangladesh: Arsenic exposure and other etiological factors: A report from gonoshasthaya kendra. Bulletin of the World Health Organization. 2008; 86:172–177. [PubMed: 18368203]

Concha G, Vogler G, Lezcano D, Nermell B, Vahter M. Exposure to inorganic arsenic metabolites during early human development. Toxicological sciences : an official journal of the Society of Toxicology. 1998; 44:185–190. [PubMed: 9742656]

Di Mario S, Say L, Lincetto O. Risk factors for stillbirth in developing countries: A systematic review of the literature. Sexually transmitted diseases. 2007; 34:S11–21. [PubMed: 17592385]

Farzan SF, Li Z, Korrick SA, Spiegelman D, Enelow R, Nadeau K, et al. Infant infections and respiratory symptoms in relation to in utero arsenic exposure in a u.S. Cohort. Environmental health perspectives. 2016; 124:840–847. [PubMed: 26359651]

Gardner RM, Nermell B, Kippler M, Grander M, Li L, Ekstrom EC, et al. Arsenic methylation efficiency increases during the first trimester of pregnancy independent of folate status. Reproductive toxicology (Elmsford, NY). 2011; 31:210–218.

Hall M, Gamble M, Slavkovich V, Liu X, Levy D, Cheng Z, et al. Determinants of arsenic metabolism: Blood arsenic metabolites, plasma folate, cobalamin, and homocysteine concentrations in maternal-newborn pairs. Environ Health Perspect. 2007; 115:1503–1509. [PubMed: 17938743]

He W, Greenwell RJ, Brooks DM, Calderon-Garciduenas L, Beall HD, Coffin JD. Arsenic exposure in pregnant mice disrupts placental vasculogenesis and causes spontaneous abortion. Toxicological sciences : an official journal of the Society of Toxicology. 2007; 99:244–253. [PubMed: 17569693]

Heinegard D, Tiderstrom G. Determination of serum creatinine by a direct colorimetric method. Clinica Chimica Acta. 1973; 43:305–310.

Hopenhayn-Rich C, Browning SR, Hertz-Picciotto I, Ferreccio C, Peralta C, Gibb H. Chronic arsenic exposure and risk of infant mortality in two areas of chile. Environmental Health Perspectives. 2000; 108:667–673. [PubMed: 10903622]

Hopenhayn C, Huang B, Christian J, Peralta C, Ferreccio C, Atallah R, et al. Profile of urinary arsenic metabolites during pregnancy. Environmental Health Perspectives. 2003; 111:1888–1891. [PubMed: 14644662]

Hughes MF. Biomarkers of exposure: A case study with inorganic arsenic. Environmental Health Perspectives. 2006; 114:1790–1796. [PubMed: 17107869]

IARC. 2004; 84 http://www.Inchem.Org/documents/iarc/vol84/84-01-arsenic.Html.

Ihrig MM, Shalat SL, Baynes C. A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. Epidemiology. 1998; 9:290–294. [PubMed: 9583421]

Joseph T, Dubey B, McBean EA. A critical review of arsenic exposures for bangladeshi adults. Science of the Total Environment. 2015; 527-528:540–551. [PubMed: 26004539]

Kumar S. Occupational, environmental and lifestyle factors associated with spontaneous abortion. Reproductive sciences (Thousand Oaks, Calif). 2011; 18:915–930.

Lee, EW., Wei, LJ., Amato, DA. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In: Goel, PK., K, JP., editors. Survival analysis: State of the art. Dordrecht, Netherlands: Kluwer Academic Publishers; 1992. p. 237-247.

Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: An updated systematic analysis. Lancet. 2015; 385:430–440. [PubMed: 25280870]

Maull EA, Ahsan H, Edwards J, Longnecker MP, Navas-Acien A, Pi J, et al. Evaluation of the association between arsenic and diabetes: A national toxicology program workshop review. Environmental Health Perspectives. 2012; 120:1658–1670. [PubMed: 22889723]

McClure EM, Nalubamba-Phiri M, Goldenberg RL. Stillbirth in developing countries. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2006; 94:82–90.

Milton AH, Smith W, Rahman B, Hasan Z, Kulsum U, Dear K, et al. Chronic arsenic exposure and adverse pregnancy outcomes in bangladesh. Epidemiology. 2005; 16:82–86. [PubMed: 15613949]

Moon K, Guallar E, Navas-Acien A. Arsenic exposure and cardiovascular disease: An updated systematic review. Current Atherosclerosis Reports. 2012; 14:542–555. [PubMed: 22968315]

Myers SL, Lobdell DT, Liu Z, Xia Y, Ren H, Li Y, et al. Maternal drinking water arsenic exposure and perinatal outcomes in inner mongolia, china. Journal of Epidemiology & Community Health. 2010; 64:325–329. [PubMed: 19692727]

Navarro PA, Liu L, Keefe DL. In vivo effects of arsenite on meiosis, preimplantation development, and apoptosis in the mouse. Biology of Reproduction. 2004; 70:980–985. [PubMed: 14656726]

Nermell B, Lindberg AL, Rahman M, Berglund M, Persson LA, El Arifeen S, et al. Urinary arsenic concentration adjustment factors and malnutrition. Environmental research. 2008; 106:212–218. [PubMed: 17900556]

Nixon DE, Mussmann GV, Eckdahl SJ, Moyer TP. Total arsenic in urine: Palladium-persulfate vs nickel as a matrix modifier for graphite furnace atomic absorption spectrophotometry. Clinical Chemistry. 1991; 37:1575–1579. [PubMed: 1893592]

Punshon T, Davis MA, Marsit CJ, Theiler SK, Baker ER, Jackson BP, et al. Placental arsenic concentrations in relation to both maternal and infant biomarkers of exposure in a us cohort. Journal of exposure science & environmental epidemiology. 2015; 25:599–603. [PubMed: 25805251]

Quansah R, Armah FA, Essumang DK, Luginaah I, Clarke E, Marfoh K, et al. Association of arsenic with adverse pregnancy outcomes/infant mortality: A systematic review and meta-analysis. Environ Health Perspect. 2015; 123:412–421. [PubMed: 25626053]

Rahman A, Vahter M, Ekstrom EC, Rahman M, Golam Mustafa AH, Wahed MA, et al. Association of arsenic exposure during pregnancy with fetal loss and infant death: A cohort study in bangladesh. Am J Epidemiol. 2007; 165:1389–1396. [PubMed: 17351293]

Rahman A, Persson LA, Nermell B, El Arifeen S, Ekstrom EC, Smith AH, et al. Arsenic exposure and risk of spontaneous abortion, stillbirth, and infant mortality. Epidemiology (Cambridge, Mass). 2010; 21:797–804.

Rahman A, Vahter M, Ekstrom EC, Persson LA. Arsenic exposure in pregnancy increases the risk of lower respiratory tract infection and diarrhea during infancy in bangladesh. Environmental health perspectives. 2011; 119:719–724. [PubMed: 21147604]

Rivera-Nunez Z, Meliker JR, Linder AM, Nriagu JO. Reliability of spot urine samples in assessing arsenic exposure. International Journal of Hygiene and Environmental Health. 2010; 213:259–264. [PubMed: 20427236]

Rudnai P, Varro M, Borsanyi M, Paldy A, Von Hoff K, Sarkany E, et al. Arsenic in drinking water and pregnancy outcomes: An ecological study. Epidemiology. 2006; 17:S329–S330.

Sanchez TR, Perzanowski M, Graziano JH. Inorganic arsenic and respiratory health, from early life exposure to sex-specific effects: A systematic review. Environmental research. 2016; 147:537–555. [PubMed: 26891939]

Shah PS, Zao J, Al-Wassia H, Shah V. Pregnancy and neonatal outcomes of aboriginal women: A systematic review and meta-analysis. Women's health issues : official publication of the Jacobs Institute of Women's Health. 2011; 21:28–39.

Tsuji JS, Garry MR, Perez V, Chang ET. Low-level arsenic exposure and developmental neurotoxicity in children: A systematic review and risk assessment. Toxicology. 2015; 337:91–107. [PubMed: 26388044]

von Ehrenstein OS, Guha Mazumder DN, Hira-Smith M, Ghosh N, Yuan Y, Windham G, et al. Pregnancy outcomes, infant mortality, and arsenic in drinking water in west bengal, india. American journal of epidemiology. 2006; 163:662–669. [PubMed: 16524957]

Woods JS, Martin MD, Leroux BG. Validity of spot urine samples as a surrogate measure of 24-hour porphyrin excretion rates. Evaluation of diurnal variations in porphyrin, mercury, and creatinine concentrations among subjects with very low occupational mercury exposure. Journal of Occupational and Environmental Medicine. 1998; 40:1090–1101. [PubMed: 9871886]

Highlights

- Adverse association between moderate to high prenatal arsenic and stillbirth.
- Possible adverse association with child mortality and prenatal arsenic exposure.
- Arsenic remediation strategies for women of child-bearing age should be considered.

Table 1

Selected maternal characteristics for all reported pregnancies in BEST (n=598)

Characteristic	Overall (n=598)	Urinary total arsenic (μg/g creatinine)		P value	Pregnancy outcome		Crude OR (95% CI)
		17 – 555 (n=299)	555 – 3,712 (n=299)		Livebirth (n=489)	Adverse birth (n=109)	
Mean maternal age, year ± SD	32.2 ± 4.3	32.2 ± 4.2	32.1 ± 4.4	0.45	31.8 ± 4.0	33.9 ± 5.2	1.12 (1.07, 1.17)
Pregnancy outcome, N (%)							
Livebirth	489 (81.7)	254 (84.9)	235 (78.6)		–	–	–
Stillbirth	23 (3.9)	7 (2.3)	16 (5.4)	0.12	–	–	–
Spontaneous abortion	60 (10.0)	28 (9.4)	32 (10.7)		–	–	–
Therapeutic/elective abortion	26 (4.4)	10 (3.3)	16 (5.4)		–	–	–
Maternal education, years, N (%)							
0	108 (18.1)	44 (14.7)	64 (21.4)	0.02	82 (16.8)	26 (23.9)	1.56 (0.92, 2.64)
≤5	141 (23.6)	68 (22.7)	73 (24.4)		117 (23.9)	24 (22.0)	1.01 (0.58, 1.70)
>5	349 (58.4)	187 (62.5)	162 (54.2)		290 (59.3)	59 (54.1)	1 (ref)
BEST treatment assignment, N (%)							
Placebo	147 (24.6)	56 (18.7)	91 (30.4)		115 (23.5)	32 (29.4)	1 (ref)
Selenium	146 (24.4)	76 (25.4)	70 (23.4)	0.01	119 (24.3)	27 (24.8)	0.82 (0.46, 1.46)
Vitamin E	156 (26.1)	84 (28.1)	72 (24.1)		124 (25.4)	25 (22.9)	0.72 (0.41, 1.26)
Vitamin E + selenium	149 (24.9)	83 (27.8)	66 (22.1)		131 (26.8)	25 (22.9)	0.69 (0.38, 1.23)
Skin lesion severity, N (%)							
Mild	276 (46.2)	131 (44.0)	145(48.5)	0.27	229 (46.9)	47 (43.1)	1 (ref)
Severe	321 (53.8)	167 (56.0)	154 (51.5)		259 (53.1)	62 (56.9)	1.17 (0.77, 1.76)
Received prenatal care, N (%)	344 (67.2)	186 (71.3)	158 (63.0)	0.05	327 (66.9)	17 (73.9)	1.44 (0.56, 3.69)
Mean number of prenatal visits ± SD	3.1 ± 2.4	3.3 ± 2.5	2.7 ± 2.2	0.02	3.1 ± 2.4	2.9 ± 2.0	0.97 (0.81, 1.16)
Maternal smoking, N (%)	4 (0.8)	2 (0.8)	2 (0.8)	0.97	4 (0.8)	0 (0.0)	--
Passive tobacco smoke exposure, N (%)	200 (39.1)	99 (37.9)	101 (40.2)	0.59	190 (38.9)	10 (43.4)	1.12 (0.49, 2.59)
Gestational hypertension, N (%)	46 (9.0)	25 (9.6)	21 (8.4)	0.63	43 (8.8)	3 (13.0)	1.79 (0.51, 6.31)
Preeclampsia, N (%)	8 (1.6)	2 (0.8)	6 (2.4)	0.14	7 (1.4)	1 (4.4)	3.11 (0.36, 26.91)
Gestational diabetes, N (%)	4 (0.8)	3 (1.2)	1 (0.4)	0.34	3 (0.6)	1 (4.4)	7.59 (0.73, 78.41)
Mean gravidity ± SD	3.9 ± 1.7	3.7 ± 1.6	4.0 ± 1.8	0.12	3.9 ± 1.6	4.0 ± 2.5	1.03 (0.75, 1.43)
Mean parity ± SD	3.5 ± 1.5	3.4 ± 1.4	3.7 ± 1.6	0.20	3.6 ± 1.5	2.8 ± 1.2	0.68 (0.50, 0.94)

Characteristic	Overall (n=598)	Urinary total arsenic (μg/g creatinine)		P value	Pregnancy outcome		Crude OR (95% CI)
		17 – 555 (n=299)	555 – 3,712 (n=299)		Livebirth (n=489)	Adverse birth (n=109)	
Prior stillbirth pregnancy, N (%)	84 (16.4)	37 (14.2)	47 (18.7)	0.17	76 (15.5)	8 (34.8)	3.64 (1.66, 7.98)

SD, standard deviation; N, number of subjects; BEST, Bangladesh vitamin E and Selenium Trial; OR, odds ratio

Table 2

Crude and adjusted odds ratios (95% CIs) for the associations between prenatal arsenic exposure and adverse pregnancy outcomes

Model	Urinary total arsenic (μg/g creatinine)		
	17 – 555	556 – 3,712	P-value
Any adverse pregnancy outcome			
Unadjusted	1 (ref)	1.53 (1.00, 2.35)	0.05
Adjusted for maternal age	1 (ref)	1.58 (1.02, 2.42)	0.04
Fully adjusted[a]	1 (ref)	1.59 (1.02, 2.46)	0.04
Stillbirth/spontaneous abortion			
Unadjusted	1 (ref)	1.50 (0.92, 2.45)	0.10
Adjusted for maternal age	1 (ref)	1.51 (0.93, 2.47)	0.10
Fully adjusted[a]	1 (ref)	1.57 (0.96, 2.56)	0.07
Stillbirth			
Unadjusted	1 (ref)	2.41 (1.00, 5.85)	0.05
Adjusted for maternal age	1 (ref)	2.41 (0.99, 5.85)	0.05
Fully adjusted[b]	1 (ref)	2.50 (1.04, 6.01)	0.05
Spontaneous abortion			
Unadjusted	1 (ref)	1.26 (0.72, 2.20)	0.41
Adjusted for maternal age	1 (ref)	1.27 (0.72, 2.24)	0.42
Fully adjusted[a]	1 (ref)	1.33 (0.76, 2.32)	0.32
Therapeutic/elective abortion			
Unadjusted	1 (ref)	1.67 (0.75, 3.73)	0.21
Adjusted for maternal age	1 (ref)	1.69 (0.75, 3.81)	0.21
Fully adjusted[a]	1 (ref)	1.58 (0.70, 3.56)	0.27

[a] Adjusted for maternal age (years), maternal education (years), BEST treatment assignment, and skin lesion severity.

[b] Adjusted for maternal age (years), maternal education (years), BEST treatment assignment, skin lesion severity, parity, and previous stillbirth.

Table 3

Crude and adjusted hazard ratio (95% CIs) for the association between in utero arsenic exposure and child mortality

Model	Urinary total arsenic (μg/g creatinine)		
	17 – 555 (n=249)	556 – 3,712 (n=234)	P value
Unadjusted	1 (ref)	1.72 (0.71, 4.16)	0.23
Adjusted for maternal age	1 (ref)	1.72 (0.71, 4.15)	0.23
Fully adjusted[a]	1 (ref)	1.92 (0.78, 4.68)	0.15

[a]Adjusted for maternal age (years), maternal education (years), child sex, BEST treatment assignment, maternal skin lesion severity, and exposure to passive tobacco smoke (yes, no).